HONG KONG PHARMACEUTICAL
JOURNAL

News & Short Communications

A Community Pharmacist Can Make a Difference - An Interview with Anita Chan

Cross Sensitivity Reaction of Different Drug Classes (2 CE Units)

No Improvement in Hand Skin Quality by Coenzyme Q10 Topical Formulation among Young and Old Healthy Female Volunteers

"Chinese Medicines are Toxic" is a Misconception

Hong Kong Pharmacy Conference 2014

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SPECIAL ISSUE

ACPE Abstracts of 8th Asian Conference on Pharmacoepidemiology: "Applying pharmacoepidemiology to improve health care in Asia" Hong Kong

The Pharmaceutical Society of Hong Kong
The Practising Pharmacists Association of Hong Kong
The Society of Hospital Pharmacists of Hong Kong

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INSTRUCTIONS FOR AUTHORS

The Hong Kong Pharmaceutical Journal is a journal of the pharmacists, for the pharmacists and by the pharmacists. Submissions are welcome for the following sections:

- Pharmacy Education & Practice
- OTC & Health
- Medication Safety
- Society Activities
- Drugs & Therapeutics
- Pharmaceutical Techniques & Technology
- Herbal Medicines & Nutraceuticals
- New Products

Comments on any aspects of the profession are also welcome as Letter to the Editor.

There is no restriction on the length of the articles to be submitted. They can be written in English or Chinese. The Editorial Committee may make editorial changes to the articles but major amendments will be communicated with the authors prior to publishing.

It is preferable to have original articles submitted as an electronic file, in Microsoft Word, typed in Arial 9pt. Files can be sent to the following address:

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For detail instructions for authors, please refer to the first issue of each volume of HKPJ.

CONDOR

Celecoxib versus **O**meprazole a**N**d **D**iclofenac
in patients with **O**steoarthritis and **R**heumatoid arthritis

Celecoxib vs. Diclofenac + Omeprazole:

Patients treated with Celecoxib had a **LOWER RISK** of Clinically Significant Upper and/or Lower GI Events[1]

Patients with adjudicated clinically significant upper and/or lower GI events

Number of total cases with clinically significant upper and/or lower GI events

Diclofenac SR 75 mg bid
+
Omeprazole 20 mg qd
(Total=2,246, n=81)

Celecoxib 200 mg bid
(Total=2,238, n=20)

Decrease by 4 times
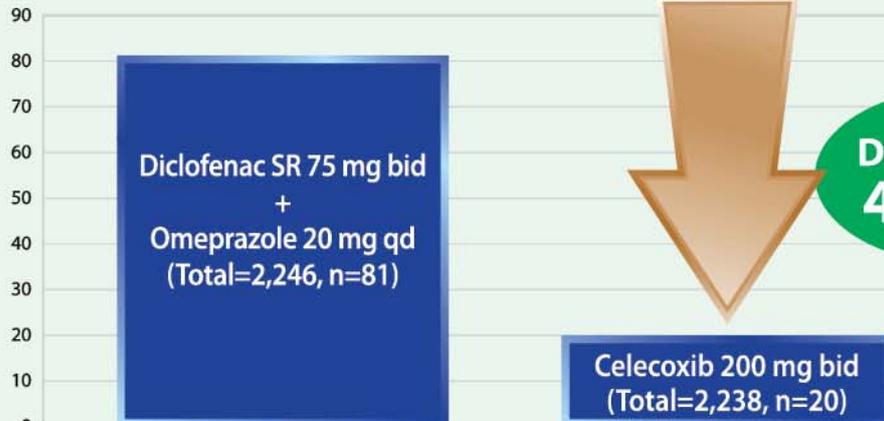
Hazard ratio was 4.3 in favour of Celecoxib, $P<0.0001$

- Proven efficacy in various pain models [2-5]
- The only FDA-approved COX-2 inhibitor [6]
- Option for millions of patients for over 10 straight years [7]

Strengthening confidence across Asia FOR OVER 10 YEARS

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Scientific Approach to the Vigilance and Risk Management of Medicines

From the front cover and the thickness of this issue of the HKPJ, readers wouldn't have difficulty to find that this is a special issue devoted to the scientific meeting of the 8th Asian Conference on Pharmacoepidemiology, which will be held in Hong Kong from October 25-27.[1] The goal of this meeting is to address, discuss or exchange ideas relevant to the vigilance and risk management of medicines. Around two hundred researchers and experts from the field of apply pharmacoepidemiology in different countries will get together to report their discovery studies on drug adverse problems or solutions of medication with aim to improve health care in Asia. A list of these participants and the title of their reports is shown in page 130-131, while abstracts of their report could also be found in this issue. This meeting is organized and hosted by the Department of Pharmacology and Pharmacy of the University of Hong Kong with the support from the Chinese Pharmaceutical Association, the Hong Kong Pharmaceutical Society and the International Society for Pharmacoepidemiology. Hence, it will certainly be a big event for all pharmaceutical professions in Hong Kong.

Although most therapeutics in use today have gone through premarketing study usually involves a few thousands of patients, it has been found that it is not a reliable tool to discover uncommon effects of a drug. A recent example was the worldwide withdrawal of a synthetic antibacterial fluoroqunolone derivative, temafloxacin, following postmarketing detection of hemolytic anaemia and other serious adverse reaction.[2,3] As defined by the medical faculty of Johns Hopkins University in Maryland, pharmacoepidemiology is the study of the utilization and effects of drugs in large numbers of people; it provides an estimate of the probability of beneficial effects of a drug in a population and the probability of adverse effects. It can be called a bridge science spanning both clinical pharmacology and epidemiology. Pharmacoepidemiology concentrates on clinical patient outcomes from therapeutics by using methods of clinical epidemiology and applying them to understanding the determinants of beneficial and adverse drug effects, effects of genetic variation on drug effect, duration-response relationships, clinical effects of drug-drug interactions, and the effects of medication non-adherence. Pharmacovigilance is a part of pharmacoepidemiology that involves continual monitoring, in a population, for unwanted effects and other safety concerns arising in drugs that are already on the market. Pharmacoepidemiology sometimes also involves the conduct and evaluation of programmatic efforts to improve medication use on a population basis.[4]

In this issue, we have paid some efforts to solicit recent cases of drug adverse effects or decisions made by the regulatory authorities in oversea countries. It was without difficulty that many cases were identified. Readers can get a glimpse of a few selected cases in the News & Communication Section of this issue (p.99-103) and obtain the details through source of information provided. Amongst the selected items, this editorial would like to draw our readers' attention to an important announcement made by the Canadian Authority on the availability and conditions of use of calcitonin. In the past, products contain calcitonin was regarded as a safe medication and has been used for long time to treat osteoporosis in postmenopausal women. Yet only after a more scientific study, it is discovered that prolonged and excessive medication with products containing calcitonin for symptomatic Paget's disease can cause cancer. Hence, it is not recommended for prolong use and should be kept to the minimum effective dose if no alternative choice available (p101). A paralleled important effect is the allergic response due to simultaneous use of different drugs, which may have advantages as well as disadvantages depending on their overall effect. Kwok and Mak reviewed some new evidences available and pointed out that cross sensitivity due to medication of different classes of drug should not be ignored. For more details about cross sensitivity reaction of different classes of drug, one should refer to page 107-114.

As with many western pharmaceuticals, some herbal remedies have risk associated with their use.[5,6] The fact that a botanical is completely natural does not necessarily make the use of botanical substance risk-free. Several botanicals, when consumed in their most natural form, can cause grave illness or even death in humans and animals. Although many of these botanical substances are routinely avoided by herbalists, scientists, and the general public because of their risks, yet hundreds of herbs and alternative medicines exist, and most of which have not been studied adequately, particularly in relation to their toxicology. A large retrospective study of admissions to the casualty department of a Taiwanese hospital found that 4% of admissions were related to herbal drug use, ranking herbal remedies third among drug categories most responsible for adverse effects. Nevertheless, over reaction to the presence of some toxic components in Chinese medicines is unnecessary. As it is pointed out by some experts that excessive amount of a toxicant in some Chinese medicines is either a tactic to combat a disease or a misunderstood of its effect. Many western drugs, in particular, chemotherapy drugs, are extremely toxic yet they are still in use as long as they are used under proper monitoring by a doctor. For more details of this discussion, readers are encouraged to read an article written by Lo and Cheung in page 120-123.

False claim of effectiveness, whether deliberately or unconsciously, is another matter deserves people as well as the regulatory authority's attention. Although it may not do immediate harm to a patient, it is an economic lost, and may deprive the right of receiving an expected effect or a proper treatment for the person. Tong reported that addition of Coenzyme Q10 into topical hand skin preparation failed to enhance skin barrier function in comparison to that of a placebo (page 116-119). Although the study was far from perfect and has many rooms for further improved, it does review that inadequate or inappropriate dissemination of information to the public, combined with poor study or weak regulation, can lead unwary consumers to use these products that can cause dangerous adverse reactions. Manufacturers and dealers of dietary supplements and herbal medicines spend millions of dollars each year on advertising their products. Existing regulations for product labeling of diet or herbal supplements fail to provide ample warning of risks to consumers. Indeed, many advertisements could be considered misleading or at least of questionable accuracy, despite regulatory authority has limited their claims only to proper health maintenance.

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Cheung Hon-Yeung
Editor-in-Chief
16th October, 2013

Boxed Warning on Increased Mortality and Severe Renal Injury and Risk of Bleeding on the Use of Hydroxyethyl Starch Solutions

Date: June 25, 2013

FDA has analyzed recent data that indicate an increased risk of (i) mortality and renal injury requiring renal replacement therapy in critically ill adult patients, including patients with sepsis and those admitted to the ICU; and (ii) excess bleeding particularly in patients undergoing open heart surgery in association with cardiopulmonary bypass. FDA has concluded that Hydroxyethyl Starch (HES) solutions should not be used in critically ill adult patients, including patients with sepsis and those admitted to the ICU, and a Boxed Warning to include the risk of mortality and severe renal injury is warranted. In addition, FDA has reviewed a meta-analysis of studies conducted in patients undergoing open heart surgery in association with cardiopulmonary bypass and has determined that an additional warning about excessive bleeding is needed in the Warnings and Precautions Section of the package insert.

Source: http://www.fda.gov/../ucm358349. htm?source=govdelivery

Updates on the Use of Codeine: Restrictions on Use of Codeine for Pain Relief in Children

Date: June 29, 2013

A review was conducted by the EMA (European Medicines Agency)'s Pharmacovigilance Risk Assessment Committee (PRAC), which investigated reports of serious and fatal respiratory depression in children after taking codeine for pain relief. Most of the cases occurred after surgical removal of the tonsils or adenoids for obstructive sleep apnoea (frequent interruption of breathing during sleep). The PRAC concluded that a number of risk minimisation measures are necessary to ensure that only children for whom the benefits are greater than the risks are given the medicine for pain relief. The risk of side effects with codeine may also apply to adults. Codeine should therefore not be used in people of any age who are known to be ultra-rapid metabolisers nor in breastfeeding mothers.

The United Kingdom: MHRA confirmed that codeine-containing medicines should only be used in children over 12 years old to treat acute (short lived) moderate pain, and only if it cannot be relieved by other painkillers such as paracetamol or ibuprofen. Where it is used in children it should be used at the lowest effective dose and only for the shortest period of time recommended by the doctor. This is because some patients may be at an increased risk of rare but serious adverse reactions as a result of the way the body handles codeine and younger children may be particularly susceptible. It has also been concluded that codeine should not be used at all in any patient under 18 years old who undergoes the removal of tonsils or adenoids for the treatment of sleep apnoea. This is due to an increased risk of severe breathing difficulties.

Source: http://www.mhra.gov.uk/NewsCentre/Pressreleases/ CON287048

Source: http://www.ema.europa.eu/../news_detail_001829. jsp&mid=WC0b01ac058004d5c1

Updates on the Use of Diclofenac

Date: June 29, 2013

The MHRA confirmed that patients with serious underlying heart conditions, such as heart failure, heart disease, circulatory problems or a previous heart attack or stroke should no longer use diclofenac, This follows completion of a European review which found a small increased risk of heart attack and stroke. Dr. Sarah Branch, Deputy Director of the MHRA's Vigilance and Risk Management of Medicines Division said: "Whilst this is a known risk and warnings have been included in patient and healthcare information for some time, this advice is now being updated. For many patients diclofenac will continue to provide safe and effective pain relief but is no longer suitable for certain at risk groups. Those with underlying heart conditions currently taking diclofenac should speak to their GP or pharmacist at their next routine visit to consider an alternative pain relief treatment. Patients with certain cardiovascular risk factors such as high blood pressure, raised cholesterol, diabetes and smoking should only use diclofenac after careful consideration with their GP or pharmacist."

Source: http://www.mhra.gov.uk/NewsCentre/Pressreleases/ CON287042

Management of the
SIDE EFFECT resulting from
Chemotherapy / Radiotherapy

Chemotherapy / Radiotherapy

- Compromise patients' immune system.
- Lead to oral inflammation[1,2]
  - Mucous membrane shredding

Poor Oral Hygiene Negatively
impacts Chemotherapy / Radiotherapy

- Disrupt cancer therapy[4]
- Impose potential source of life-threatening systemic infections[3]
- Affect patient quality of life[4,5]

Povidone-Iodine (BETADINE)
Gargle & Mouthwash
helps manage Oral Inflammation[6]

- Reduce the incidence, severity and duration of radiation-induced oral inflammation
- Delay the onset of oral inflammation
- Speed-up recovery from oral-mucositis by as much as 45 days ($p < 0.001$)

BETADINE Gargle & Mouthwash contains PVP-I

- Reduces the risk of developing serious oral inflammation by 70% ($p < 0.005$)[6]
- Help relieve the oral inflammation symptoms
- Possess broad spectrum killing power against bacteria, viruses and fungi[7]

G+	G−	Spores	Fungi	Virus
√√√	√√√	√√√	√√√	√√

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Canada: Important Changes to the Availability and Conditions of Use for Drugs Containing Calcitonin

Date: August 1, 2013

Health Canada is informing Canadians of important changes to the availability and recommended conditions of use of drugs containing calcitonin. Calcitonin is used as a nasal spray to treat osteoporosis (loss of calcium in bones) in postmenopausal women and as an injection to treat Paget's disease (a chronic bone disorder) and hypercalcemia (high blood calcium).

A safety review conducted by Health Canada has concluded that there is a slightly increased risk of cancer associated with the prolonged use of calcitonin products. A review of the benefits and risks of the nasal spray products found that there was not enough evidence of benefit to continue using calcitonin nasal sprays in treating osteoporosis, given the increased risk of cancer. As a result of these reviews, calcitonin nasal spray products will no longer be authorized for sale in Canada as of October 1, 2013. This transition period will allow patients using calcitonin nasal spray to be transferred to other treatments.

Calcitonin injectable products will continue to be authorized for sale in Canada. The benefits of these products are considered to outweigh the risks when the product is used as directed in the Product Monograph (i.e., for Paget's disease and hypercalcemia). However, the labels for calcitonin injectable products are being updated to include a new warning about this risk, and to recommend that treatment with calcitonin solution for injection be limited to the shortest possible time, using the minimum effective dose. Treatment of symptomatic Paget's disease with calcitonin medicine should be limited to patients who are unable to use other treatments. Patients who are taking a calcitonin medicine and who have questions should speak to their healthcare practitioner before making any change to their treatment. There are other medications authorized in Canada for the treatment of osteoporosis, Paget's disease and hypercalcemia. Patients should speak to their pharmacist regarding the safe disposal of calcitonin nasal spray products.

Source: http://healthycanadians.gc.ca/recall-alert-rappel-avis/ hc-sc/../34843a-eng.php

Increased Glucose Level May Increase the Risk of Dementia

Date: August 8, 2013

Studies have found that, not only diabetes is a risk factor for dementia, higher glucose levels may also increase the risk of dementia in people without diabetes. In an observational study involving 2067 participants without dementia to examine the relationship between glucose levels and the risk of dementia. During a median follow-up of 6.8 years, 524 participants developed dementia (74 with diabetes and 450 without). Among the participants without diabetes, higher average glucose levels within the preceding 5 years were related to an increased risk of dementia (P = 0.01); with a glucose level of 115 mg/dL (6.4 mmol/L), as compared to 100 mg/dL (5.5 mmol/L) in the group without developing dementia, the adjusted hazard ratio for dementia was 1.18 (95% confidence interval [CI], 1.04 to 1.33). On the other hand, among the participants with diabetes, higher average glucose levels were also related to an increased risk of dementia (P = 0.002); with a glucose level of 190 mg.dL (10.5 mmol.L), as compared to 160 mg/dL (8.9 mmol/L), the adjusted hazard ratio was 1.40 (95% CI, 1.12 to 1.76). The study suggested that higher glucose levels may associate with a higher risk for dementia.

Source: New England Journal of Medicine

Singapore: Potential Interaction between Warfarin and Health Supplements Containing Vitamin K

Date: August 30, 2013

Healthcare professionals are reminded to be aware of a potential interaction between warfarin and health supplements containing vitamin K. A local adverse event report was received from a doctor involving an 80-year-old patient on long-term warfarin therapy and concurrent use of Centrum Silver®. The patient, who was a long-term user of Centrum Silver®, had been on the same warfarin dose for the past three years with International Normalised Ratio (INR) within the therapeutic range. During a routine blood test, the INR was unexpectedly reduced to a sub-therapeutic level. Further investigations revealed that the Centrum Silver® taken by the patient was a new formulation with an additional 25mcg of vitamin K1, which was not present in the earlier formulation. Small amounts of vitamin K1 (e.g., 10-25mcg) contained in multivitamin supplements are generally considered safe in patients undergoing warfarin anticoagulation therapy. Healthcare professionals managing patients on warfarin are encouraged to monitor their patients' INRs and counsel them on their vitamin K intake from health supplements and food.

Source: http://www.hsa.gov.sg/publish/hsaportal/../potential_ interaction.html

New Partner State Key Laboratory Pushes Frontiers in Metabolic Medicine

Date: September 2, 2013

In a strategic collaboration between the University of Hong Kong and Nanjing University, a new Partner State Key Laboratory of Pharmaceutical Biotechnology has now been established at the Li Ka Shing Faculty of Medicine. The Chinese Ministry of Science and Technology granted official approval for the laboratory in early July this year. The Laboratory will strengthen research ties between scientists on the Mainland and in Hong Kong. It is the fifth State Key Laboratory to be set up at The University of Hong Kong. State Key Laboratories are seen as hubs for research excellence and significantly contribute to China's development in science and technology. In addition to research collaboration, they also facilitate academic exchange between China and the overseas scientific community.

Led by Professor Aimin Xu at the Department of Pharmacology and Pharmacy, and the Department of Medicine, the State Key Laboratory for Pharmaceutical Biotechnology will carry out vital research on metabolic medicine, with particular emphasis on obesity, diabetes and the associated complications. Professor Ian Wong, Head of Department of Pharmacology and Pharmacy, said the Key State Laboratory is extremely important for the pharmacy profession in Hong Kong and China. He said pharmacists' unique skills are essential to the development of appropriate formulations for new drug molecules. The State Key Laboratory will also apply state-of-the-art pharmaceutical technology to "pharmaceutical translational research" to develop formulations for existing drug molecules, he added. "The immediate implication is that we can build a long term and sustainable platform for our research," said Xu, "It's the first such laboratory to focus on metabolic medicine."

Currently, Xu is exploring the potential for adipokines to be used as diagnostic markers for the early prediction of diabetes and diabetic complications; and as a therapeutic target to develop a cure for diabetes. "We have many anti-diabetic drugs available but none can cure the disease, simply because we do not know the early pathogenesis. Adipokines can be used as an early bio-marker and also as a therapeutic target for early intervention," Xu says.

A significant challenge for diabetic management in China, as with many developing countries, is that over 50% of people with diabetes are not diagnosed until complications set in. "Once you have diabetic complications it's too late," says Xu. Raised blood glucose levels are a late indication so the search is underway for an assay for early diagnosis or even risk prediction of diabetes.

There is stiff competition. Xu and his team are not the only ones after the Holy Grail of a cure for diabetes. "But, we are the leading group in the world," he said proudly, "We have discovered several new adipokines, originally discovered in our laboratory." To date, they have developed a wide range of assay kits for diagnosis. A number of these are currently used in clinical trials and every effort is being made to get a further two to the clinical trial stage in China. Xu cites an example in Australia where one of their assay kits is being used in an anti-lipid clinical trial of over 20 000 subjects.

Xu's view is that biomarkers will become a key component in personalised diabetic management. "Although all diabetic patients have hyperglycaemia, each patient is different, they have different genetic and environmental factors which contribute to its development, so it's very important in the future to have these personalised," he said.

Canada: Association of Sutent (sunitinib malate) with Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

Date: September 7, 2013

Pfizer Canada Inc., in collaboration with Health Canada, has informed healthcare professionals and the public of an important revision to the Product Monograph, including the consumer information section, for Sutent (sunitinib malate).

According to Health Canada, Sutent is indicated for the treatment of gastrointestinal stromal tumour (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance. It is also indicated for the treatment of metastatic renal cell carcinoma (MRCC) of clear cell histology and for the treatment of patients with unresectable locally advanced or metastatic, well-differentiated pancreatic neuroendocrine tumours (pancreatic NET), whose disease is progressive. A statement has been recently added to the Canadian Product Monograph to inform healthcare professionals and patients about a potential association between the use of Sutent and severe cutaneous reactions suggestive of Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). Early recognition is important in improving prognosis. Cases of Toxic Epidermal Necrolysis (TEN) and Stevens-Johnson Syndrome (SJS), including fatal cases, have been very rarely reported, mostly in the post-marketing setting, in patients who have used Sutent. Health Canada advised healthcare professionals that if signs or symptoms of SJS or TEN are present, Sutent treatment should be discontinued; and if the diagnosis of SJS or TEN is confirmed, treatment must not be restarted. The Canadian Product Monograph has been updated to reflect this risk.

The potential risk of the cutaneous adverse events of Toxic Epidermal Necrolysis (TEN), and Stevens-Johnson Syndrome (SJS), with sunitinib use was evaluated using a review of currently available safety data from published literature, the Pfizer global safety database containing clinical trial serious adverse events and post-marketing reports, the US FDA Adverse Event Reporting System (AERS) database, and the Canada Vigilance database. Out of an estimated 214,848 patients exposed to sunitinib between 26 January 2006 and 30 April 2013, there were 4 reported cases of TEN and 5 reported cases of SJS internationally, although diagnosis was not confirmed in all cases. Two of the potential TEN cases had fatal outcomes. There have been no Canadian cases reported as of 30 April 2013.

Hong Kong Pharmacist Won the 2013 Royal Pharmaceutical Society Leadership Award Recognizing Work in Elderly Homes Medicines Safety

Date: September 9, 2013

The 2013 Royal Pharmaceutical Society (RPS) awards were presented last night at a gala dinner at the RPS Conference to celebrate the achievements of teams and individuals within the Pharmacy profession. Mr. Peter Suen, Chief Pharmacist of Active Care Pharmacy, Hong Kong won the RPS Leadership in Pharmacy Award, which recognized his work in Old Age Homes medication management in Hong Kong. Over 350 guests cheered the finalist and eight award winners whose excellence and innovation in improving and enhancing patient care proved truly outstanding. The awards encompass all sectors within the profession and range across all career stages, from Student of the Year to our Lifetime Achievement Award.

RPS Chief Executive Helen Gordon said: "Huge congratulations to all of our finalists and award winners. I'm delighted the achievements of members have been recognised by our annual awards programme. The innovative and proactive approach they demonstrate towards improving patient care is genuinely inspiring."

Mr. Peter Suen said: "The work in Old Age Homes medication management was initiated by the Pharmaceutical Society of Hong Kong under the leadership of Mr. Benjamin Kwong and continuously supported by Mrs. Mary Cheng and members of the General Council over the years." In Hong Kong, because of a shortage of nursing and pharmaceutically trained staff, some nursing homes allowed unqualified workers to prepare and administer medicines. There is a need to develop a training course for the unqualified nursing home workers and to develop a medication management systems and guidelines to allow appropriate systems to be implemented in nursing homes. Mr. Peter Suen, in partnership with the Pharmaceutical Society of Hong Kong and the Caritas Institute of Higher Education, took the initiative to develop a course, involving 99 hours of teaching and practical part time study for nursing home workers. Based on the initial software used by the Pharmaceutical Society of Hong Kong, he invested in the development of a new bilingual data medication management system allowing web-based management with ISO 9001 certification. He also applied for a grant from the Hong Kong government's trade and industrial department to pilot an implementation study of a medication management system. The system is now suitable for the use of Hong Kong nursing homes and helps prevent medication administration errors in the nursing homes. Professor Ian Wong, Head of Department of Pharmacology and Pharmacy of the Hong Kong University, nominated Mr. Peter Suen. He said "Peter Suen has expanded substantial effort to improve the use of medicines in nursing homes. He has been a leader who is able to work with the professional body, the care providers and the government's social welfare department to improve pharmaceutical care of the elderly in Hong Kong."

Open to any sector, this will be awarded to those who have shown leadership within pharmacy, whether that be industrial developing a new process, hospital delivering an innovative service, community selling the benefits of pharmacy above and beyond, academia for a new research paper or novel teaching process, primary care for innovative ways of working.

Source: http://www.rpharms.com/home/home.asp
and www.pjonline.com

Peter Suen(left) and Stephen Howard, FRPharmS, superintendent pharmacist at Lloyds pharmacy who presented the award

Erratum for Volume 20(1) January- March, 2013

There is a printing error on page 21 for Table 2 in the "Overview of Targeted Therapies for Renal Cell Carcinoma"

For T3+N0 or N1 disease, the disease staging should be in Stage III instead of Stage IV. Correct Table 2 as below:

Table 2. AJCC TNM Staging System for kidney cancer. [Adapted from Edge, et al][23]						
Primary Tumor (T)			**Regional Lymph Nodes (N)**			
	Involvement	**Extent of disease**	NX	Regional lymph nodes cannot be assessed		
TX	Primary tumor cannot be assessed		N0	No regional lymph node metastasis		
T0	No evidence of primary tumor lymph node(s)		N1	Metastasis in a single regional		
T1a	Tumor ≤ 4 cm	limited to kidney	**Distant Metastasis (M)**			
T1b	Tumor ≥ 4 cm to ≤ 7 cm		M0	No Distant Metastasis		
T2a	Tumor >7cm to ≤ 10cm		M1	Distant Metastasis		
T2b	Tumor > 10 cm		**Staging**			
T3a	Into renal vein or its segmental branches	not beyond Gerota's fascia	Stage I	T1	N0	M0
T3b	into vena cava	below the diaphragm	Stage II	T2	N0	M0
T3c	Into vena cava or invades wall of vena cava	above the diaphragm	Stage III	T1 or T2	N1	M0
				T3	N0 or N1	M0
T4	invades beyond Gerota's fascia	Including contiguous extension into the ipsilateral adrenal gland	Stage IV	T4	Any N	M0
				Any T	Any N	M1

A Community Pharmacist Can Make a Difference - An Interview with Anita Chan

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INTRODUCTION

Anita Chan shares her career path and role as a community pharmacist at the Philanthropic Community Pharmacy of St. James' Settlement.

Background

Ms. Anita Chan

After gaining her Pharmacy undergraduate degree in the US, Anita decided not to study medicine as intended. Instead, she began her career in a community pharmacy where she met her first mentor. During this period she was deeply impressed by how her mentor showed wholehearted care during patient counseling despite the concept of pharmaceutical counseling was not prevalent at that time. This made a huge impact on Anita's career as a community pharmacist.

After nine-year of practice in two chain pharmacies, Anita joined Walmart in Chicago and managed a new niche of pharmacy business – operation of a community pharmacy at a warehouse store that targeted the upper middle-class. She began to involve in more customer service and business operation work. Through establishing strong customer relationship and providing good patient counseling service, the value of the warehouse pharmacy became recognized over time. Six years later Anita progressed to another position in Walmart in California, where she became the Director of Operation. She oversaw the operations of pharmacy in 4 different states and managed the human resources of the pharmacy including recruiting and retaining pharmacists. In addition, she was involved in the management of profit-generating and image building of the pharmacy.

After 20 years of living in the US, Anita decided to move back to her roots - Hong Kong, with her families in 2009, hoping that her children can learn about the traditional Chinese culture and receive education in Hong Kong. At the beginning, Anita expected to start her career from scratch. She embarked on working as a community pharmacist in a chain pharmacy. Soon thereafter she resigned from the job and joined St. James' Settlement (SJS) where she helped found the Philanthropic Community Pharmacy - the first nonprofit community pharmacy in Hong Kong.

PJ: Why did you choose to join St. James' Settlement?

Anita: In fact, I didn't plan what to do when I came back to Hong Kong. I knew that I have to start everything from scratch like a fresh graduate. At the time I joined SJS, I just knew it's a NGO (non-governmental organization) that was planning to set up a nonprofit community pharmacy. So I thought my past experience of establishing new community pharmacy in the business sector might help in this aspect. Therefore, I decided to give this a try.

PJ: What are the criteria when determining the target service group of different projects?

Anita: Unlike my previous job, I am lucky that I do not have to worry too much about the profit of the pharmacy now. Our goal is to help as many people as possible to receive

appropriate treatment. There is a very clear goal when we set up the pharmacy: all patients should have the chance to receive appropriate treatment regardless of their background (病者有其藥). Patients with financial burden should not receive an inferior treatment or bear more side effects. Besides, I am grateful to have the support from SJS which allows me to promote the role of a community pharmacist - our second goal of running the pharmacy. Together with our dispenser, we hope to let the public recognize the role of a community pharmacist and dispenser in drug education and help them acquire proper knowledge of taking drugs (知藥用藥). We do not just instruct the patients on how to take the drugs; we make sure they are taking the drugs correctly. For example, we use a cardboard with cartoons of a sun and a moon to illustrate the administration time for illiterate elderly.

PJ: How do you gain support from the pharmaceutical companies?

Anita: At the beginning, there was a huge resistance from the pharmaceutical companies. They did not see the point in selling the drugs to us at a lower price, and were concerned about the negative feedback from physicians and other community pharmacies. Fortunately, they gradually perceived the positive value of our work. They realized that patients who are in need can really benefit from getting the drug through our service, and this has fulfilled their corporate social responsibility. Moreover, the program provides physicians with an option to choose new expensive drug for suitable patients who are not able to pay for the drug out of their own pocket. This group of patients can acquire their needed medications at a much affordable price or even free at times, which can largely improve their health outcome and quality of life. After all, with more physicians willing to prescribe new drugs and more patients being able to benefit from this, pharmaceutical companies become more supportive to our program.

PJ: Does your previous work experience in the US help your job at present?

Anita: Definitely yes. Although discrimination in the US is very uncommon, I unfortunately had a bad experience with my store manager in my previous workplace. He was a 6'5'' tall man who came from New York. He disliked Asian people and was not happy about the high salary of pharmacist. Initially, we were in a very hostile relationship. He would threaten me with words when things went wrong in the pharmacy. But then I realized that communication and mutual understanding were the keys to solve the conflict. I shall look at things from his point of view and show him what a pharmacist is actually doing everyday and how we contribute to generating income for the store. I might also join the manager meeting to assist development of the store. I learned a lesson from this experience that I can apply to the relationship between healthcare professionals and patients. There shouldn't be a hierarchy between pharmacists and patients. We shall communicate with patients in an equal

position. Having this in mind, we have created an environment in the pharmacy that facilitates mutual communication.

PJ: Can you share with us the things that you feel happy or unhappy about with your current job?

Anita: To be honest, I am really happy and satisfied with my job. I gain different learning every day, and I have many chances to try out a variety of things, for example, writing newspaper articles and participating in radio program about drug education.

Besides, I am so glad to meet different pharmacy students as I can share my experience with them. It's so nice to see our future pharmacists having such a good academic background and I am sure that they will continue contributing to our pharmacy society.

PJ: Do you feel discouraged when you see patients unable to afford the drugs?

Anita: Yes, I do feel sorry about this. But I'd see things in a different way – I am an optimistic person; I'd take it as an opportunity for me to reflect on myself and treasure people around me and things that I have. We will do our best to help all patients who come to our pharmacy.

PJ: What is most rewarding about your job at SJS?

Anita: First of all, working at SJS allows me to have learning every day, for example, I learned about the job of a social worker and the operation of a NGO, etc. Second of all, I am happy to receive positive feedbacks from the patients. It is such a great job satisfaction to me. Through applying my drug knowledge in communicating with patients, it can really have a noticeable impact on their healthcare.

I feel blessed that I have the ability to help those who are deprived and underprivileged.

Another thing is that - many people think that community pharmacists do not have much opportunity to use their clinical knowledge. But in fact, there are plenty of opportunities to use your clinical skills in community pharmacy setting, for example we need to know at what glucose level/blood pressure level we should contact the physician, etc. Therefore, community pharmacists also need to be well-equipped with clinical knowledge.

Besides, I am delighted to collaborate with our dispenser who assists in patient education through conducting visits to the patient's home. This facilitates us to address the actual need of the patient. It also enables every one of us to use our skills and knowledge to our greatest potential.

PJ: Have you encountered any challenges at work?

Anita: Yes, one of the challenges is that people don't understand the role of a pharmacist. Patients who are

going to purchase their medication at our pharmacy need to make an appointment first. So that we can have a proper counseling with them that usually lasts for 15-20 minutes. However, some patients dislike and complain about the booking procedure because they just want to get the drugs as early as possible and they don't realize the importance of medication counseling. To deal with this, I need to help them understand the operation and mission of our pharmacy and recognize the role of a pharmacist.

The second challenge comes from gaining support from the pharmaceutical companies that I mentioned previously.

PJ: Have you come across any memorable cases?

Anita: There are indeed a lot of memorable cases. I particularly remember an old lady who has hypertension – she really appreciates our help and calls us for assistance over time. We have built a genuine relationship that she is like a good friend to all of us now. One of the reasons is that we do not only concern about the physiological problem of the patient, we also care about their inner needs, which is in fact one of our major objectives.

There is another patient who suffered from liver cancer. Unfortunately he has passed away already. It was sad that he progressed from hepatitis B to liver cancer because he was not able to afford the medications for treatment of hepatitis B at earlier stage. Before he left, he told us that he always recalled our words of encouragement ("Be strong! We support you.") during tough times. I never thought that our small action can have such a meaningful impact on patients.

PJ: What is the future direction of development of Philanthropic Community Pharmacy?

Anita: We hope to expand our pharmacy services. We'd like to have more collaboration with different parties, for example to maximize the role of dispensers in drug education.

PJ: What is your personal plan for future?

Anita: I hope that I can continue helping more people in different classes.

PJ: What advice would you offer to a newly registered pharmacist?

Anita: Do your job with your heart, no matter which sector you are working in. Do not just focus on money. Money is only a short-term target that shouldn't be your first priority. You should find a job you love and enjoy doing. People can definitely feel your enthusiasm and appreciate your positive attitude towards your job. Last but not least, I want to point out that community pharmacists also have lots of opportunities to apply their clinical knowledge. A pharmacist should not limit their career to hospital pharmacy only.

PJ: Do you have anything that you'd like to share with the readers?

Anita: I am so happy to come back to Hong Kong where I can attempt and try out different things in a completely flexible and new approach. Lastly, I just want to say - no matter which country or which sector you are working in, you can still achieve your goal if you do your job with your heart.

CONCLUSION

Attitude is a little thing; but it can make a big difference. Anita has shown us that a community pharmacist can really make an impact on people's healthcare and quality of life.

REMARK

Anita Chan, at the point of publication of this interview, has departed from her role at St. Jame's Settlement. She is currently the Medical Affairs Manager at Pfizer Hong Kong.

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Cross Sensitivity Reaction of Different Drug Classes

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ABSTRACT

Allergic reaction is a common drug-related problem. Cross sensitivity between different drug classes has been debatable with the emerging new evidence available. Knowledge about cross sensitivity is very important in clinical setting as it will greatly affect the choice of drugs. This article discusses cross sensitivity between different drug classes including Penicillin and Cephalosporin, Penicillin and Carbapenem, Sulfa drugs, Non-steroidal anti-inflammatory drugs (NSAID) and Anti-convulsants. The difference in the mechanism of action, different types of hypersensitivity reactions and how the chemical structures of the drugs affect the cross sensitivity are also discussed.

Keywords: Cross sensitivity, hypersensitivity reaction, antibiotics, anti-convulsants, NSAID

INTRODUCTION

Allergic drug reaction is not uncommon. It accounts for 5% to 20% of all cases of adverse drug reaction.[1-4] The Hospital Authority has taken the lead to prevent allergic drug reactions by implementing various measures. Drug allergies and histories column on the Medication Administration Record (MAR) and the drug allergy module in the Clinical Management System (CMS) are useful tools to allow proper documentation of drug allergy history about the presentation and the time of occurrence. Better documentation of drug allergies and histories can alert clinicians to the risk of allergic drug reaction when agents within the same drug class are being used.

Allergic drug reactions can be classified into four types based on their immunological responses. Type I allergic drug reactions are anaphylactic reactions. It describes a process in which drug-hapten reacts with IgE antibody on the surface of mast cells and basophils. This process causes the release of mediators to trigger immunological response. The clinical manifestation of this type of reaction ranges from pruritus to circulatory collapse and death. Anaphylactic reactions to antibiotics and radiographic contrast media occur in 1 in every 5,000 exposures with 10% mortality.[5]

Type II reactions are cytotoxic reactions which involve IgG or IgM mediated reactions through different mechanisms. Common clinical manifestations of this type of reactions include hemolytic anemia, thrombocytopenia and granulocytopenia. Type III reactions are immune-complex-mediated reactions, which are triggered by the formation of drug-antibody complexes in serum which often deposit in blood vessel walls and subsequently activate complement and endothelial cell injury.[5] This type of reactions is sometimes referred to as serum sickness, with symptoms of fever, urticaria and lymphadenopathy 7 to 21 days after exposure.[6-7] Type IV is the cell-mediated (delayed) reactions. It involves direct activation of T cell-mediated reaction by the drug. It often manifests as delayed type of contact dermatitis with the distinct patterns of cytokine release and effector-cell recruitment.

As allergic drug reactions can be categorized into different types of reactions with different mechanisms, cross sensitivity can also be anticipated and explained by these mechanisms and the structural similarity between drug groups. The mechanism and frequency of occurrence of cross sensitivity of different drug classes will be further elaborated in this article.

PENICILLIN AND CEPHALOSPORIN

IgE hypersensitivity reactions and non-IgE hypersensitivity reactions were both proposed to explain the cross hypersensitivity reaction between penicillins and cephalosporins. IgE hypersensitivity reaction involves combination of antibiotics with a carrier protein. The beta-lactam ring opens under physiological conditions and covalently binds to a protein to form an antigenic determinant. Penicillyoyl-determinant is one of the major type of determinants which contributes to 75% of IgE mediated allergic reactions.[8] Cephalosporins with similar side chains would form a structurally similar antigenic determinant which contributes to cross sensitivity reactions of penicillins and cephalosporins with similar side chains.[9]

As shown in Figure 1, the side chains of Ampicillin and Cephalexin (a first generation cephalosporin) are the same. When the beta-lactam ring is opened and attached to a protein, the side chain will be exposed and form a determinant with similar structure. It could explain the high cross sensitivity rate between penicillins and first generation cephalosporins. While
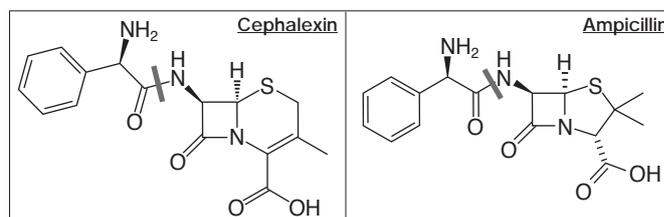
Figure 1: *Structures of Ampicillin and Cephalexin*

the structural similarity of the side-chain between penicillin and first generation cephalosporin is high, that for second and third generation cephalosporin is lower. A correspondingly lower cross-sensitivity rate between penicillin and the second and third generation cephalosporin is therefore anticipated.

Back in 1970s, Dash and Petz suggested that the cross sensitivity reaction between penicillins and cephalosporins should be around 8.1% which is 4-fold higher when compared to patients without history of penicillin allergy which was considered to be around 1.9%.[10-11] The cross sensitivity rate was then quoted to be around 10%.[12] With the assumption of hapten formation and the reaction of side chains, the cross sensitivity rate between penicillins and cephalosporin is now considered to be around 0.5 – 6.5% with greater contribution from first generation cephalosporin.[16] Another possible explanation for the previously reported higher incidence of cross sensitivity between penicillins and cephalosporins is that penicillin related compound was produced by cephalosporium mold at the early stage of drug development.[17]

Non-IgE type hypersensitivity reaction

Another proposed mechanism for drug hypersensitivity is the p-i concept (pharmacological interaction with immune receptors). It proposed that drugs can bind directly to immune receptors like T-cell receptors (TCR) by van der Waals forces, electrostatic or hydrogen bonds and present to Major Histocompatibility Complex (MHC) to trigger T cell response. Stimulation may only occur under certain circumstances, (i) the drug has a certain affinity for the particular TCR; (ii) a supplementing interaction of the TCR with the MHC molecule takes place; and (iii) the T cell is ready to react to such a minor signal given by the drug-TCR interaction.[13]

Cross sensitivity of this type applies to drug class with structural similarities and precursor frequency of drug-specific T (or B) cells. For severe and delayed hypersensitivity reaction, T-cell precursors are detectable for years after acute events.[14] Clinical symptoms arise when drug-specific T cells expand sufficiently to reach a certain number at the inflammatory site and cause inflammation. If only a small fraction of drug-specific T cells cross react and the starting precursor frequency remains low, the symptoms may be delayed. Therefore, if the causative agent is stopped early enough, no obvious symptoms may be seen. However, such interaction does not apply to IgE-mediated reactions.

Drugs which differ by only a hydroxyl group (-OH) are more cross-reactive than drugs which are different in a longer side-chain. Previous study showed T-cell clones that react with amoxicillin also react with ampicillin which differs from amoxicillin only a hydroxyl group[15] (Figure 2). No cross sensitivity was seen between these amoxicillin-specific T-cell reaction and cephalosporins.
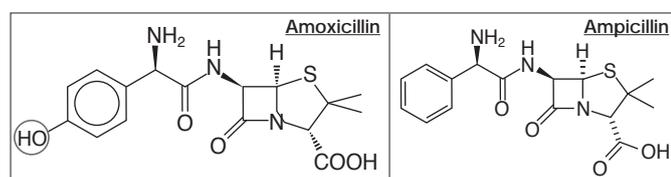
PENICILLIN AND CARBAPENEM

Carbapenem group also shares the similar chemical structure as other beta-lactam antibiotics (Figure 3). Historically, it was reported to have 50% cross sensitivity of IgE reaction between penicillin and carbapenem.[36] This study involved 40 patients with documented allergic history to penicillin and 19 of them showed positive skin test to penicillin. Further skin test was performed to test the allergic reaction to imipenem by skin test. Nine of them showed positive result. Since then, 25% cross sensitivity based on skin test and 50% cross sensitivity based on history were reported. Several retrospective studies were conducted recently to estimate the cross sensitivity rate of penicillin and carbapenem, which was found to be around 9.5 – 12.2%.[37-39] An even lower rate of 0.8-0.9% was observed in prospective studies.[40-42] Patients with negative skin test tolerated subsequent challenges with carbapenem. Skin test was then recommended in clinical setting to estimate the risk of carbapenem hypersensitivity. This test, however, is not readily available in HA hospitals.
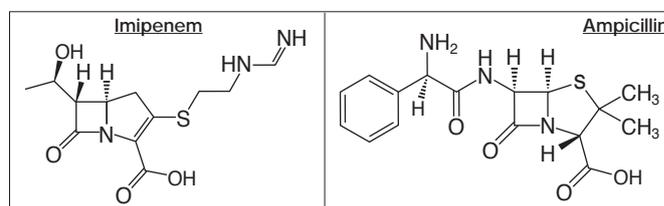
Figure 3: Structures of Imipenem and Ampicillin

Summary

As cross sensitivity among beta-lactam antibiotics can occur through different mechanism of actions, both structural similarity together with the type of hypersensitivity reaction should be carefully evaluated when clinical judgment has to be made.

SULFA DRUGS

"Sulfa" allergy is a generic term used to describe allergic reaction to sulfonamide antibiotics. It does not imply allergy to compounds containing sulfur, inorganic sulfate or sulfites.[18] Sulfonamide antibiotics are derivatives of sulfanilamide.[19] The term sulfonamide is used to describe any compound with an SO_2NH_2 moiety regardless if it directly links to a benzene ring. Sulfonamide antibiotics are differentiated from other sulfonamide non-antimicrobials by two main features in their chemical structures. The first feature is that the amine group of the arylamine group is situated at the para position of the SO_2NH_2 moiety. Another characteristic is a 5- or 6- member aromatic heterocyclic ring with ≥1 nitrogen at the N1 position (as seen in the structure of sulfamethoxazone) (Figure 4).

Figure 2: Structures of Amoxicillin and Ampicillin
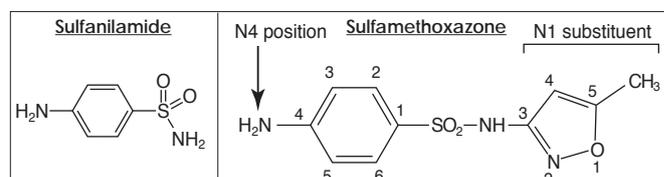
Figure 4: Structures of Sulfanilamide and Sulfamethoxazone

Sulfonamide non-antibiotics are chemicals that contain SO_2NH_2 moiety without the above mentioned characteristics, for example, furosemide (Figure 5).
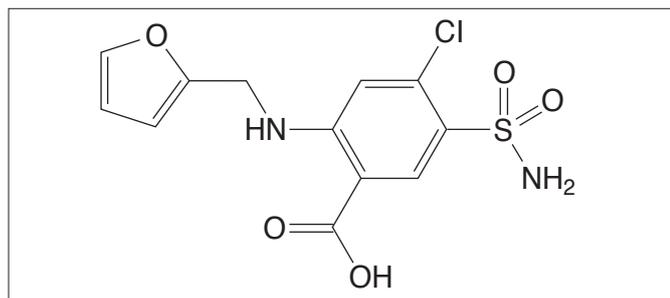
Figure 5: *Structures of Furosemide*

IgE type hypersensitivity reaction

Sulfonamide antibiotics can trigger all four types of immunological reactions. Previous study showed that serum IgE antibodies can be detected in patients who experienced true type I reaction to sulfonamide antibiotics.[20] Interaction between IgE and sulfonamide antibiotics is shown to be highly stereospecific and it is mediated by specific structure in the molecule. The nitrogen heterocyclic ring has been showed to be immunogenic but not the sulfonamide group. The methyl group in the beta-position of an isoxazole ring, which can be found in sulfamethoxazole only, is the most powerful determinant of IgE binding.[21-22] Furosemide (a.k.a Frusemide) does contain a sulfonamide group and is considered a drug to be avoided in patients with allergy history of sulfonamide antiobiotics.[23] However, a study in 2002 showed that serum-derived anti-sulfamethazine antibodies from allergy patients did not bind to furosemide.[24] It was concluded that cross sensitivity between furosemide and sulfonamide antibiotics is unlikely.

Non-IgE type hypersensitivity reaction

Non-type I reactions however may not be follow the same mechanism of action. Three possible etiologies were proposed to explain the non-type I reactions. The first possible etiology is that the parent sulfonamide antibiotic or its metabolite binds to cellular protein and causes tissue damage by direct cytotoxicity. Another possible etiology involves similar stimulation of immune recognition of haptens. The last possible etiology suggests interaction directly between sulfonamide antibiotic and T-cells or antibodies without haptenation.

The first two etiologies suggest haptenation before stimulation of immune response. Evidence suggested that most of the non-type I hypersensitivity reactions of sulfonamide antibiotics were caused by metabolites.[25] It, therefore, makes the study of metabolites more interesting. One of the important metabolites is sulfamethoxazole hydroxylamine. Around 5% of sulfonamide absorbed will go through hydroxylation at N4 position by cytochrome P450 (CYP) 2C9. The sulfamethoxazole hydroxylamine is believed to cause both immunologic and non-immunologically mediated toxicities including thrombocytopenia, hepatitis, nephritis, lupus erythematosus and the classic sulfonamide hypersensitivity syndrome.[26-27]

Sulfamethoxazole hydroxylamine can be auto-oxidized intracellularly to a highly reactive nitroso-sulfonamide metabolite (Figure 6). Nitroso-sulfonamide can be acetylated and excreted by urine. Alternatively, it can be reduced back to the original sulfonamide hydroxylamine by intracellular glutathione. Such redox cycling occurs in many cell types including erythrocytes. Superoxide radicals produced by the repeated redox cycling cause oxidative stress and are believed to be associated with Methemoglobinemia which is non-immune, direct cytotoxicity.
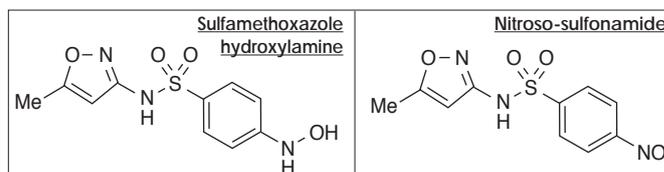
Figure 6: *Structures of Sulfamethoxazole hydroxylamine and Nitroso-sulfonamide*

Besides direct cytotoxicity, nitroso-sulfonamides are also potent immunogens. It can bind covalently to T-cells or native proteins to induce type II, III or IV immune responses. These responses range from mild maculopapular rashes to life-threatening toxic epidermal necrolysis and Stevens-Johnson syndrome. The metabolic pathway of all these active metabolites starts from formation of sulfamethoxazole hydroxylamine by CYP2C9. And CYP2C9 is commonly expressed in skin, macrophages and liver. It was suggested that some skin rashes associated with sulfonamide antibiotics are due to formation of metabolite locally instead of systemically. Classic sulfonamide hypersensitivity syndrome is also known as a metabolite-mediated immune response.[25]

Patient and disease specific hypersensitivity reactions

Non-type I hypersensitivity response to sulfonamide is also believed to be patients and disease specific. Previous study isolated peripheral blood monocytes from patients with history of hypersensitivity and compared with patients without hypersensitivity. It found that their monocytes were more susceptible to damage by sulfonamide metabolites. Monocytes collected from parents of this group of patients also showed intermediate toxicity. It suggested predisposing pharmacogenetic defect though further information was needed to describe the relationship.[28] Another study also showed a possible link between HLA-B22 haplotype and susceptibility to sulfamethoxazole hypersensitivity.[29]

Incidence of sulfonamide antibiotic-associated hypersensitivity in AIDS patients is around 60% compared with 3% in general population. The reason for this observation is still unclear. One of the possible explanations is that the altered redox status of AIDS patients facilitates the transformation of sulfonamide hydroxylamines to nitroso-sulfonamides.[30]

Parent compound or its metabolites?

The above mentioned possible etiologies of non-type I hypersensitivity reaction stressed the importance of metabolites. Such etiology makes cross sensitivity between sulfonamide antibiotics and non-antibiotics impossible as they do not share the same metabolic pathways and yield the same kind of metabolites. Previous study supported the hypothesis that hypersensitive patients typically do not produce antibodies against the parent sulfonamide antibiotic.[31] It is, therefore, generally believed that un-metabolized non-haptenated drugs are immunologically benign.

This assumption was further affirmed by a recent study.[32] This study showed that 9.9% of patients, who were documented to have allergic reaction to a sulfonamide antibiotic, also experienced an allergic reaction to a sulfonamide non-antibiotic. On the contrary, only 1.6% of patients without history of sulfonamide antibiotic experienced hypersensitivity reaction to sulfonamide non-antibiotic. Higher percentage of concurrent sensitivity of both sulfonamide antibiotic and non-antibiotic apparently suggested cross sensitivity. However, this study showed even higher frequency (14%) of concurrent penicillin allergy in patients with history of sulfonamide antibiotic. The author finally concluded that allergic reactions to sulfonamide antibiotic and non-antibiotic are likely multiple, independent allergic reactions instead of cross sensitivity.

Case reports, however, showed contradictory results.[33-34] Two case reports showed cross sensitivity between trimethoprim-sulfamethoxazole with rofecoxib and nimesulide. Fixed drug eruptions were observed with similar appearance at identical location in both cases. As drug eruptions are often T-cell-mediated response, these two cases highly suggest a cross sensitivity between sulfonamide antibiotic and non-antibiotic in T-cell-mediated reaction. An in-vitro study indirectly suggested the possibility of cross sensitivity between sulfonamide antibiotic and non-antibiotic. It demonstrated T-cell proliferation in patients with history of allergic reaction to sulfonamide antibiotic when exposed to un-metabolized, non-haptenated sulfonamide.[35] It showed T-cell recognition of parent sulfonamide antibiotic in triggering allergic reaction. However, it cannot show whether T-cell recognizes the sulfonamide moiety or other parts of the molecule. Further study is definitely warranted in eluting the non-type I cross sensitivity reaction between sulfonamide antibiotic and non-antibiotic.

To summarize, IgE cross sensitivity reactions are largely unlikely between sulfonamide antibiotic and non-antibiotic as it is highly stereospecific and mediated by specific structure within the molecule (Table 1). Opinion about non-type I cross sensitivity is less consistent. Most evidence suggested low possibility of cross sensitivity as non-type I reactions are often preceded by metabolic transformation or haptenation. Direct T-cell responses are also observed in some cases and in-vitro study. Consensus therefore cannot be concluded in this circumstance.

Table 1. Examples of drugs that belong to sulfonamide antibiotic and non-antibiotic	
Sulfonamide antibiotic	**Sulfonamide non-antibiotic**
Sulfonamide antibiotics	**Carbonic Anhydrase Inhibitors**
Sulfamethoxazole Sulfadiazine	Acetazolamide Dorzolamide
Sulfacetamide Sulfasalazine	**Sulfonylureas**
Sulfonamide antiretrovirals	Gliclazide Glimepiride
Amprenavir Fosampranavir	Glibenclamide Gliperizide
	Loop Diuretics
	Frusemide Bumetanide
	Thiazide Diuretics
	Hydrochlorothiazide Indapamide
	Chlorthalidone Metolazone
	Diazoxide
	Anti-inflammatory
	Celecoxib
	Other (sulfonamide moiety without benzene ring)
	Dapsone Sumatriptan
	Topiramate Sotalol
	Probenecid

NSAID

Non-steroidal anti-inflammatory drugs (NSAID) were reported to be the second most common cause of drug-induced hypersensitivity second to penicillin.[43] Clinical manifestations could be much diversified. They range from acute immediate type of allergic reactions to delayed type of reactions which can happen days or even weeks after drug exposure.

Within the group of NSAID, drugs of many different kinds of chemical structures are included. It is then impossible to explain the reaction with just one mechanism. Based on the cross-sensitivity pattern and manifestation with co-existing diseases, a few possible mechanisms of action have been suggested.

Aspirin-Exacerbated Respiratory Disease (AERD)

Also known as aspirin triad, asthma triad, Widal's syndrome, Samter's syndrome, aspirin-induced asthma, aspirin intolerant asthma or aspirin-sensitive rhinosinusitis / asthma syndrome,[44] AERD refers to the hypersensitivity reaction to aspirin and other NSAIDs in patients with upper airway (rhinosinusitis / nasal polyps) and lower airway (asthma) diseases. Until recently, it was stressed to be the underlying chronic inflammatory disease only occasionally exacerbated by aspirin or other NSAIDs.[45]

It was proposed that this is not an immunological reaction as cross-sensitivity reactions occur with NSAIDs of different chemical structures. Interestingly, NSAIDs with strong cyclooxygenase (COX) inhibition, like indomethacin, naproxen, diclofenac or ibuprofen tend to cause symptoms in a significant number of aspirin-hypersensitive patients (30-80%).[46] On the other hand, NSAIDs with weaker COX inhibition or higher selectivity to COX-2 seem to be better tolerated by patients with AERD.[47]

It is then reasonable to correlate AERD to COX inhibition. It has been proposed that inhibition of COX-1 (but not COX-2) would increase the local and systemic generation of cysteinyl leucotrienes and over-expression of $cycLT_1$ receptors as a result of the prostaglandin E2 deprivation.[48-49] Genetic polymorphisms and abnormal baseline arachidonic acid metabolism are also observed in this group of patients.[50-51] They often have increased levels of urinary leucotrienes and up-regulation of LTC4 synthase or cysteinyl LT receptors in the airway tissue.[50-51]

Clinically, it often happens in patients in around their 30's with a history of asthma and/or chronic rhinosinusitis complicated by recurrent nasal polyps.[52] Intake of various dose of aspirin (or NSAID) could trigger the reaction within 30 to 120 minutes. Aspirin doses ranging from 3mg to 600mg were reported to be able to trigger a reaction. At higher doses (100 – 600 mg), the incidence rate was lowered but the symptoms were often more severe and could be life-threatening. Common respiratory symptoms including rhinorrhea, nasal congestion, paranasal head pain, conjunctivitis, periorbital edema, laryngospasm, and asthma can occur upon the first exposure of a new NSAID. Extrapulmonary symptoms like flushing, transient hives, abdominal cramping pain, and less often, hypotension can also occur.[55]

As the risk of AERD cannot be easily predicted until the first ingestion of aspirin or NSAID, history of AERD and

avoidance of potential agents are essentially important in preventing future event. As previously mentioned, incidence of AERD is higher when patients with aspirin hypersensitivity were exposed to strong COX-1 inhibitors.[46] Strict avoidance of NSAIDs with moderate to strong COX-1 inhibitory activity is necessary. NSAIDs with weaker COX-1 inhibition can possibly be attempted with caution.

Paracetamol has relatively low COX-1 inhibitory activity. It could be a safe alternative for pain control. At low doses (below 500mg), the prevalence of adverse reaction ranges from 0–8.4% in NSAID- sensitive patients.[56] However, the prevalence of bronchial reactions increases up to 30% after ingestion of 1000mg paracetamol in NSAID-sensitive patients.[57] An oral tolerance test with a lower dose of paracetamol is therefore recommended.[51]

Preferential COX-2 inhibitors, e.g. Meloxicam and nimesulide, are quite well tolerated. About 86–96% of NSAID-sensitive patients can tolerate these agents at low dose.[58] Again, selectivity and tolerance are lost at higher doses. Hypersensitivity reactions can possibly be induced by preferential COX-2 inhibitors at higher dose.[59] Tolerance test should therefore be considered as well. Selective COX-2 inhibitors are generally well tolerated in AERD patients.[58] Desensitization may be necessary in some circumstances, e.g. coronary ischemic disease, when aspirin is left to be the best possible choice. Regular, daily ingestion of aspirin has to be maintained as tolerance disappears within 2-5 days after treatment interruption.[60] It was also observed that chronic treatment of aspirin after desensitization alleviates symptoms of rhinosinusitis and asthma and reduces systemic corticosteroid requirement.[61-62] It offers additional benefits in pharmacological treatment of AERD where treating the underlying chronic disease, which is equally important.

NSAIDs-exacerbated urticaria/angioedema

Ingestion of aspirin / NSAIDs in patients with chronic urticaria can exacerbate the underlying disease and induce hypersensitivity reaction with or without angioedema. Cross-sensitivity reaction is often seen in patients taking COX-1 inhibitors. It was therefore suggested that the mechanism of action is similar to that of AERD.[46] The theory was further supported by the observations of eicosanoids release in patients with skin eruption after ingestion of aspirin.[51, 63-64]

Urticaria can happen within 15 minutes of aspirin / NSAIDs ingestion or it can happen up to 24 hours after ingestion of the causative agent. The usual onset of symptoms is 1-4 hours.[51] Skin eruptions often take a few hours to resolve, but it may also persist for several days.[51] Symptoms can be fluctuating and it relates to the activity of the underlying chronic disease.[64]

As this type of hypersensitivity reaction is believed to be related to COX-1 inhibition, NSAIDs with COX-1 inhibition should be avoided. Paracetamol again was shown to be tolerated by 89.8% of patients.[65] However, selective COX-2 inhibitors may not be a solution to the problem. Tolerability to COX-2 inhibitors showed inconsistent results. One study showed good tolerability to rofecoxib, celecoxib and etoricoxib.[66] Another study showed celecoxib and rofecoxib induced skin reactions in 7-33% of patients upon controlled challenges.[67] Use of selective COX-2 inhibitors in this group of patients is still a controversy.

Probable IgE-mediated reactions to aspirin and NSAIDs

Some case reports of single-agent hypersensitivity reactions to aspirin and NSAIDs describe hypersensitivity symptoms which greatly resemble the symptoms the IgE-mediated reactions. Generalized urticaria, skin swelling and mucosal angioedema can be developed within minutes after ingestion of the causative agent. Symptoms progress to anaphylactic shock or even death. Anaphylactic shock was observed in 18-30% of patients hypersensitive to pyrazolones in the study.[68-69] However, the evidence showing the presence of IgE is limited.[51]

In patients with single-drug hypersensitivity reactions to pyrazolones, positive skin test and drug-specific serum IgE were found.[70] For other single-drug reactors, only anecdotal reports were able to detect specific IgE.[71] The most commonly found agents with this kind of reaction are pyrazolones, paracetamol, ibuprofen, diclofenac and naproxen.[68-69] As the evidence of the relationship between this kind of single-agent hypersensitivity reactions and IgE is unclear, it was suggested that the term *"Probable IgE-mediated reaction"* be used to describe this single-agent reaction and to differentiate it from COX-1 inhibiting reactions.

To prevent probable IgE-mediated reactions, strict avoidance of the causative agent and other chemically similar compounds is recommended. NSAIDs with different chemical structures can be attempted, but they should be used cautiously with tolerance test whenever possible.[51]

Delayed reactions

Symptoms which occur 24 hours after drug exposure are defined as delayed reactions although symptoms may develop in several days or weeks.[51] Limited data suggest that it could be a type IV reaction which is associated with drug-specific, cytotoxic T-cell reaction. However, systematic studies on this topic are lacking.[73-74]

Summary

As different mechanisms of action can be involved in the hypersensitivity reactions of NSAIDs, it is important to carefully study the natural history of symptoms and decide whether alternative agent is possible with the help of tolerance test when needed.

ANTICONVULSANT

Anticonvulsant Hypersensitivity Syndrome (AHS) is often associated with aromatic anticonvulsant drugs, e.g. phenytoin, carbamazepine and phenobarbital. It is a rare but serious adverse event. The incident rate is around 1 in every 1000 – 10,000 exposures. Clinical manifestations include a triad of symptoms including dermatologic rashes, fever and systemic organ involvement. It often leads to hospitalization or even death.[75] In this part, we will mainly discuss the rationale of cross-sensitivity, familial and genetic association, possible treatment and related co-morbidity.

Clinical Manifestation

Fever and rash happen in almost all of the patients with AHS.[75] The onset of symptoms varies; it ranges from 6 days to 12

weeks after the drug intake.[76-77] The type of rash of AHS may also vary. It could manifest as maculopapular rashes or as an exfoliative type like Steven-Johnson syndrome (SJS) or toxic epidermal necrolysis syndrome (TENS). As the clinical manifestations of both types of exfoliative rashes (SJS and TENS) are similar to AHS, and they often associate with drugs like aromatic anticonvulsants and sulphonamides, it is often hard to differentiate AHS with SJS and TENS. In that case, the possibility of AHS is easily ruled out.

Other systemic symptoms and signs, including lymphadenopathy, eosinophilia, lymphocytosis, leukocytosis, hepatitis, conjunctivitis or rarely myocarditis, could also be found in AHS. Reactivation of latent herpes viruses was also observed. Human herpes viruses including HHV-5 (cytomegalovirus), HHV-6 and HHV-7 were detected in some cases.[75] It is often detected 2-4 weeks after initial symptoms and it is often more severe.[75, 83]

Mechanism of Action

Although cross-sensitivity was observed between anticonvulsants with similar chemical structures, it was suggested that AHS was not an IgE-mediated reaction.[79] Instead, it was suggested that it was a type IV, T-cell mediated, delayed hypersensitivity reaction.[75] The exact mechanism of action was not fully elucidated, but it was considered to be related to deficiency or abnormality of the epoxide hydroxylase enzyme.

Aromatic anticonvulsants, like phenytoin, carbamazepine and phenobarbital (Figure 7A) are metabolized hepatically. After aromatic hydroxylation, arene oxides are formed (Figure 7B). Arene oxides are toxic reactive intermediates that are further metabolized to non-toxic metabolites. One of the important pathways involves microsomal epoxide hydroxylase (MEH). When there is a deficiency or abnormality of MEH, arene oxides cannot be metabolized. Accumulation of arene oxides can then cause cellular toxicity and cell death by covalently binding to macromolecules or by acting as antigens.[75, 80-82] Arene oxides are also considered to cause latent HHV reactivation by T-cell stimulation.[83]

Cross-sensitivity

A retrospective study found that 14 of 663 patients exposed to anticonvulsant drugs developed cross-sensitivity between two or more drugs, and it was primarily associated with exposure of phenytoin and carbamazepine.[84] In patients who initially

developed a rash with carbamazepine, 10 of 25 patients developed a rash with phenytoin; whereas in patients who developed a rash with phenytoin, 10 of 17 patients developed rash to carbamazepine. For patients who developed a rash with phenobarbital at first, 4 out of 5 subsequently developed a rash with either carbamazepine or phenytoin. It was then concluded that the cross-sensitivity rate among aromatic anticonvulsants was around 40-80%.[75]

Newer anticonvulsants which also contain with an aromatic ring, e.g. lamotrigine and oxcarbazepine (Figure 8) should be considered for potential cross-sensitivity based on the assumption of arene oxides production. This assumption was further supported by the case reports of AHS associated with lamotrigine.[78, 85-86] In the previously mentioned study, patients with a history of AHS can safely tolerate benzodiazepine or valproic acid without adverse effect. Benzodiazepine, valproic acid and other non-aromatic anticonvulsants (Figure 9) were then considered to be the safe alternatives for patients with a history of AHS.

Familial association is another common concern of cross sensitivity among anticonvulsants, as anticonvulsants are often used for genetically related diseases like epilepsy. In vitro test showed a genetic link between patients with AHS and
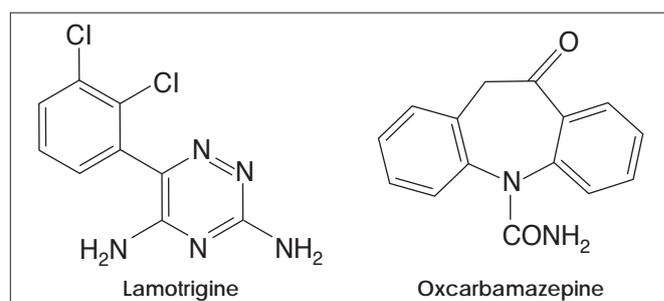
Figure 8: Examples of newer anticonvulsants containing an aromatic ring

Figure 7: Formation of arene oxides from Aromatic anticonvulsants
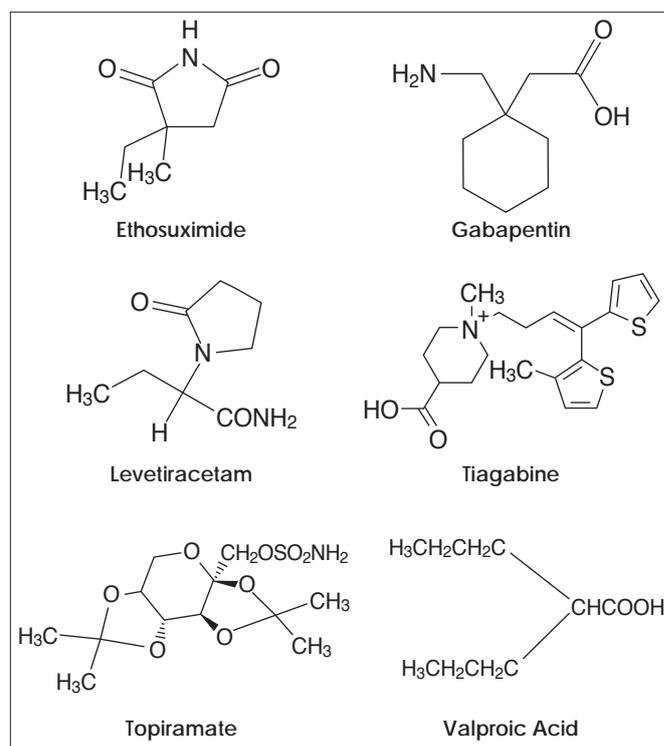
Figure 9: Examples of non-aromatic anticonvulsant

their parents. The genetic link, however, was not consistently showed in the same study.[87] Another study which involved only one family showed more supporting results.[81] Five siblings of 3 patients with AHS were studied and 4 of them showed positive results in in-vitro cross-sensitivity test. Based on these results, familial association cannot be ruled out. It is then recommended to avoid aromatic anticonvulsants in family members of patients with a history of AHS.[75]

Treatment

Identification of anticonvulsant hypersensitivity syndrome is very important, provided that there are quite a lot of other possible diagnoses in the context of similar clinical manifestations. Discontinuation of the causative agent is definitely the first thing to do. After that, systemic corticosteroid is often used. A wide range of doses of corticosteroid have been used.[75, 88-91] As a usual practice, steroid should be tapered down slowly; but in this case, not just because of steroid withdrawal, but also because of reoccurrence of AHS. In the previously mentioned case reports, AHS was worsened when steroids were discontinued prematurely.

Other treatment options have also been used, like antihistamines and intravenous immunoglobulin. However, data supporting their uses are limited. One study even showed increased mortality after treating SJS patients with intravenous immunoglobulin.[89, 92] Intravenous immunoglobulin was therefore recommended to be reserved for critically ill patients as a last resort.[75]

Summary

Cross-sensitivity reactions with anticonvulsants are often associated with aromatic anticonvulsants. Avoidance of aromatic anticonvulsants is often necessary in patients with a history of Anticonvulsant Hypersensitivity Syndrome (AHS). Other considerations like family association and the treatment of delayed Human Herpes Virus (HVV) reactivation should also be born in mind.

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Questions for Pharmacy Central Continuing Education Committee Program

(Please be informed that this article and answer sheet will be available on PCCC website concurrently. Members may go to PCCC website (www.pccchk.com) to fill in their answers there.)

2 CE Units
Cross Sensitivity Reaction of Different Drug Classes

1. **Which one of the following drugs has the highest degree of chemical structure similarity with Penicillin?**
   A. Cephalexin (Ans)
   B. Cefuroxime
   C. Cefixime
   D. Ceftriaxone

2. **What is the percentage of cross sensitivity reaction between Penicillin and Cephalosporin?**
   A. 0.5 – 6.5% (Ans)
   B. 6.5 – 9%
   C. 9 – 12%
   D. 40 – 80%

3. **What is the percentage of cross sensitivity reaction between Penicillin and Carbapenem?**
   A. 0.5 – 6.5%
   B. 6.5 – 9%
   C. 9 – 12% (Ans)
   D. 40 – 80%

4. **What is the definition of Sulfonamide?**
   A. Any compound containing sulphur
   B. Antibiotics derived from sulfanilamide
   C. Any compound with an SO_2NH_2 moiety (Ans)
   D. Any compound with an SO_2NH_2 moiety with a benzene ring.

5. **Which of the following populations has the highest incidence of sulfonamide antibiotic-associated hypersensitivity reaction?**
   A. Paediatric population
   B. Geriatric population
   C. AIDS population (Ans)
   D. Post-transplant population

6. **Which of the following patients has the highest risk of Aspirin hypersensitivity?**
   A. A 30 years old white woman with asthma (Ans)
   B. A 10 years old boy with eczema
   C. A 30 years old white man with eczema
   D. A 10 years old girl with eczema

7. **Which one of the following statements is true?**
   A. NSAID cross sensitivity tends to be related to structure similarity
   B. Cross sensitivity between Aspirin and NSAID tends to be related to the degree of COX inhibition (Ans)
   C. NSAID hypersensitivity reaction tends to be related to T-cell reaction
   D. Patients with NSAID hypersensitivity tends to have normal baseline arachidonic acid metabolism

8. **Which one of the following symptoms is NOT a common symptom of NSAID hypersensitivity?**
   A. Abdominal cramping pain
   B. Hypotension
   C. Chest pain (Ans)
   D. Paranasal head pain

9. **What is the percentage of cross sensitivity among aromatic anticonvulsants?**
   A. 0.5 – 6.5%
   B. 6.5 – 9%
   C. 9 – 12%
   D. 40 – 80% (Ans)

10. **What is the best first line treatment option for patients with Anticonvulsant Hypersensitivity Syndrome (AHS)?**
    A. Intravenous Antihistamine
    B. Intravenous Immunoglobulin
    C. Oral Corticosteroid (Ans)
    D. Topical Corticosteriod

Answers will be released in the next issue of HKPJ.

CE Questions Answer for 202(D&T)

New approaches to HER2-positive breast cancer

| 1. B | 2. D | 3. D | 4. C | 5. C | 6. D | 7. C | 8. D | 9. C | 10. D |

No Improvement in Hand Skin Quality by Coenzyme Q10 Topical Formulation among Young and Old Healthy Female Volunteers

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ABSTRACT

Objective: This study aimed to evaluate the effectiveness of 0.085% coenzyme Q10 topical formulation (Q10-TF) in the improvement of hand skin quality among young and old healthy Chinese female volunteers. **Methods:** 102 healthy female undergraduates and 70 healthy female elderly were recruited in this double-blind, randomized and placebo-controlled trial. In Day 0, 14 & 28, subjects were assessed with transpidermal water loss (TEWL) measurement, and questionnaire with self-rated scores in hand skin's appearance, intactness, moisture, sensation, scaliness and wrinkles. After exclusion of subjects with hypersensitivity and non-compliance to interventions assigned, 71 female undergraduates and 68 female elderly were available for data analysis. **Results and Discussion:** Compared with placebo, Q10-TF offered no additional advantages in skin barrier function in terms of TEWL measurements, and all subjective evaluations of hand skin quality via questionnaire survey, over a period of 28 days. Vehicle-effect was pronounced among both younger and older subjects, particularly in self-rated scores in intactness, moisture, and wrinkles. **Conclusion:** A topical formulation containing coenzyme Q10 at the level of 0.085% was found to be ineffective in enhancing skin barrier function, in terms of TEWL values, and ineffective in improving subjective feelings in appearance, intactness, moisture, sensation, scaliness and wrinkles, compared with its control vehicle.

Keywords: Coenzyme Q10, Topical formulation, Skin quality, Clinical trial

INTRODUCTION

Coenzyme Q10 is used extensively in cosmetic products for a wide range of marketing claims due to its cutaneous anti-oxidizing and energizing properties. Since last century, it has already been shown to prevent photo-aging by effectively alleviating the UVA mediated oxidative stress present in human keratinocytes.[2] More current research in coenzyme Q10 anti-aging effects demonstrated that the mechanism of coenzyme Q10 involved may be related to epidermis protection against oxidative stress and enhancement of epidermal basement membrane components production.[6]

Low concentrations of topical coenzyme Q10, i.e., 0.01%, was found to stabilize isolated epidermal keratinocytes upon UV irradiation in healthy volunteers if applied twice daily for 7 days.[7] In a study investigating the inhibitory effect of coenzyme Q10 on UVB-induced wrinkle formation, twice daily application of 1% coenzyme Q10 cream for three months resulted in less wrinkle grade score.[3] Novel delivery methods of coenzyme Q10 have been reported, such as liposomal coenzyme Q10,[5] nanostructured lipid carriers[8] and solid lipid nanoparticles.[1]

Although there have been much advances in cosmetic efficacy of coenzyme Q10 in selected populations, such as those with photo-damaged skins, and new delivery strategies of the cosmetic active, there is still an important question remaining unanswered in literature: Can the beneficial effects observed for coenzyme Q10 in photo-damaged skin be translated to those with chronologically aged skin, or even to those young in ages? If coenzyme Q10 is useful for the chronologically-aged skin, or even for young skin, there should be improvement in both skin barrier function and subjective feeling of hand skin quality upon continuous applications. In this study, we aimed to address the question by conducting a double-blind, randomized and placebo-controlled trial among both young and old healthy female subjects for 28 days. Skin barrier function in terms of TEWL values would be evaluated, and self-rated scores in a validated hand skin evaluation questionnaire would be surveyed, allowing direct comparison between placebo and Q10-TF groups for both young and old healthy subjects.

MATERIALS AND METHODS

Formulations

The placebo and Q10-TF utilized in this study were manufactured by Macau Union Pharmaceutical Limited (Macao SAR, China) under GMP environment. Although there was minor color differences between the two preparations (Figure 1), subjects were unable to differentiate which one was actually coenzyme Q10 containing preparation. Master formula of the two preparations is summarized in Table 1. All chemical compositions, except coloring agent present in placebo and coenzyme 10 present in Q10-TF, are the same between the two preparations. Placebo was formulated as

a gel-based moisturizing preparation, as local consumers in Macao generally preferred the sensation of less greasy feeling for hand skin preparations. Coenzyme Q10 concentration at 0.085% was chosen because commercial cosmetic preparations in traditional formulations, i.e., gel, cream, lotion, usually contained coenzyme Q10 at the level of 0.01% - 0.2%. For instances, a cosmetic cream in market was found to contain 0.05% coenzyme Q10 upon HPLC analysis.[9]

Figure 1: Physical appearance of placebo (left) and Q10-TF (right).

Table 1. Master formula of placebo and 0.085% coenzyme Q10 topical formulations

Ingredient	Function	Placebo (%)	Q10-TF (%)
Carbopol 940	Thickener	0.50%	0.50%
Triethanolamine	pH adjustment	0.40%	0.40%
Glycerin	Humectant	10.00%	10.00%
Methyl paraben	Preservative	0.15%	0.15%
Propyl paraben	Preservative	0.05%	0.05%
Propylene glycol	Humectant	1.50%	1.50%
Coenzyme Q10	Active ingredient	--	0.085%
Coloring agent	Coloring agent	q.s.	--
Purified water	Solvent	to 100%	to 100%

HPLC analysis was performed to double-check the content of coenzyme Q10 in the two preparations. The protocol documented in Japanese Pharmacopoeia 15th edition was employed for HPLC analysis. Coenzyme Q10 eluted at retention time of 8.28 ± 0.05min (n=3). Excellent linearity (R^2 > 0.9999) was observed for the standard curve of peak area over coenzyme Q10 concentrations between 0.5mg/L and 200mg/L. It was confirmed that placebo and Q10-TF contained 0.000% ± 0.000% (n=3) and 0.085% ± 0.005% (n=3) coenzyme Q10 respectively, suitable for further clinical evaluations.

Subjects enrollment

102 healthy Chinese female undergraduates were recruited within School of Health Sciences, Macao Polytechnic Institute. The study period for the female undergraduates was from November, 2010 to December, 2010. 70 healthy Chinese female elderly were recruited in 4 elderly day care centers. The study period for the female elderly was from November, 2010 to February, 2011. The study period is within the seasons of late autumn to winter in Macao, where winter xerosis in hand skin is not uncommon among local populations, making it as the ideal timing for this cosmetic study.

Informed consents were obtained for all recruited subjects. The study has been approved by the research & ethics committees in both of School of Health Sciences, Macao Polytechnic Institute and the 4 elderly day care centers prior to subject enrollment. Subjects, who were pregnant, lactating, or hypersensitive to any ingredients in the two formulations, were excluded from the study. Subjects were randomly assigned to either placebo or Q10-TF group, according to the random number generated by a computer program during subject enrollment. All subjects were instructed to apply the assigned preparation with reasonable amounts three times daily for a consecutive 28 days, to maintain their normal daily activities, and to avoid application of other hand creams during the study period. Subjects could withdraw voluntarily at any times of the study. All subjects and assessors in cosmetic evaluations in this study were blinded from the knowledge of placebo and Q10-TF, and only the author knows the true identity of topical formulations during the whole course of study.

Cosmetic evaluations

In Day 0, 14 & 28, transepidermal water loss (TEWL) of subject's hand skin was assessed by Vapometer (Delfin Technologies Ltd, Finland). Subjects were not allowed to contact with water by their hands 1 hour before TEWL measurement. For the female undergraduates, all TEWL measurements were performed in standard laboratory conditions at 20 ± 1ºC and 40-60% relative humidity. For the female elderly, all TEWL measurements were performed in air-conditioned rooms at 20-25ºC inside the 4 elderly day care centers.

During each visit in Day 0, 14 & 28, every subject was required to fill a self-evaluation questionnaire on hand skin quality. The self-evaluation questionnaire was adopted from literature,[4] covering six 7-point Likert scale typed questions in hand skin's appearance, intactness, moisture, sensation, scaliness and wrinkles with 7-point being the highest quality and 1-point being the poorest quality in that category.

Data analysis

Data analysis was conducted by the author, who was not blinded during data evaluation. Subjects with fewer than 33% compliance, i.e., less than one application of topical preparation per day, were excluded from data analysis. Subject who missed the appointments in Day 14 and/or Day 28 were excluded for data analysis for those particular days, but their data available in other days were still retained for statistical analysis. Statistical analysis was then conducted to detect for the potential differences between pre- and post-tests, and between placebo and Q10-TF groups respectively.

RESULTS AND DISCUSSION

Population demographics

One subject among young ladies, and one subject among old ladies, were found to be allergic to the topical preparation assigned and were excluded from the study.

30 female undergraduates had less than once application of their assigned topical preparation per day, and therefore, were excluded for any further data analysis because of their non-compliance. Population demographics and TEWL Day 0 values in female undergraduates are shown in Table 2a. No statistical differences in age and TEWL Day 0 values were observed between placebo and Q10-TF groups in female undergraduates. There were also no significant differences between dropout subjects and subjects available for data analysis among female undergraduates (data not shown). For old ladies, all of them had at least once application of their assigned topical preparation per day, and their compliance was in general much better than their younger counterparts. Population demographics and TEWL Day 0 values in female elderly are shown in Table 2b. No statistical differences in age and TWEL values were observed between placebo and Q10-TF groups in female elderly. The results indicated that the baseline skin water retention functions, prior to any topical treatments, were similar between placebo and Q10-TF groups among both young and old ladies in this study.

Scores of 6 questions, i.e., appearance, intactness, moisture, sensation, scaliness and wrinkles, in self-evaluation questionnaire among female undergraduates and elderly are presented in Table 3a and Table 3b respectively. No statistical differences in any Day 0 scores were observed between placebo and Q10-TF groups in both populations. There were also no significant differences between dropout subjects and subjects available for data analysis among female undergraduates (data not shown). Both young and old subjects had high ratings on their skin appearance, intactness, scaliness and sensation, and moderate ratings on their skin moisture and wrinkles. While the results are understandable for the female elderly, the female undergraduates perceive their hand skin quality as not good enough. This could be due to the fact that the female undergraduates were indeed nursing, medical laboratory technician and pharmacy technician students, who were frequently exposed to hand disinfectant during their clinical internship. Hand damages among nurses were well-documented in literature.[4]

Effects of 0.085% coenzyme Q10 on hand skin quality

The differences of TEWL values between Day 14 and Day 0, and Day 28 and Day 0 among female undergraduates and elderly are summarized in Table 2a and 2b. No statistical significant differences were observed between placebo and Q10-TF groups in both populations. The score differences in self-evaluation questionnaire between Day 14 and Day 0, and Day 28 and Day 0 among female undergraduates and elderly are listed in Table 3a and 3b respectively. No statistical significant differences were again observed between placebo and Q10-TF groups in both populations. Overall speaking, the data indicated that the inclusion of 0.085% coenzyme Q10 in the topical formulation under investigation in this study did not offer any additional benefits in both skin barrier function, in terms of TEWL values, and self-rated scores in appearance, intactness, moisture, sensation, scaliness and wrinkles.

Vehicle-effects on hand skin among young and old ladies were evident in self-rated appearance, intactness, moisture, sensation, scaliness and wrinkles scores, and the effect was particularly pronounced in self-rated moisture scores (Tables 3a-3b). Although this study is a negative report in Q10-TF on TEWL measurements, and self-rated scores in appearance, intactness, moisture, sensation, scaliness and wrinkle, compared with placebo, it does suggest that coenzyme Q10 at 0.085% concentration in a conventional topical moisturizing formulation offers no additional benefits in skin barrier function and subjective improvement, and the observed benefits are solely due to vehicle-effect. It should be noted that in commercial cosmetic hand cream preparations, it is not uncommon for coenzyme Q10 to be present at concentrations lower than 0.085%, and therefore, their claimed efficacy is highly questionable.

CONCLUSION

Compared with the control vehicle, 0.085% coenzyme Q10 topical formulation offers no additional benefits in terms of skin

Table 2a. Summary of TEWL data in Chinese female undergraduates			
	Placebo	**Q10-TF**	**p-value**
Age	19.2 ± 1.3 (n = 51)	18.7 ± 1.0 (n = 51)	NS
TEWL values ($g\ m^{-2}\ h^{-1}$)			
Day 0	17.60 ± 4.70 (n = 36)	20.18 ± 6.91 (n = 35)	NS
Day 14	15.43 ± 11.54 (n = 33)	15.11 ± 5.26 (n = 29)	NS
Day 28	21.25 ± 10.10 (n = 33)	20.75 ± 3.82 (n = 32)	NS
Differences in TEWL values ($g\ m^{-2}\ h^{-1}$)			
Day 14 – Day 0	-2.21 ± 13.13 (n = 33)	-5.15 ± 9.37** (n = 29)	NS
Day 28 – Day 0	+3.62 ± 12.14 (n = 33)	+0.38 ± 7.82 (n = 32)	NS

Remark: * indicates the data in a particular group are statistically significant different between the two dates at p < 0.05
** indicates the data in a particular group are statistically significant different between the two dates at p < 0.01
NS indicates statistical non-significance at p > 0.05

Table 2b. Summary of TEWL data in Chinese female elderly			
	Placebo	**Q10-TF**	**p-value**
Age	77.5 ± 7.8 (n = 36)	78.6 ± 6.2 (n = 33)	NS
TEWL values ($g\ m^{-2}\ h^{-1}$)			
Day 0	19.56 ± 13.00 (n = 36)	19.85 ± 9.30 (n = 32)	NS
Day 14	17.35 ± 8.02 (n = 35)	19.43 ± 11.36 (n = 30)	NS
Day 28	18.52 ± 10.30 (n =29)	17.32 ± 12.66 (n = 27)	NS
Differences in TEWL values ($g\ m^{-2}\ h^{-1}$)			
Day 14 – Day 0	-2.09 ± 9.31 (n = 35)	-0.35 ± 8.47 (n = 30)	NS
Day 28 – Day 0	-2.32 ± 9.17 (n = 29)	-3.04 ± 8.57* (n = 27)	NS

Remark: * indicates the data in a particular group are statistically significant different between the two dates at p < 0.05
** indicates the data in a particular group are statistically significant different between the two dates at p < 0.01
NS indicates statistical non-significance at p > 0.05

barrier function analyzed by TEWL measurements, and self-rated scores in appearance, intactness, moisture, sensation, and wrinkles, among young and old healthy Chinese ladies. Large vehicle-effects are observed in all subjective evaluations, particularly in intactness, moisture and wrinkles, in both young and old subjects in this study.

DISCLOSURE

The author receives no financial rewards from Macau Union Pharmaceutical Limited (Macao SAR, China).

Author's background

Dr. Henry Tong *obtained both his BPharm and PhD degree at the School of Pharmacy, the Chinese University of Hong Kong. He is now the Professor and Program Coordinator in Division of Biomedical Sciences of the Macao Polytechnic Institute. His email address: henrytong @ipm.edu.mo*

Table 3a. Summary of self-evaluation data in Chinese female undergraduates

	Placebo (n=34) Median (IQR)	Q10-TF (n=33) Median (IQR)	p-value between placebo & Q10-TF
Appearance:			
Day 0	7.00 (1.00)	6.00 (1.00)	0.712
Day 14 – Day 0	0.00 (1.00)*	0.00 (1.00)*	0.825
Day 28 – Day 0	0.00 (1.00)	0.00 (1.00)	0.527
Intactness			
Day 0	6.00 (2.00)	5.00 (2.00)	0.181
Day 14 – Day 0	0.00 (1.00)*	1.00 (2.00)**	0.088
Day 28 – Day 0	0.00 (1.00)	1.00 (1.00)**	0.321
Moisture			
Day 0	4.00 (2.00)	5.00 (1.00)	0.208
Day 14 – Day 0	1.00 (2.00)**	1.00 (2.00)*	0.253
Day 28 – Day 0	1.00 (2.00)**	1.00 (3.00)*	0.333
Sensation			
Day 0	7.00 (1.00)	6.00 (1.00)	0.373
Day 14 – Day 0	0.00 (1.00)	0.00 (1.00)	0.852
Day 28 – Day 0	0.00 (1.00)	0.00 (1.00)	0.727
Scaliness			
Day 0	6.00 (2.00)	6.00 (1.00)	0.952
Day 14 – Day 0	1.00 (2.00)**	1.00 (1.00)**	0.994
Day 28 – Day 0	0.00 (1.00)*	1.00 (1.00)*	0.802
Wrinkles			
Day 0	4.00 (2.00)	5.00 (3.00)	0.266
Day 14 – Day 0	0.50 (1.00)**	0.00 (2.00)	0.039
Day 28 – Day 0	1.00 (2.00)**	0.00 (1.75)*	0.271

Remark: * indicates the data in a particular group are statistically significant different between the two dates by Wilcoxon signed ranks tests at p < 0.05
** indicates the data in a particular group are statistically significant different between the two dates Wilcoxon signed ranks tests at p < 0.01

Table 3b: Summary of self-evaluation data in Chinese female elderly

	Placebo (n=36) Median (IQR)	Q10-TF (n=32) Median (IQR)	p-value between placebo & Q10-TF
Appearance:			
Day 0	7.00 (0.00)	7.00 (0.00)	0.789
Day 14 – Day 0	0.00 (0.00)	0.00 (0.00)	0.548
Day 28 – Day 0	0.00 (0.00)	0.00 (0.00)	0.732
Intactness			
Day 0	7.00 (1.00)	7.00 (2.00)	0.439
Day 14 – Day 0	0.00 (1.00)*	0.50 (1.25)**	0.240
Day 28 – Day 0	0.00 (1.50)	0.00 (1.00)*	0.761
Moisture			
Day 0	4.00 (3.00)	3.00 (2.75)	0.301
Day 14 – Day 0	2.00 (4.00)**	2.00 (2.00)**	0.424
Day 28 – Day 0	2.00 (3.50)**	2.00 (4.00)**	0.431
Sensation			
Day 0	7.00 (1.00)	7.00 (1.00)	0.874
Day 14 – Day 0	0.00 (1.00)	0.00 (0.00)*	0.929
Day 28 – Day 0	0.00 (1.00)**	0.00 (0.00)*	0.484
Scaliness			
Day 0	7.00 (0.00)	7.00 (1.00)	0.104
Day 14 – Day 0	0.00 (0.00)	0.00 (1.00)*	0.134
Day 28 – Day 0	0.00 (0.00)	0.00 (0.00)	0.410
Wrinkles			
Day 0	4.00 (2.00)	3.00 (3.00)	0.166
Day 14 – Day 0	0.00 (3.00)	0.00 (4.00)	0.936
Day 28 – Day 0	1.00 (3.00)	0.00 (3.00)*	0.617

Remark: * indicates the data in a particular group are statistically significant different between the two dates by Wilcoxon signed ranks tests at p < 0.05
** indicates the data in a particular group are statistically significant different between the two dates Wilcoxon signed ranks tests at p < 0.01

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"Chinese Medicines are Toxic" is a Misconception

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ABSTRACT

Recent widespread rumors that "Chinese Medicines are toxic" are misunderstood. As experts commented whether a substance is toxic or not, very often depends on its physicochemical form, part, method of processing, and period of consumption. Depending on how and when it is used, the effect of Chinese Medicines (CM) could also be significantly different. Various results have been described and it is misleading to be uniformly saying that they are toxic. In Europe and the United States, most CM are regulated under food standards and safety. This reflects that the majority of CM are safe as long as they are properly prescribed and used. Since the philosophical approach between Western and Chinese medical practice is different, consumers have frequently been misled by the media on the effects of CM. The worse aspect of CM is their improper use by people as far as the safety issue of CM is concerned.

Keywords: Chinese medicines (CM), Western drugs, Toxicity, Safety, Heavy metals, Cinnabar, Betel Nut, Ranunculaceae aconitum, aristolochic acid

INTRODUCTION

Chinese medicines (CM) are the traditional treasures of China. Their uses in medical treatment and health improvement have been introduced over several millennia. Nevertheless, it is an old topic that CM contains excessive levels of heavy metals and other toxicants. Hence, people regard them as toxic and should not be used. In this article, we would like to address and explore a few incidences which lead to the public getting the conception that CM are unsafe for consumption.

REPORTED CASES OF UNSAFE USES OF CM

Recently, there has been widespread concern about excessive levels of heavy metals in CM. In fact, this is an old topic in the field.[1-3] Amongst these so-called "excessive" events, one of the most typical features is reported by the media that overseas markets found excessive toxic CM, which caused uproar within the country. For instance, the Department of Health in Hong Kong announced that there are certain amounts of "Jiantiwubuwan" (Fig. 1A) pills manufactured by Tongrentang (TRT) which were found to contain an excessive level of mercury.[4] In other reported cases, two products, namely "NiuHuangqianjinsan" (Fig. 1B) and "Xiaoerzhibaowan" pills (Fig. 1C) were found with excessive levels of cinnabar.[5]

Figure 1: Some Chinese proprietary medicinal products containing high level of cinnabar. A = Jiantiwubwan ; B = NiuHuangqianjinsan; C = Xiaoerzhibaowan.

Although both cinnabar and mercury are "Gong" (mercury) in Chinese, they represent two different forms of the same thing.[6] Professor Qian Zhongzhi, the chief consultant of the Chinese Pharmacopoeia Commission, commented that the toxicity of mercury on the human body mainly depends on its physicochemical form. The main form of cinnabar is mercury sulfide (HgS), which is a typical covalent compound, chemically stable, less or almost insoluble in hydrochloric acid and nitric acid. It is difficult to decompose in the stomach and absorbed by the body. Therefore, evaluation of the amount of cinnabar and proprietary Chinese medicines (pCM) containing cinnabar cannot simply be applied to determine the toxicity of "Gong". Instead people should be educated to distinguish the physicochemical forms and the valence state of these two forms of "Gong". Hence, the toxicity of Gong in cinnabar is incomparable to the other form even though they are derived from the sane chemical element.[7] Professor Xu Rongqian, who is a Pediatrics doctor in Beijing Dongzhimen Hospital, commented that cinnabar is frequently used clinically in risky, acute, severe illnesses. He personally has never come

across a case of poisoning or adverse reactions due to the treatment with cinnabar or proprietary Chinese medicine containing cinnabar ingredients in children. Indeed, cinnabar is present in many famous traditional Chinese medicines for first aid, e.g. "3 Treasures": "Angongniuhuangwan" (Fig. 2A), "Quofangbaoyuen" (Fig. 2B) and "Zixue Dan" (Fig. 2C). When Miss LIU Hairuo, who was a Phoenix TV reporter, was declared brain dead due to a car accident in the UK, she recovered from this fatal damage and could even speak and walk after switching to TCM treatment in China. In the course of the treatment process, "Angongniuhuangwan" was used. Hence, it demonstrates that what looks toxic can actually heal a patient.[8]

Prior to this event, another Chinese medicine "Zhengtian Wan" (Figure 2D), produced by China Resources Sanjiu Group that has been used for the treatment of headache, was claimed toxic to the heart and nervous system in the UK media because it contains Aconitum grass, which was regarded by ancient Greeks as "the queen of poison" herbs. However, an official response from Sanjiu Group denied that the Aconite added into "Zhengtian Wan" pills was a processed not the native aconite. It is true that this herb, which is the sub-root of *Ranunculaceae aconitum*, possesses highly toxic substance in its native form. However, after heat processing the monkshood Aconitum, whose toxicity due to the presence of aconite alkaloids, is significantly reduced.[9,10]
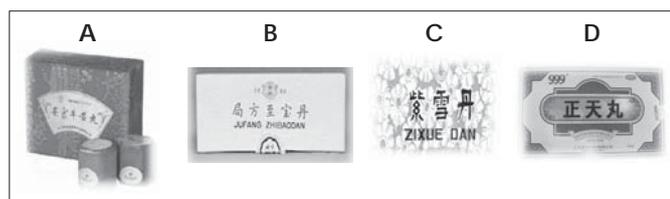
Figure 2: *Chinese proprietary medicinal products containing some toxic botanical materials in their native form. Product A = Angongniuhuangwan; B = Quofangbaoyuen; C = Zixue Dan and D = Zhengtian Wan.*

"CHEWING BETEL NUT" AND "BETEL NUT MEDICINE"

In another case, "Simontang", which is Hansen Pharm's first launched pharmaceutical product, was accused of containing carcinogens of betel nut.[11,12] The accusation in 2003 stemmed from an article that listed betel nut, tobacco and another 118 kinds of substances under the category of carcinogens. Subsequently, many articles written by journalists in Southeast Asia, such as Malaysia, Thailand and India jumped to the conclusion that prolonged chewing of betel nut will promote a higher incidence of oral cancer based on an epidemiological survey.[13,14]

Truly continuous chewing of the betel nut may lead to the development of oral cancer but taking the betel nut as a medicine is a fundamentally different issue.[15] In response to these reports, Li Lianda from the Chinese Academy of Engineering summed up by listing a few "differences". Firstly, he commented that the raw material used for medication is not the same part of the herb. Betel nuts used for chewing are the young fruit and those for medication purposes are mature medicinal betel nuts. Secondly, the nuts collected at two different stages are not processed by the same method. In brief, "chewing betel nut" is soaked with lime, an alkaline substance

which can easily cause irritation to oral mucosa. Chinese betel nut for medication purposes, however, is subjected to a series of processes including cleaning, extraction and decoction. Throughout the whole process, obvious detoxification takes place. Thirdly, there is no similarity as far as the entrance site is concerned. For chewing betel nut, some people chew for a few hours, while the Chinese betel nut is orally taken in a decoction form, not long enough to stimulate the oral mucosa. Fourthly, the amount of consumption is not the same. There is no limit for chewing the betel nut; which means a substantially high amount of carcinogens might be absorbed while for medical purposes, generally 3-5 grams of betel nut per day are prescribed.

DIFFERENCES BETWEEN THE PHILOSOPHY OF THE WESTERN AND THE CHINESE MEDICINES

Fang Shuting, who is the Chairman of the Chinese Medicine Association in China, commented that the misconception is attributed to misunderstanding of CM by some overseas consumers.[16] Since the philosophical practice of Western medicine is different from that of Chinese medicine, it is quite likely that medicines are harmful if people view them as substance to combat other molecules in our body. However, if they are treated as part of an organic body, they can serve as a health promoting substance.[17]

IMPROPER USE OF CM COULD BE HARMFUL TO HEALTH

The key issue of the clinical safety of CM is not its' toxicity but whether it is medicated properly. Improper use of CM is indeed the worse scenario. The "Longdanxieganwan incident", which happened from 1990's to the early years of this century, is a typical example. The incident stemmed from peoples' ignorance of the practice of Chinese medicine. As they did not practice according to the differentiation theory of TCM, patients were prescribed with long-term use of traditional Chinese medicines containing aristolochic acid, which resulted in kidney failure in the patients.[18] Consequently, some people made use of this incident to hype the media, and ultimately as many as 70 kinds of Chinese herbal medicines were implicated, causing an "aristolochic acid event."[19-22]

Liang Aihua is a researcher in the China Academy of Chinese Medical Sciences. She pointed out that practice of Chinese medicines in China follows the compliance and syndrome differentiation theory of TCM, which causes no serious problems. While there is no proper coaching abroad during the practice problem arise is inevitable. But even a few problems arise in foreign countries should not put the use of CM under a ban or generate any ill feelings. Western medicine has its side effects too, yet they are not banned. The key solution is rational use of the drug.

There an ancient saying the evil of drugs is medicated not properly. Leaving the overall concept of TCM, diagnosis and treatment, and not understanding the differentiation of symptoms and monarch, disorderly use or abuse of TCM, it is easy to go wrong. As Xu Lingtai, a famous doctor in the Qing Dynasty said, herbal substances like licorice and ginseng could become poisons if they are improperly used. Wang Chengde, who is a CPPCC member, commented whether

medicine is toxic or non-toxic depends on whether it is certified to use. As long as it is properly used in the right way, toxic substances are also safe. Contrary, incorrect treatment, even nontoxic herbs could be poisonous. He suggested that people should be educated with correct understanding of the toxicity of traditional Chinese medicine.[23]

Another old saying hints that one should not take a doctor's medicine if he has insufficient experiences of treatment. This means if medical doctors do not have solid medical knowledge, avoid taking their drugs. It was pointed out by Liu Changhua, who is a researcher from the China Academy of Traditional Chinese, that the major reason cinnabar mercury might induce toxic effect is the improper use of the substance as a health product for excessive and prolonged periods of time instead of a short term medication as a drug. Chinese medication always pays attention to "the disease lasts", as long as under the guidance of a doctor. In accordance with the safe dosage, taking medication should not lead to health problems.

A Beijing Traditional Chinese Medicine Bureau officer referred to documents in "Shen Nong's Herbal Classic" and commented that heavy metals and other minerals, such as cinnabar, native copper and gypsum have indeed been used as therapeutic substances in traditional Chinese medicines. These minerals have more than several thousand years of clinical practices. Many veterans reported that they provide better clinical effects over other drugs. Their efficacy is better than some generic drugs as they do not give significant effects. Hence, heavy metals added into CMs have their advantages and they should be treated as an integral part in the Chinese medicines. In fact, the safety issue of medicines at the clinical stage lies not in its toxicity, but rather whether they are properly used. Many toxic drugs can give therapeutic effects at clinical stage as long as they are properly used based on proper monitor of compound compatibility and accurate diagnosis.[24]

Toxicity does not exist only in traditional Chinese medicines and Chinese medicines, indeed, many damaging effects on the human body are also observed in many western medicines; for instances, development of deaf is always associated with the usage of streptomycin, and it is a risky treatment whenever applying gentamycin as it causes damage in kidney after prolong use. However, the toxic effects of these drugs do not constitute a full stop of their uses by doctors as long as they are properly monitored according to Liang Aihua's opinion.

Another medical expert, Qian Zhongzhi commented that about 30% of drugs sold in market and used today have some toxicity and side effects. No one can guaranteed a 100% safe of their use. Hence, it is impossible to find a drug free from any risks. By following the doctor's medication guide to patient and his experiences, we can effectively avoid drugs risks.

WRONG APPROACH TO EVALUATING THE SAFETY OF CM

TCM is not recognized as medicine in Europe and in the United States. Hence, food standards are used as the basis for assessing TCM no matter it is sold in domestic or exported oversea. Many countries and regions, including Hong Kong, Southeast Asian countries and Japan, mandate heavy metal limits for TCM, as is used in food standards.[25]

Drugs consisting of heavy metals cannot simply be assessed with the standard for food but only for reference because drugs are not the same as food. They are not consumed largely and frequently. They should be taken under the guidance of a doctor temporarily under limited usage. Wang Chengde commented that if food standard were adopted for CM, it will limit its use. In particular, for traditional Chinese medicines containing high amount of heavy metals, it would be concluded that they should not be used as they are toxic. Consequently, many distinctive Chinese medicine treatment methods would be banned or lost and therapeutic efficacy of some CM would be greatly reduced.[26,27]

CONCLUSION

The so-called Chinese "exceeded" event is actually caused by different standards, different measurement methods, which make the different valuation results. When cinnabar made medicine, the determination of which toxic soluble mercury free, the current international approach are destroyed digestion method, the result is that in the destruction and elimination of the organic disturbance, while insoluble cinnabar (HgS) into the toxic Hg^{2+}, Hg^+. Since the testing of material and people taking the subsistence is not the same kind of form' it will come to result that CM mercury exceeded ten and hundreds of times.

Li Lianda worried that the development of TCM industry would be hampered if CM are banned once any components in CM found toxic according to the criteria of food standards. Liang Aihua also commented that it is irrational to come to conclusion that a CM is unsuitable for use based merely on the toxicity of a single component without considering other characteristics and processing. Liu Changhua mentioned that CM stress on the nature treatment, while Western medicine based on ingredients. There are significant differences between Chinese and Western medicine, Chinese medicine with western medicine criteria to evaluate it is a lack of respect for traditional Chinese medicine. Mercury is used in chemical atomic absorption method, is detected by all the mercury components cinnabar, and not only free mercury. Therefore, in order to accuse toxic medicine is unreasonable.

It is an important issue for the development of TCM industry to promote quality evaluation system research in the field. Qian Zhongzhi mentioned that it is a new job to regulate the levels and limits of heavy metal in TCM. It is eventually expected to form a scientific standard under the conditions of safety considering the availability of resources and other factors continue to accumulate data and experiences. Qian Zhongzhi agreed that it is an important and urgent matter to develop a method for testing different forms of mercury whether it is the valence or the element form of Hg. The method will benefit the quality control of CM containing cinnabar. This task has been commissioned by the Chinese Pharmacopoeia Commission to Shanghai Institute for Drug Control. A new method is expected to be available and officially listed in the 2015 edition of the Chinese Pharmacopoeia.[28,29]

Author's background

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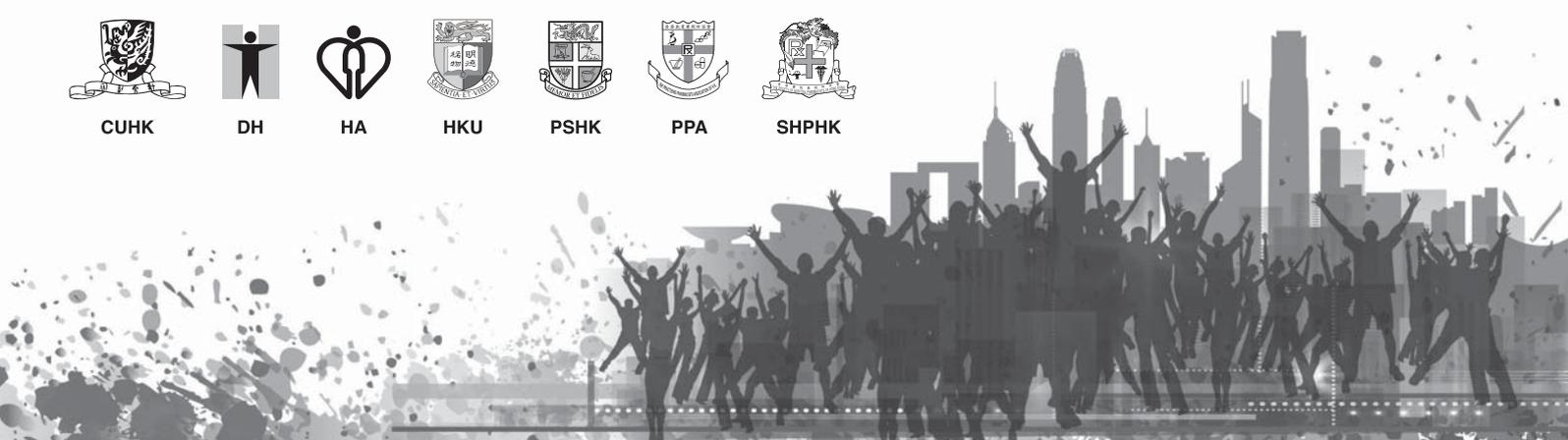
AFINITOR®
(Novartis Oncology)

Active Ingredient:
Everolimus

Presentation:
Each tablet containing 10 mg of everolimus and 297 mg lactose; each tablet contains 5 mg of everolimus and 149 mg lactose

Pharmacological Properties:
Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, protein kinase inhibitors, ATC code: L01XE10 . Everolimus is a selective mTOR (mammalian target of rapamycin) inhibitor. mTOR is a key serine-threonine kinase, the activity of which is known to be upregulated in a number of human cancers. Everolimus binds to the intracellular protein FKBP-12, forming a complex that inhibits mTOR complex-1 (mTORC1) activity. Inhibition of the mTORC1 signaling pathway interferes with the translation and synthesis of proteins by reducing the activity of S6 ribosomal protein kinase (S6K1) and eukaryotic elongation factor 4E-binding protein (4EBP-1) that regulate proteins involved in the cell cycle, angiogenesis and glycolysis. S6K1 is thought to phosphorylate the activation function domain 1 of the oestrogen receptor, which is responsible for ligand-independent receptor activation. Everolimus reduces levels of vascular endothelial growth factor (VEGF), which potentiates tumour angiogenic processes. Everolimus is a potent inhibitor of the growth and proliferation of tumour cells, endothelial cells, fibroblasts and blood-vessel-associated smooth muscle cells and has been shown to reduce glycolysis in solid tumours in vitro and in vivo.

Indications:
Hormone receptor-positive advanced breast cancer
Afinitor is indicated for the treatment of hormone receptor-positive, HER2/neu negative advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor.
Neuroendocrine tumours of pancreatic origin
Afinitor is indicated for the treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease.
Renal cell carcinoma
Afinitor is indicated for the treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy.

Dosage and Administration:
The recommended dose is 10 mg everolimus once daily. Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs. If a dose is missed, the patient should not take an additional dose, but take the usual prescribed next dose.
Dose adjustment due to adverse reactions

Management of severe and/or intolerable suspected adverse reactions may require dose alterations. Afinitor may be dose reduced or temporarily withheld (e.g. for one week) followed by reintroduction at 5 mg daily. If dose reduction is required, the suggested dose is 5 mg daily).
Paediatric population
The safety and efficacy of Afinitor in children aged 0 to 18 years have not been established. No data are available.
Elderly patients (≥65 years)
No dose adjustment is required.
Renal impairment
No dose adjustment is required.

Hepatic impairment
For patients with moderate hepatic impairment (Child-Pugh class B), the dose should be reduced to 5 mg daily. Everolimus has not been evaluated in patients with severe hepatic impairment (Child-Pugh class C) and is not recommended for use in this patient population.

Method of administration
Afinitor should be administered orally once daily at the same time every day, consistently either with or without food. Afinitor tablets should be swallowed whole with a glass of water. The tablets should not be chewed or crushed.

Contraindications:
Hypersensitivity to the active substance, to other rapamycin derivatives or to any of the excipients.

Warnings:
Non-infectious pneumonitis
Non-infectious pneumonitis is a class effect of rapamycin derivatives, including Afinitor. Non-infectious pneumonitis (including interstitial lung disease) was described in 12% of patients taking Afinitor. Some cases were severe and on rare occasions, a fatal outcome was observed. A diagnosis of non-infectious pneumonitis should be considered in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough or dyspnoea, and in whom infectious, neoplastic and other non-medicinal causes have been excluded by means of appropriate investigations. Patients should be advised to report promptly any new or worsening respiratory symptoms.

Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue Afinitor therapy without dose adjustments If symptoms are moderate, consideration should be given to interruption of therapy until symptoms improve. The use of corticosteroids may be indicated. Afinitor may be re-initiated at 5 mg daily.

For cases where symptoms of non-infectious pneumonitis are severe, Afinitor therapy should be discontinued and the use of corticosteroids may be indicated until clinical symptoms resolve. Therapy with Afinitor may be re-initiated at 5 mg daily depending on the individual clinical circumstances.

Infections

Afinitor has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoan infections, including infections with opportunistic pathogens. Localised and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections such as aspergillosis or candidiasis, and viral infections including reactivation of hepatitis B virus, have been described in patients taking Afinitor. Some of these infections have been severe (e.g. leading to respiratory or hepatic failure) and occasionally fatal.

Physicians and patients should be aware of the increased risk of infection with Afinitor. Pre-existing infections should be treated appropriately and should have resolved fully before starting treatment with Afinitor. While taking Afinitor, be vigilant for symptoms and signs of infection; if a diagnosis of infection is made, institute appropriate treatment promptly and consider interruption or discontinuation of Afinitor.

If a diagnosis of invasive systemic fungal infection is made, Afinitor treatment should be promptly and permanently discontinued and the patient treated with appropriate antifungal therapy.

Hypersensitivity reactions

Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnoea, flushing, chest pain or angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) have been observed with everolimus.

Oral ulceration

Mouth ulcers, stomatitis and oral mucositis have been observed in patients treated with Afinitor. In such cases topical treatments are recommended, but alcohol- or peroxide-containing mouthwashes should be avoided as they may exacerbate the condition. Antifungal agents should not be used unless fungal infection has been diagnosed.

Pregnancy and lactation:

Women of childbearing potential/Contraception in males and females

Women of childbearing potential must use a highly effective method of contraception (e.g. oral, injected, or implanted non-oestrogen-containing hormonal method of birth control, progesterone-based contraceptives, hysterectomy, tubal ligation, complete abstinence, barrier methods, intrauterine device [IUD], and/or female/male sterilisation) while receiving everolimus, and for up to 8 weeks after ending treatment.

Pregnancy

There are no adequate data from the use of everolimus in pregnant women. Studies in animals have shown reproductive toxicity effects including embryotoxicity and foetotoxicity. The potential risk for humans is unknown.

Everolimus is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is not known whether everolimus is excreted in breast milk. However, in rats, everolimus and/or its metabolites readily pass into the milk. Therefore, women taking everolimus should not breast-feed.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Patients should be advised to be cautious when driving or using machines if they experience fatigue during treatment with Afinitor.

Side effects:

a) Summary of safety profile

Three randomised, double-blind, placebo controlled phase III studies contribute to the safety profile. The respective exposure in the phase III studies was:

- BOLERO-2 (CRAD001Y2301): everolimus in combination with exemestane in the treatment of postmenopausal women with oestrogen receptor-positive, locally advanced or metastatic breast cancer who were previously treated with either letrozole or anastrozole. In total, 191 (40%) patients were exposed to everolimus therapy for ≥32 weeks. The rates of adverse reactions resulting in permanent discontinuation were 21% and 3% for the everolimus plus exemestane and the placebo plus exemestane treatment groups, respectively.
- RADIANT-3 (CRAD001C2324): everolimus plus best supportive care in patients with advanced neuroendocrine tumours of pancreatic origin. In total, 63 (31%) patients were exposed to everolimus 10 mg/day for ≥52 weeks. The rates of adverse reactions resulting in permanent discontinuation were 14% and 2% for the everolimus and placebo treatment groups, respectively.
- RECORD-1 (CRAD001C2240): everolimus plus best supportive care in patients with metastatic renal cell carcinoma. In total, 165 patients were exposed to everolimus 10 mg/day for ≥4 months. The rates of adverse reactions resulting in permanent discontinuation were 7% and 0% for the everolimus and placebo treatment groups, respectively. Most adverse reactions were grade 1 or 2 in severity.

The most frequent grade 3-4 adverse reactions (incidence ≥2% in at least one phase III study) were anaemia, fatigue, diarrhoea, infections, stomatitis, hyperglycaemia, thrombocytopenia, lymphopenia, neutropenia, hypophosphataemia, hypercholesterolaemia, diabetes mellitus, and pneumonitis. The grades follow CTCAE Version 3.0.

b) Tabulated summary of adverse reactions

Table 2 shows the incidence of adverse reactions reported for patients receiving everolimus 10 mg/day in at least one of the pivotal studies. All terms included are based on the highest frequency reported in a pivotal study. Adverse reactions are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2 Adverse reactions

Infections and infestations
Very common	Infections[a, *]

Blood and lymphatic system disorders
Very common	Anaemia, thrombocytopenia
Common	Leukopenia, lymphopenia, neutropenia
Uncommon	Pure red cell aplasia

Immune system disorders
Not known	Hypersensitivity

Metabolism and nutrition disorders
Very common	Hyperglycaemia, hypercholesterolaemia, hypertriglyceridaemia, anorexia
Common	Diabetes mellitus, hypophosphataemia, hypokalaemia, hyperlipidaemia, hypocalcaemia, dehydration

Psychiatric disorders
Common	Insomnia

Nervous system disorders
Very common	Dysgeusia, headache
Uncommon	Ageusia

Eye disorders
Common	Conjunctivitis, eyelid oedema

Cardiac disorders
Uncommon	Congestive cardiac failure

Vascular disorders
Common	Hypertension, haemorrhage [b]
Uncommon	Flushing, deep vein thrombosis

Respiratory, thoracic and mediastinal disorders
Very common	Pneumonitis [c], dyspnoea, epistaxis, cough
Common	Pulmonary embolism, haemoptysis
Uncommon	Acute respiratory distress syndrome

Gastrointestinal disorders
Very common	Stomatitis [d], diarrhoea, mucosal inflammation, vomiting, nausea
Common	Dry mouth, abdominal pain, oral pain, dysphagia, dyspepsia

Hepatobiliary disorders
Common	Alanine aminotransferase increased, aspartate aminotransferase increased

Skin and subcutaneous tissue disorders
Very common	Rash, dry skin, pruritus, nail disorder
Common	Palmar-plantar erythrodysaesthesia syndrome, erythema, skin exfoliation, acneiform dermatitis, onychoclasis, skin lesion, mild alopecia
Uncommon	Angioedema

Musculoskeletal and connective tissue disorders
Common	Arthralgia

Renal and urinary disorders
Common	Creatinine increased, renal failure (including acute renal failure)*, proteinuria*

General disorders and administration site conditions
Very common	Fatigue, asthenia, peripheral oedema, pyrexia
Common	Chest pain
Uncommon	Impaired wound healing

Investigations
Very common	Weight decreased

* see also Description of selected adverse reactions"
[a] Includes all reactions within the 'infections and infestations' system organ class (such as pneumonia, sepsis, and isolated cases of opportunistic infections [e.g. aspergillosis, candidiasis and hepatitis B)
[b] Includes different bleeding events not listed individually
[c] Includes pneumonitis, interstitial lung disease, lung infiltration, pulmonary alveolar haemorrhage, pulmonary toxicity, and alveolitis
[d] Includes stomatitis and aphthous stomatitis, and mouth and tongue ulceration

Forensic Classification
P1S1S3

Edarbi ® Tablets
(Takeda Pharmaceutical)

Prepared by Anthony Fan and edited by Lucillia Leung

Active Ingredient:
Azilsartan Medoxomil

Presentation:
Each tablet contains 40 mg or 80 mg azilsartan medoxomil in the pack of 28's.

Pharmacological Properties:
Azilsartan medoxomil is an orally active prodrug that is rapidly converted to the active moiety, azilsartan, which selectively antagonises the effects of angiotensin II by blocking its binding to the AT1 receptor in multiple tissues. Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium.

Blockade of the AT1 receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increases in plasma renin activity and angiotensin II circulating levels do not overcome the antihypertensive effect of azilsartan.

Indications:
Edarbi is indicated for the treatment of essential hypertension in adults.

Dosage and Administration:
The recommended starting dose is 40 mg once daily, with or without food. The dose may be increased to a maximum of 80 mg once daily for patients whose blood pressure is not adequately controlled at the lower dose. Near-maximal antihypertensive effect is evident at 2 weeks, with maximal effects attained by 4 weeks.

No initial dose adjustment with Edarbi is necessary in elderly patients (65 years and over), although consideration can be given to 20 mg as a starting dose in the very elderly (≥ 75 years), who may be at risk of hypotension.

The safety and efficacy of Edarbi in children and adolescents 0 to < 18 years have not yet been established.

For hypertensive patients with severe renal impairment and end stage renal disease, caution should be exercised, as there is no experience of use of Edarbi in these patients. Hemodialysis does not remove azilsartan from the systemic circulation. No dose adjustment is required in patients with mild or moderate renal impairment.

Edarbi has not been studied in patients with severe hepatic impairment and therefore its use is not recommended in this patient group. As there is limited experience of use of Edarbi in patients with mild to moderate hepatic impairment close monitoring is recommended and consideration should be given to 20 mg as a starting dose.

For patients with possible depletion of intravascular volume or salt depletion (e.g. patients with vomiting, diarrhoea or taking high doses of diuretics), Edarbi should be initiated under close

medical supervision and consideration can be given to 20 mg as a starting dose.

Caution should be exercised in hypertensive patients with congestive heart failure as there is no experience of use of Edarbi in these patients.

No dose adjustment is required in the black population, although smaller reductions in blood pressure are observed compared with a non-black population. This generally has been true for other angiotensin II receptor (AT1) antagonists and angiotensin-converting enzyme inhibitors. Consequently, uptitration of Edarbi and concomitant therapy may be needed more frequently for blood pressure control in black patients.

Contraindications:
Hypersensitivity to the active substance or to any of the excipients, second and third trimester of pregnancy is contraindicated.

Precautions:
In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with congestive heart failure, severe renal impairment or renal artery stenosis), treatment with medicinal products that affect this system, such as angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists, has been associated with acute hypotension, azotaemia, oliguria or, rarely, acute renal failure. The possibility of similar effects cannot be excluded with Edarbi.

Caution should be exercised in hypertensive patients with severe renal impairment, congestive heart failure or renal artery stenosis, as there is no experience of use of Edarbi in these patients.

Excessive blood pressure decreases in patients with ischaemic cardiomyopathy or ischaemic cerebrovascular disease could result in a myocardial infarction or stroke.

There is currently no experience on the use of Edarbi in patients who have recently undergone kidney transplantation.

Edarbi has not been studied in patients with severe hepatic impairment and therefore its use is not recommended in this patient group.

In patients with marked volume- and/or salt-depletion (e.g. patients with vomiting, diarrhoea or taking high doses of diuretics) symptomatic hypotension could occur after initiation of treatment with Edarbi. Hypovolemia should be corrected prior to administration of Edarbi, or the treatment should start under close medical supervision, and consideration can be given to a starting dose of 20 mg.

Patients with primary hyperaldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of Edarbi is not recommended in these patients.

Based on experience with the use of other medicinal products that affect the renin-angiotensin-aldosterone system, concomitant use of Edarbi with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other medicinal products that may increase potassium levels (e.g. heparin) may lead to increases in serum potassium in hypertensive patients (see section 4.5). In the elderly, in patients with renal insufficiency, in diabetic patients and/or in patients with other co-morbidities, the risk of hyperkalaemia, which may be fatal, is increased. Monitoring of potassium should be undertaken as appropriate.

Special caution is indicated in patients suffering from aortic or mitral valve stenosis, or hypertrophic obstructive cardiomyopathy (HOCM).

Angiotensin II receptor antagonists should not be initiated during pregnancy. Unless continued angiotensin II receptor antagonist therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.
As with other angiotensin II receptor antagonists the combination of lithium and Edarbi is not recommended.

Drug Interactions:
During concurrent use of lithium and angiotensin-converting enzyme inhibitors, reversible increases in serum lithium concentrations and toxicity have been reported. A similar effect may occur with angiotensin II receptor antagonists. Due to the lack of experience with concomitant use of azilsartan medoxomil and lithium, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended.

When angiotensin II receptor antagonists are administered simultaneously with NSAIDs (i.e. selective COX-2 inhibitors, acetylsalicylic acid (> 3 g/day) and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Furthermore, concomitant use of angiotensin II receptor antagonists and NSAIDs may lead to an increased risk of worsening of renal function and an increase in serum potassium. Therefore, adequate hydration and monitoring of renal function at the beginning of the treatment are recommended.

Concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other medicinal products (e.g. heparin) may increase potassium levels. Monitoring of serum potassium should be undertaken as appropriate.

No clinically significant interactions have been reported in studies of azilsartan medoxomil or azilsartan given with amlodipine, antacids, chlortalidone, digoxin, fluconazole, glyburide, ketoconazole, metformin, and warfarin.

Azilsartan medoxomil is rapidly hydrolysed to the active moiety azilsartan by esterases in the gastro intestinal tract and/or during drug absorption. In vitro studies indicated that interactions based on esterase inhibition are unlikely.

Side Effects:
Dizziness and diarrhoea.

Forensic Classification:
P1S1S3

ACPE

8th Asian Conference on Pharmacoepidemiology:

"Applying pharmacoepidemiology to improve health care in Asia" Hong Kong

25th Oct 2013 Education Workshop:
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The Pharmaceutical Society
of Hong Kong

The University of Hong Kong

International Society for
Pharmacoepidemiology

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Validation and extension of Sequence Symmetry Analysis as a Tool for Multi-Country Rapid Safety Signal Detection

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Aim/Objectives: The objective of post-market surveillance of medicines is to rapidly detect adverse drug reactions. While countries can undertake this work individually, cross-national studies have the advantage of large populations available for study with resultant increased power to detect rare and often serious adverse reactions. Implementation of global surveillance requires a reliable quantitative technique which is robust to confounding and differences in data quality and quantity. Sequence symmetry analysis (SSA) is a potential tool to achieve rapid surveillance due to its computational speed and minimal data set requirement. To date the power and sample size requirements for use of SSA as a rapid signal detection tool have not been investigated.

Aim: To evaluate the validity and sample size requirements of SSA as a signal detection tool for newly marketed medicines

Methods: Randomly simulated prescription supplies were generated for two medicines, DrugA (medicine of interest) and DrugB (adverse event) for varying population sizes. Scenarios were created by varying medicine utilization trends and associations between medicines were injected. 1000 simulations were generated for each scenario. To evaluate the performance of SSA approach, relative bias and coverage probabilities (percentage of CI's which contained the expected ASR) were calculated. Sample size calculations were performed by varying the proportion of medicine use in the population to determine the prevalence of medicine use to achieve 80% power.

Results: In scenarios where DrugA and DrugB were associated (ASR=2), unadjusted SR's ranged from 1.90 (95% Confidence Interval 1.68-2.15) for no trend in DrugA to 1.57 (95% CI 1.42-1. 74) for a steeply increasing trend. After adjustment ASR estimates were 1.90 (95% CI 1.67-2.14) and 1.87 (95% CI 1.69-2.07) respectively. Sample size calculations suggest that for a population of 1 million, SSA will have adequate power to detect increased risks greater than 1.5 if medicines have a population incidence of 10% or more. At least 15% population incidence was required to have adequate power to detect increased risks less than 1.2.

Conclusion: This study has identified that PSSA has a place as a complementary tool to existing methods as a safety signal detection tool for newly marketed medicines in sufficiently large claims databases.

Effect of GLP-1 agonists on weight control in type 2 diabetes-a network meta-analysis

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Aim/Objective: The direct internal comparison results of GLP-agonists are relatively rare.

Purpose: To compare the efficacy of weight control of different GLP-1 agonists in type 2 diabetes patients.

Data Sources: Medline, EMBASE, Cochrane Library, ClinicalTrials.gov electronic database and pharmaceutical website.

Method: Randomized Controlled trials that evaluated the effects of GLP-1 agonists on weight control among type 2 diabetic patients.

Results: Sixty nine studies involving 24949 participants with a mean duration of 28 weeks were included. Compared with placebo, weight increase can be seen in traditional hypoglycemic drugs insulin (2.53kg [95%CI, 1.66 to 3.39kg]), sulfonylureas (3.44kg [95%CI, 2.40 to 4.46kg]), sitagliptin (0.17kg [95%CI, -0.96 to 1.30kg]), and thiazolidinediones (2.70kg [95%CI, 1.54 to 3.86kg]), and weight loss was seen with nearly all GLP-1 agonists especially exenatide and tasglutide. GLP-1 agonists showed obvious better performance in weight control compared with traditional hypoglycemic agents.

Limitations: Quality of included trials varied, most of which with duration over 24 weeks, but there are still a few studies with duration shorter than 24 weeks. Studies of new GLP-1 agonists are respectively rare, so the network analysis of these new agents mainly relies on indirect comparison, which inevitably lowers the power and increases the uncertainty of outcome. The method we adopt for detection of publication bias is the Bayesian application of Copas selection model, this model applies to star-shaped network, so some information may be missing in the process.

Conclusion: There is strong evidence implying that GLP-1 agonists outperforms traditional hypoglycemic drugs in matter of weight control, yet no clear difference is seen in comparison among GLP-1 agonists except that EX10BID is better than most GLP-1 agonists with statistical significance.

Anti-obesity drug prescribing in children and adolescents: a population-based study in the UK

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Aim/Objectives: To investigate prescribing patterns of anti-obesity drugs (orlistat and sibutramine) to children and adolescent aged 0-18 years in the UK.
Methods: Using the UK General Practice Research Database (GPRD), we carried out a retrospective cohort study between January 1999 and December 2006. The cohort comprised of all children and adolescents aged 0-18 years who received at least one anti-obesity drug prescription. The overall, age, and sex-specific prevalence of prescribing was calculated. The duration of anti-obesity drug treatment was also analysed. Treatment was considered as stopped if there were no further prescriptions issued within 90 consecutive days after the date of the last prescription. The Kaplan-Meier survival analysis was used to investigate treatment duration.
Results: A total of 452 subjects received 1333 prescriptions during the study period. The annual prevalence of anti-obesity drug prescriptions rose significantly from 0.006 per 1000 (95 % CI :0.0007-0.0113) in 1999 to 0.091 per 1000 (95% CI: 0.07- 0.11) in 2006; a 15-fold increase. The sex-specific prevalence was significantly increasing in both boys and girls over the study period (p<0.05). The use of orlistat accounted for the majority of anti-obesity drug prescriptions (78.4%). The mean duration of orlistat use was significantly shorter (3.0 months; 95%CI: 2.72 to 3.47) compared with sibutramine (4.2 months; 95%CI: 3.4 to 5.0) (p=0.003). Approximately 45% of orlistat prescriptions were discontinued within the first month and about 25% of sibutramine prescriptions were discontinued within the first month.
Conclusion: Prescribing of anti-obesity drugs in young people has dramatically increased during past few years. However, the majority of prescriptions are rapidly discontinued during the first 3 months, suggesting tolerability and effectiveness may be low in routine clinical use. Further research into the effectiveness and safety of anti-obesity drugs in children and adolescents in a clinical population is needed.
Key words: obesity, anti-obesity drug, children, adolescents, general practice

Antihyperlipidemic drugs and risk of diabetes mellitus in Japanese population of working age

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Aim/Objectives: To examine the association between antihyperlipidemic drugs and incident diabetes in Japanese population of working age.
Methods: A retrospective cohort study was conducted using the data of health-care claims and enrolment status between January 2005 and March 2011 for 215,307 beneficiaries aged 20 to 74 in private health insurances provided by the Japan Medical Data Center (JMDC). The JMDC also provided the data of annual health screenings mandatory for all Japanese workers and optional for their family members. We identified a study population (n=94,630) who had hyperlipidemia (total cholesterol ≥220, low density lipoprotein ≥140, high density lipoprotein <40 or triglyceride ≥150 mg/dL) in the health screening (defined as the index screening). In the analysis, we excluded patients who had already had diabetes at the index screening or had already used antihyperlipidemic drugs during the 6 months prior of the index screening. We identified cases of incident diabetes that had new diagnosis of diabetes or medication of diabetes after the index screening. We estimated the risk for incident diabetes of antihyperlipidemic drugs using the Cox proportional hazards model adjusted for age, gender, HbA1c and other confounding factors.
Results: Statins and fibrates were associated with the increased risk of incident diabetes compared with non-users of antihyperlipidemic drugs and the adjusted hazard ratio for statins was 2.54 (95%CI: 2.11-3.06) and that for fibrates was 2.05 (1.28-3.29).
Conclusion: The use of antihyperlipidemic drugs (fibrates and statins) was associated with the incident diabetes. Further study is required to address this association in Japanese population.
Keywords: retrospective cohort study, statins, fibrates, diabetes

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Dramatic decrease in fluoroquinolones in pediatrics: impact of regulatory action in Korea

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Aim/Objective: Fluoroquinolones, which is an antibiotic agent, are not recommended for routine use in pediatrics due to the risk of development of arthropathy with erosions of cartilage. In December 2009, Korea Ministry of Food and Drug Safety (MFDS) announced that fluoroquinolones should not be used in pediatric patients under 18 years and informed the contraindication to physicians and pharmacists through nationwide computerized drug utilization review (DUR) system. This study is to evaluate the impact of the MFDS's 2009 regulatory action regarding fluoroquinolones in pediatrics patients.

Methods: We conducted time series analysis using Korea Health Insurance Review & Assessment Service National Patients Sample (HIRA-NPS) database. Study subjects consisted of the pediatrics under 18 years old who were prescribed least once with antibiotics (ATC code, J01) before (January 2009-December 2009) and after implementation (January 2010-December 2011). Contraindicated use of fluoroquinolones was defined as use of the following antibiotics at least one day in pediatrics under 18 years: ofloxacin, ciprofloxacin, norfloxacin, lomefloxacin, levofloxacin, or gemifloxacin. We calculated monthly percentage of fluoroquinolone prescriptions in pediatric patients. The difference between the proportion for before and after years was estimated as relative reduction in contraindicated use. We calculated 95% confidence intervals (CI) based on the sample-weight adjustment.

Results: During the study period, we identified 5,388,483 antibiotics prescriptions in 634,812 pediatric patients (median age 4 [Interquartile range (IQR) 2-9 years]. The patient population was 45.6% female. During the 12-month period before the implementation, the percentage of contraindicated use of quinolones was 5.1% (95% CI: 5.0%-5.2%, N=9,225). We observed a rapid decrease in monthly proportion of fluoroquinolone use in pediatric population after the implementation of regulatory action (P for trend<0.01). In the year after the regulatory action, only 0.67% (95% CI: 0.65%-0.69%, N=1,754) represented the contraindicated use. Ciprofloxacin showed the sharpest decrease among the six fluoroquinolones studied. Relative reductions were 94.3%, 93.4% and 88.0%, respectively, for ciprofloxacin, norfloxacin and ofloxacin. Overall, there was 86.8% relative reduction (95% CI: 83.3%-90.4%) in contraindicated use of fluoroquinolones.

Conclusion: The Korea regulatory action regarding fluoroquinolone through nationwide DUR system had an effect of reduced use in pediatric population.

Keywords: fluoroquinolone, pediatrics, contraindication, regulatory action, drug utilization review

Investigation on Effectiveness and Safety of Osteoporosis Drugs in Taiwan

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Aim/Objective: Currently, information on the compliance, relative effectiveness and safety of osteoporosis drugs in Asian population is lacking. Our study intended to investigate the compliance with alendronate and its impact on hip fracture risk, to compare the relative effectiveness of osteoporosis drugs in preventing secondary non-vertebral fractures and to investigate the incidence and risk of venous thromboembolism (VTE) among Taiwan osteoporotic fracture population.

Method: 3 retrospective cohort studies were conducted respectively. From 2003-2006, enrollees in the National Health Insurance Research Database (NHIRD) aged above 50 years, with vertebral/hip fracture and new to osteoporosis therapy were recruited. Patients had Paget's disease or cancer during baseline period were excluded. Patients were classified into alendronate, calcitonin or raloxifene group according to the exposure after follow-up. Patients compliance were measured by Medication Possession Ratio (MPR). The impact of patient compliance on secondary hip fracture risk, the relative effectiveness of osteoporosis drugs and the safety of bisphosphonates were estimated by using Cox modeling to correct effects of covariates and their correlation with outcomes. Results were examined in series sensitivity analyses, including different cumulative doses group. SAS 9.2 will be used for data management and statistical purpose.

Results: We found only 38% of the study population remained compliant during the first year of treatment. Over the 4-year follow-up period, the risk of hip fracture among the compliant patients was 70% lower than in non-compliant patients (adjusted HR, 0.30). As for the relative effectiveness, the fracture rates were highest in calcitonin recipients (4.57/100 person-years), followed by raloxifene and alendronate. Results from Cox analyses showed raloxifene (HR, 1.47; 95%CI, 1.29-1.67) and calcitonin (HR, 1.51; 95%CI, 1.29-1.75) had higher non-vertebral fracture risk as compared with alendronate. We also did not observe higher incidence and risk of VTE for alendronate recipients, as compared with raloxifene/calcitonin recipients.

Conclusion: The compliance of osteoporosis population in Taiwan is suboptimal. The effectiveness of alendronate in Taiwan is best within drug classes, and the potential risks for serious adverse events (VTE) were low. Efforts and policies should be implanted to osteoporosis patients by the regulatory agencies and healthcare professionals to improve their compliance.

Keywords: pharmacoepidemiology; osteoporosis; alendronate; raloxifene; compliance; venous thromboembolism

The trigger tool development for medication safety for hospitalized patients at five Thai hospitals

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Aim/Objectives: To develop the trigger tool for ADE detecting in Thai hospitalized patients and to determine the rate and characteristics ADEs occurring by this tool.

Methods: This study was conducted with an observational design. Five selected provincial hospitals across Thailand participated. The hospitalized patients who admitted at medical wards were recruited by convenience sampling. The ADE trigger tool which consisted of modified 24 triggers were screened by manual chart review and then suspected ADE was determined. The numbers of positive triggers which were able to detect ADE was recorded. The characteristics of trigger and ADE detection data were analyzed using descriptive statistics.

Results: A total of 1,489 medical charts (599 males and 890 females) were recruited. The mean age of those patients was 56.0 + 18.4 years old. Total 101 ADEs were detected from 97 patients. The rate of ADEs was 6.8 events per 100 patients and 16.0 events per 1,000 patient- days. Forty-six ADEs (46.5%) were classified as preventable ADEs. The most common frequency positive triggers consisted of abrupt medication stop (58.9%), INR > 6 (58.3%), and rash (43.9%). The most ADEs expressed as hypoglycemia (20.8%), rash (9.9%), upper gastrointestinal bleeding (9.9%), and warfarin over dose (9.9%). Anti-diabetics agents (14.9%), anticoagulants/ anti-platelets (18.8%), antibacterial (11.9%), and antivirals (11.9%) were common drug groups caused ADEs.

Conclusions: The trigger tool has a potential role in detecting ADE and driving quality improvement for medication safety. However, the results of positive triggers and ADE occurring suggest a modification of ADE triggers.

The global registry program on long-term oral anti-thrombotic treatment in patients with atrial fibrillation (GLORIA-AF): Objectives, design and initial results from Phase I

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Aim/Objective: While Vitamin K antagonists (VKA) have been the standard of care for decades for patients with atrial fibrillation (AF), new oral anticoagulants (NOACs), e.g. dabigatran etexilate (DE), offer new treatment options. Patients prescribed newly-marketed drugs may have a different prognosis from those on existing treatments.

Methods: With approximately 56,000 patients GLORIA-AF will be one of the largest international prospective registry programs of antithrombotic therapy in newly diagnosed AF patients. It will collect structured data from routine care in 3 different phases addressing potential channelling bias for new treatments. In Phase I, treatment patterns before approval of NOACs are evaluated. Phase II, beginning after DE approval, monitors the safety of DE and assesses channelling between DE and VKA therapy. Phase III starts after channelling has stabilized (evaluated using propensity scoring) and longitudinal data of all patients will be collected to assess comparative effectiveness.

Results: Phase I of GLORIA-AF was completed, collecting data in 1075 patients from 75 sites in 9 countries. China contributed 715 patients, from 25 sites, constituting two thirds of the collected data set. Mean age of Chinese patients was 67+12 yrs and 43% female. Final results on baseline characteristics, co-morbidities, co-medications and treatment choice in Phase I will be available Sep 2013, for first presentation at the ACPE.

Conclusion: GLORIA-AF offers a unique opportunity to understand treatment patterns, safety and effectiveness of oral anticoagulation in a real-world AF population based on a novel design that adapts to the changing treatment patterns of a newly marketed treatment option.

Keywords: atrial fibrillation, registry

Impact of mis-modeling of the exposure effect in observational studies of adverse effects of medications: a simulation study

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Aim/Objectives: Most pharmacoepidemiological studies represent drug exposure by an a priori selected exposure metric, e.g. current use, any use within last 3 months or cumulative dose. It is often unclear if the selected model accounts accurately for the effect of past and current exposures on the risks of the adverse event.

Objectives: To evaluate, through simulations, the ability of goodness-of-fit criteria to identify the correct exposure model and the impact of using an 'incorrect' model on the inference about the drug effect.

Methods: We simulated hypothetical cohort studies with time-varying patterns of drug use and doses, and assumed different 'true' models linking exposure with the risk. Then, the hypothesis of no association was tested in each of 10 Cox regression models, with alternative time-varying exposure metrics. Fit of alternative models was compared with AIC.

Results: AIC criterion identified the correct exposure model in more than 92% of simulated samples. In contrast, a priori choice of an incorrect model substantially reduced the power to detect an association. E.g. if risks depended on the cumulative past dose, using current exposure reduced the power to 22% compared to 98% for the 'correct' cumulative dose model.

Conclusion: Pharmacoepidemiological studies should consider alternative exposure models and use statistical criteria to identify the model most consistent with a specific data structure.

Opioid analgesic prescribing in Australia: a focus on gender and age

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Aim/Objectives: The use of prescription opioid analgesics has been increasing over the last few decades in Australia. In particular, oxycodone and fentanyl have increased substantially.

We examined the gender and age trends in the prescribing of subsidised opioid analgesics in the Australian population from 2002 to 2009 for non-palliative care indications.

Methods: We analysed the Medicare Australia and Drug Utilisation Sub-Committee databases for script data from 2002 to 2009 in ten-year age groups and by gender. Scripts were converted to Defined Daily Doses (DDD)/1000/day using Australian Bureau of Statistics population data.

Results: Overall use increased progressively in 2002-2009 from 5.14 to 8.44 DDD/1000 population/day. Tramadol was the most widely used agent followed by oxycodone then morphine. Dispensed use increased in those aged in their 20s and 30s to plateau between 30 and 59 years for the three most preferred analgesics. The peak use of the higher dose formulations of oxycodone were seen in those aged in their 40s: use was much higher in males.

Conclusions: The dispensed use of opioid analgesics increased markedly between 2002 and 2009. The gender differences in prescribing reflect the higher prevalence of chronic nonmalignant pain in men. Higher dose formulations are preferred in younger patients. The high use of some of these drugs (especially tramadol) in elderly people (≥80 years) warrants further exploration.

Keywords: analgesics, opioids, oxycodone, prescribing

Registration control to promote rational drug use: Experience from Drug Regulatory Authority of Nepal

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Aim/Objective: The objective of this study is to review the regulatory interventions of Department of Drug Administration (DDA), Drug Regulatory Authority of Nepal, to promote rational drug use.

Methods: We carried out retrospective review of regulatory interventions by DDA to ensure the availability of safe, effectives and quality drugs as assured by the Drug Act, 1978. All the regulations, codes and rules enforced were critically reviewed and analyzed.

Results: For the efficient and effective enforcement of Drug Act the following regulations and codes have been implemented:

a.   Constitution of Drug Consultative Council and Drug Advisory Committee Regulation, 2037
b.   Drug Registration Regulation, 2038
c.   Interrogation and Inspection Regulation, 2040
d.   Codes on Drug Manufacturing, 2041
e.   Sales and Distribution Codes, 2041
f.   Drug Standard Regulation, 2043

Hundreds of drugs and its combinations have been banned in Nepal. Gatifloxacin and CoX-2 selective inhibitors are still not registered on the ground of safety issues. The availability of total brands has been limited to around 10,000. Formulations of National Drug Policy, Essential Drug Lists, National Nepalese Formulary and Standard Treatment Schedule for Health post and Sub-health post level are the supportive tools to promote rational drug use.

Conclusion: Even though, the DDA is suffering from limited human and financial resources, it is efficient to ensure and control the availability of safe, effective and quality drugs within the country. However, the regulatory framework and supportive rules, regulations and polices need to be updated, revised and added to harmonize with the current trend in drug regulation.

Keywords: rational drug use, drug regulatory authority, Nepal

Impact of patient medication counselling on medication adherence in a cardiology outpatient clinic

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Aim/Objective: To assess the impact of patient medication counselling on medication adherence in patients with myocardial infarction (MI) and also to identify the predictors for non-adherence.

Methods: Patients who are known cases or newly diagnosed and prescribed with medication for treating MI were enrolled and divided into interventional and non-interventional groups. Baseline assessment of medication adherence in both the groups was assesed using Brief Medication Questionnaire on day 15 post discharge (baseline visit). Interventional group were counselled on their medication after baseline assessment and provided with patient information leaflets. Follow up visits in both groups were conducted on day 30, 60 and 90 from the baseline visit to assess the impact of counselling measured by paired 't' test. Predictors of medication non adherence were identified using multiple logistic regression analysis.

Results: 75 among 82 patients in interventional group and 69 among 78 patients in non-interventional group completed all three follow up visits. A significant increase in medication adherence among interventional group was observed from baseline to final follow up for antiplatelets, statins, angiotensin converting enzyme inhibitors, beta blockers, calcium channel blockers ($p<0.05$), but not for angiotensin II receptor blockers ($p=0.391$). A significant decline in medication adherence in non-interventional group was observed for antiplatelets, statins and beta blockers ($p<0.05$). Age, occupation and annual income were the significant predictors for non-adherence among both the groups.

Conclusions: Our study concluded that patient education has a positive impact on medication adherence among patients with MI.

Keywords: medication adherence, myocardial infarction patients, brief medication questionnaire

Pharmacogenetics algorithms for individualizing warfarin dosing: meta-analysis of randomized controlled trials

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Aim: Due to the inconsistent and limit of clinical application of pharmacogenetics (PG) – guided warfarin in clinical practice , the study was attempted to determine the efficacy and safety of PG-guided warfarin dosing algorithms in the initial stage of warfarin dosing by meta-analysis of RCTs.

Methods: All relevant RCTs were systematically searched online in January 2013. After assessment carefully by two independent reviewers, a pooled analysis was performed with the odds ratio (OR) for dichotomous data or weighted mean difference (WMD) for continuous data with 95% confidence interval (CI) by the Revman 5.1.0 software.

Results: A total of nine RCTs involving 1077 subjects were included in our meta-analysis. Most studies had high or unclear risk of bias. Results of meta-analysis showed that PG-guided warfarin dosing algorithms shortened the time to achieve first therapeutic international normalized ratio (INR) [WMD -3.09, 95% CI (-3.64 to -2.53), $p<0.00001$] or the time to stable dose [WMD -6.56, 95% CI (-7.00 to -6.11), $p<0.00001$], and significantly increased the percent time within therapeutic INR range [WMD 9.39, 95%CI (6.83 to 11.94), $p<0.00001$] than standard care for warfarin dosing. In addition, PG-guided algorithms increased the therapeutic INR by day 5 [OR 1.54, 95%CI (0.99 to 2.39), $p=0.06$] and therapeutic INR by day 8 (OR 2.05, 95% CI (1.31 to 3.21), $p=0.002$). Furthermore, PG-guided algorithms could significantly decreased the adverse events [OR 0.52, 95% CI (0.37 to 0.74), $p=0.0003$].

Conclusions: PG-guided warfarin dosing algorithms could improve efficacy and safety in the initial stage of warfarin dosing, suggesting that PG-guided algorithms should be considered for clinical application.

Keywords: pharmacogenetics, warfarin; algorithms, meta-analysis

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Complementary and alternative medicine use in the first trimester: safety perceptions and preference of pregnant women

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Aim/Objectives: To assess the use of complementary and alternative medicines (CAM) during the first trimester, the perceptions of the women on the safety of CAM and their preferences for CAM.

Methods: This study was carried out in two London teaching hospitals. Expectant mothers were interviewed using a structured questionnaire to ascertain their CAM use during the first trimester; perception of CAM safety in comparison to conventional medicines; and preference for CAM in treating medical conditions.

Results: Six hundred and seven women were approached of which 560 participated in the study; their age was 31.9 ± 5.1 years. 40.5% of them had used at least one form of CAM in the first trimester. When asked to compare the safety of CAM to conventional medicines, 12.3% felt CAM is safer, 27% thought both CAM and conventional medicines are equally safe, 15.9% felt CAM is less safe while 44.8% felt they did not know about the safety of CAM compared to conventional medicines. In treating a new medical condition, 17.1% of the participants would choose CAM rather than conventional medicines as their most preferred therapy.

Conclusions: These findings demonstrate that a considerable proportion of the women had used CAM in early pregnancy. Although almost half of the participants did not know about the safety of CAM compared to conventional medicines, nearly a fifth would want CAM as a first choice therapy. Therefore, routine counselling about CAM is important during antenatal assessments. Further research is also necessary to better understand CAM use in pregnancy.

Keywords: Pregnant, Complementary and alternative medicine, epidemiology

Outcomes of pregnancies for women prescribed angiotensin converting enzyme inhibitors or angiotensin receptor antagonists in semester two or three

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Aim/Objective: When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause harm and even death in the developing fetus. This study describes the dispensing patterns of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor antagonists (ARB) in pregnant women.

Methods: The study population included all women giving birth in Western Australia during 2002-2005 with a birth record in the Midwives' Notification System and a hospital admission record in the Hospital Morbidity Data System: N=96,698. Records were linked to the Pharmaceutical Benefits Scheme and the Birth Defects Registry of Western Australia. Outcomes for pregnancies of women dispensed either an ACE inhibitor or an ARB were compared with all other women not dispensed an antihypertensive.

Results: There were 95 women dispensed an ACE inhibitor and 40 women dispensed an ARB, which represented 132 individual pregnancies and 134 infants. 44 (33.3%) of these women were dispensed either medicine in trimester 2 or 3, contrary to recommendations for use in pregnancy. There were 2 (2.1%) children still born, compared with 634 (0.7%) in the children of women not dispensed an antihypertensive during their pregnancy: OR (95% CI): 2.3 (0.6-9.4).

Conclusions: A number of pregnant women are being prescribed medicines that may cause serious harm or death to their infant, contrary to recommendations.

Keywords: angiotensin converting enzyme inhibitors, angiotensin receptor antagonists, pregnancy, outcomes

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Epidemiology of antibiotic associated diarrhea in critically ill patients: a retrospective study from a tertiary care centre in India

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Aim/Objective: The aim of this retrospective study was to determine the prevalence of antibiotic associated diarrhea (AAD) in the intensive care unit of our institute and the possible risk factors in its acquisition.

Methods: The database searched all the admitted patients in our intensive care unit (ICU) between 2007 and 2012 developing diarrhea following antibiotic therapy. The number of such patients who tested positive for Clostridium difficile toxin in stool was retrieved. The time and duration of antibiotic therapy, presence of concurrent illnesses, interventions performed, if any were recorded. The patients with prior gastrointestinal diseases were excluded. Statistical analysis was performed using SPSS (version 14.0).

Results: A total of 153 (28.0%) out 546 patients developed diarrhea and 112 (20.5%) patients tested positive for Clostridium difficile toxin in stool. The median duration of diarrhea was 5 days. 58.9% patients received cephalosporins, 33.0% patients received fluoroquinolones and 8.0% patients received glycopeptides. 34.8% patients were treated with vancomycin and 57.1% patients were treated with metronidazole. The median duration of treatment was 7 days for both. In comparison to the control group, the AAD group had higher incidence of diabetes, malignancy and length of ICU stay. On multivariate analysis, exposure to chemotherapeutic drugs and malignancy were significant variables associated with AAD.

Conclusion: The study demonstrated the prevalence of AAD and Clostridium difficile associated diarrhea in our ICU. Cephalosporins were the main culprits while both vancomycin and metronidazole were effective treatments. The risk of AAD was higher in cancer patients with exposure to chemotherapeutic drugs.

Keywords: Antibiotic associated diarrhea, Clostridium difficile, intensive care unit

Risks of drug therapy in hospitalised children and adolescents in Germany – a prospective cohort study

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Aim/Objective: Children and adolescents are at particular risk during drug therapy due to off-label use, lack of age-appropriate formulations and individual dose calculations. Identifying drug related problems (DRPs) enables risk quantification; the potential impact of prevention strategies can be determined. We systematically investigated DRPs in hospitalised paediatric patients in Germany prior to the implementation of an electronic prescribing system (EPS).
Methods: An observational study was carried out during a 3-month period on a general paediatric ward. All patients aged 0 to <18 years were observed and assessed with respect to DRPs. The identification of these was based on intensive chart review and regular interviews of nurses. A modified version of the PCNE Classification for Drug related problems (V5.01) was used for categorisation.
Results: The incidence of DRPs was 79.7% (DRPs n=617, patients n=232) with a median number of 2 DRPs per patient; 59.1% (n=137) of patients had at least one severe or moderate DRP In total 0.5% (n=3) of DRPs were classified as severe, 55.3% (n=341) as moderate and 44.2% (n=273) as minor. Most DRPs were preventable and occurred during the prescribing (n=221, 39.3%) and documentation (n=179, 31.8%) process. DRPs were most frequently associated with analgesics and anti-epileptics.
Conclusion: This study clearly shows that drug therapy in children and adolescents is a high risk process. Prescribing and documentation appears to be most problematic, thus there is huge potential for EPS. This has already been shown in adult inpatients; however, paediatric data are still scarce.
Keywords: drug related problem, drug safety risk, paediatric, hospitalisation

Drug utilisation patterns in hospitalised children: An international perspective

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Aim/Objective: The majority of published drug utilisation studies in children come from primary care. Our aim was to investigate and compare patterns of drug therapy in hospitalised children in five European and Non-European countries using a standardised protocol and terminologies.
Methods: A prospective cohort study was conducted on paediatric medical wards in UK, Germany, Australia, Hong Kong (HK), and Malaysia. Drugs prescribed were classified using WHO Anatomical Therapeutic Chemical (ATC) classification. The frequency of prescriptions and exposure rates were calculated at ATC anatomic and therapeutic levels overall and stratified by country.
Results: 1278 patients were included (Australia 146, Germany 376, UK 313, HK 143, Malaysia 300). 1140 patients (89.2%) received 5367 prescriptions, median 3 per patient (IQR 2-5).
The three most frequently prescribed therapeutic groups were; systemic antibacterials [1355 (25.3%), exposure (65.1%)], analgesics/NSAIDs [1172 (21.8%), exposure (63.6%)], 'drugs for obstructive airway diseases' [472 (8.8%), exposure (23.6%)]. Number of patients exposed to these groups differed significantly between countries p<0.05. Patients' exposure to systemic antibacterials was highest in Malaysia (84.7%), lowest in HK (37.1%). Patients' exposure to analgesics/NSAIDs varied significantly between countries being highest in UK (84.2%,) and lowest in HK (35,3%), p<0.001. Paracetamol was the most frequent analgesic/NSAID in 4 countries. Metamizol was only prescribed in Germany whereas morphine was predominantly prescribed in the UK.
Conclusion: This study shows that there are similarities but also significant differences in drug utilisation patterns in hospitalised children across countries. Rational drug therapy has to be further investigated and promoted in paediatric medicine.
Keywords: drug utilisation, paediatric, international

Leukotriene receptor antagonists and suicide: a self-controlled case series study

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Aim/Objective: In March 2008 the suicide of a 15 year old boy captured media attention. The suicide was attributed to the exposure of montelukast, a leukotriene receptor antagonist (LTRA) used to treat asthma and allergies. The presence of, unknown and unmeasured confounders are limitations in observational studies, particularly in the study of suicide which has several risk factors. The self-controlled case series (SCCS) method automatically controls for fixed confounders.
Objectives: To investigate the association of suicide and LTRAs using the SCCS method in the UK.
Method: Electronic healthcare records of patients with a record of suicide attempt (including suicide and self -harm, poisoning-self-inflicted, injury–self inflicted, cause of overdose-deliberate) and exposure to LTRAs during the period of 1st January 1998 to 1st January 2011 were extracted from the Health Improvement Network (THIN) database of anonymised records from contributing UK general practices. A risk period of thirty days before and after exposure to LTRA and control periods within the observation time of each patient were identified. A Poisson analysis conditioned on the event was used to calculate the Incidence Rate Ratio (IRR).
Results: A total of 236 cases of first attempts of suicide were identified. The IRR for a risk period of 30 days after the start of treatment with LTRA was 0.32 (95% CI 0.04-2.42; P=0.268).
Conclusion: Our study does not support the association between the use of LTRA and suicide attempts within the first thirty days of exposure to LTRA. Further studies with larger number of cases are needed.

Attention-deficit/ hyperactivity disorder drug prescribing trend is increasing among children and adolescents in Hong Kong

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Aim/Objective: To investigate the prevalence of ADHD medication prescribing of children and adolescents in Hong Kong from 2001-2012 and to compare local prescribing patterns to those in other countries.
Methods: An observational study was conducted using Hong Kong Hospital Authority Clinical Data Analysis & Reporting System (CDARS) to investigate the epidemiology of children and adolescents receiving ADHD medication. Records of children and adolescents aged between 3-19 years who were prescribed either methylphenidate or atomoxetine from 2001-2012 were retrieved. The prevalence of children and adolescents prescribed ADHD medication was calculated. Microsoft Excel and Statistical Analysis System (SAS) v9.3 (SAS Inc., United States) were used for data manipulation and analysis.
Results: Prevalence of children on ADHD medication increased from 0.072% in 2001 (95% Confidence interval [CI] 0.068% to 0.077%) to 0.819% (95% CI 0.803% to 0.837%) in 2012. The prevalence demonstrated an increasing trend throughout the study period (Z=-149.735, P<0.0001). The prevalence of ADHD medication prescribing in females increased at a faster rate than that in males. The prescribing trend in kindergarten children (3-5 year-old) was relatively steady from 2001-2008 [0.025% (95% CI 0.019% to 0.033%) in 2001] until a marked increase from 2009-2012 [0.135% (95% CI 0.118% to 0.154%) in 2012].
Conclusion: The prevalence of ADHD medication prescribing in Hong Kong is increasing but still lower than most western countries. However, the prevalence of ADHD medication prescribing for kindergarten children has increased in recent years. It is important to continue to monitor the prescribing in this group of vulnerable patients.
Keywords: Attention deficit hyperactivity disorder, Hong Kong, children, prescribing

Pharmacological treatments prescribed to young people with autism spectrum disorder (ASD) in UK primary care

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Aims/Objective: Little is known about patterns of pharmacological treatment and associated co-morbidities in ASD. We assessed the prevalence of ASD, psychotropic drug prescribing and neuropsychiatric co-morbidities in young people.
Methods: A descriptive cohort study using The Health Improvement Network database of UK patient records. Individuals aged <25 years with a diagnosis of ASD during 1992-2008 were identified. Annual ASD prevalence and proportions of the cohort prescribed psychotropic medications or with neuropsychiatric co-morbidities were calculated.
Results: Psychotropic drugs were prescribed to 29% (1,619/5,651) of the cohort; the most prescribed drugs were sleep medication (9.7%), psychostimulants (7.9%), antipsychotics (7.3%). Psychostimulant prescribing increased from 1.5% to 6.3% (1999 to 2008). Neuropsychiatric co-morbidities were seen in 37% of patients; developmental difficulties/learning disability were most common (12.6%).
Conclusions: Use of psychostimulants and antipsychotics is much higher in those with ASD than in the general population. Further studies examining their efficacy and long-term safety are needed.
Keywords: autism spectrum disorder, psychotropic drugs, co-morbidities, prevalence.

Pharmacogenetics of weight gain in young people treated with Risperidone

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Aim/Objective: To investigate the association between weight gain and specific genotypes in young people treated with risperidone.
• To genotype three specific genes (HTR2c receptors, LEP and LEPR) which are thought to be likely candidates for association between risperidone and weight gain.
• To assess the association between the genotypes of each gene and weight gain.
Methods: A retrospective multicentre study was conducted in outpatient mental health clinics/hospitals in the UK and the Kingdom of Saudi Arabia. Analysis was undertaken using TaqMan technology for genotyping and for statistical analysis, SPSS 21 for Windows was used.
Results: 200 patients were genotyped, and 197 genotypes were successfully "Called". All genotyping passed Hardy-Weinberg checking. For all genes, we found no significant association with risperidone –induced weight gain after controlling for baseline weight, age, diagnosis and ethnicity. Significant association was found between baseline BMI-Z, patients with a lower baseline BMI gaining more weight; age at onset of risperidone treatment (p<0.005), younger patients tending to gain more weight (p<0.005) for all 5 SNPs tested, and a significant association between weight gain and ethnicity, individuals of Arab origin being more likely to gain weight than Caucasians (p=0.011- p=0,014) for all SNPs. No association with gender was found for any genotypes.
Conclusion: In this sample there does not appear to have been a significant association with risperidone-induced weight gain and any of the genotypes tested. Further studies exploring ethnic variations and age at onset of treatment are warranted, and a larger sample may have yielded more significant results.
Keywords: risperidone, weight gain, children, pharmacogenetics

Risk factors associated with drug-related problems in hospitalised paediatric nephrology patients

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Aim/Objective: To determine the potential risk factors for the occurrence of drug—related problems (DRPs) in hospitalised paediatric nephrology patients.

Methods: A prospective cohort study conducted in two paediatric nephrology wards over a ten-month period from December 2011 to September 2012. Inclusion criteria were all children aged 18 years and younger, received at least one drug throughout hospitalisation and given for more than 24 hours. DRPs were identified by clinical pharmacists during ward rounds and discussion with the medical team. Patients' characteristics and the nature of DRPs were documented into a specific proforma. The risk factors were tested for age, gender, length of hospital stay, number of drugs prescribed and types of renal replacement therapy using multivariate logistic regression at patient level. A p values less than 0.05 were considered statistically significant.

Results: A total of 171 patients were recruited of which 132 were included in the analysis. The multivariate modelling showed that only numbers of drug prescribed were significantly associated with the occurrence of DRP (OR 1.05, 95% CI 1.00-1.09, p=0.024).

Conclusion: Whilst many factors may be associated with drug related problems in children and their associations may be cumulative and interdependent, the only independent predictor for the occurrence of DRPs in hospitalised paediatric nephrology patients is the greater number of drugs prescribed.

Serious adverse drug events during deferiprone therapy in paediatric thalassaemia Patients

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Aim/Objective: Iron-chelation therapy is essential for transfusion-dependent thalassaemia patients. Children are particularly affected by this disease and require early chelation therapy to avoid the long term effects of iron overload. Knowledge on the incidence and nature of serious adverse drug events (e.g. neutropenia, agranulocytosis) that may lead to treatment termination is of importance in this lifelong therapy.

Methods: The Hong Kong Clinical Data Analysis and Reporting System (CDARS) comprising data of more than 7 million patients was used to extract all thalassaemia patients who were receiving deferiprone below the age of 18 years. Adverse drug events (ADE) were identified using a selected list of ICD-9 codes and laboratory data. All identified events were assessed for causality by reviewing concomitant medications, diagnoses and laboratory data.

Results: 93 patients were eligible for analysis; median age was 14 years (IQR 12-16). Median duration of deferiprone therapy was 18 months (IQR 7-32). 17 patients received monotherapy and 76 combination therapy with deferoxamine. Overall incidence rates for neutropenia, agranulocytosis, elevated liver enzymes and arthropathies were 9.7%, 5.4%, 8.6% and 3.2%; in patients with monotherapy 5.9%, 0%, 17.6% and 5.9% and with combination therapy 10.5%, 7.9%, 6.6% and 2.6%, respectively. 10 patients stopped deferiprone therapy during observation; 5, 3 and 2 patients due to agranulocytosis, arthropathies and elevated liver enzymes, respectively. 48.3% of these ADEs occurred during the first 3 months of therapy.

Conclusion: Combination therapy seems to be more prone for serious ADEs than monotherapy. This association must be further investigated in larger cohorts and clinical settings in paediatric patients.

Keywords: deferiprone, thalassaemia, adverse drug event, children

Medicine use among the frail and non-frail elderly

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Aim/Objective: To compare the use of medicines in the frail and non-frail elderly.

Methods: A cross sectional analysis using data from a longitudinal study of ageing which included 2087 participants, aged 65 year old and over. Frailty status was defined using a multidimensional frailty measure – frailty index, which consists of assessments on physical, psychological, and medical characteristics. Medicine use, number of medicines used, and types of medicine used were compared between the frail and non-frail. Logistic regression analysis was used to determine the association between frailty status and polypharmacy (≥5 medicines).

Results: 17% (366/2087) of the cohort were identified as frail. 98% in the frail group and 85% in the non-frail group were taking at least one medicine. The median number of medicines was higher in the frail group: 5 (interquartile range (IQR): 3-7) compared to 2 (IQR: 1-4) in the non-frail group. There was a significant association between frailty and polypharmacy, odds ratio: 2.84 (95% confidence interval: 2.15 – 3.76) after adjusting for age, gender, and number of comorbidities. Cardiac medicines were the most commonly used medicine class (77% in the frail and 54% in the non-frail). Benzodiazepines were used by 28% of the frail compared to only 11% of the non-frail.

Conclusion: The frail elderly are more likely to use five or more medicines. The high use of benzodiazepines in those who are frail may lead to an increased risk of adverse events.

Keywords: medicine use, elderly, frailty, polypharmacy

Prevalence of Potentially Inappropriate Medication (PIM) and Factors associated with PIM in Elderly Outpatient Prescriptions at a District Hospital in the Southern Region of Thailand

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Aim/Objective: The study's objectives are to know the prevalence of, and to describe factors associated with prescribing PIM at a district hospital in the south of Thailand.

Methods: In this cross-sectional study conducting the retrospective data in a district hospital during October 1, 2011 to September 30, 2012, the study participants were a ≥ 65-year outpatient and had at least 1 prescribed medication from the hospital. 430 out of 5,265 participants were randomized and their 2,128 prescriptions were examined. 2012 Beers criteria was applied.

Results: 39.1% of all participants were female and 53.7% aged 65-74 years; 28.1% of total prescriptions had at least 1 PIM. The highest prevalence of PIM prescription was observed in mental and behavioural disorders, while, Lorazepam was mostly frequent prescribed. There was the more likelihood of PIM prescription at outpatient department increased significantly when that prescription comprised of more than 5 medications (p<0.001). The positive association between age of participant and the presence of PIM prescription was observed (OR=1.018, p= 0.040, CI=1.001-1.035). The elderly outpatients who had more frequent outpatient visits had less PIM prescription than patients who had 1-3 visits. (4-6 vs. ≥7: OR = 0.581 [95%CI=0.408-0.828], p=0.003 vs. OR=0.704 [95%CI=0.526-0.943], p=0.019) No statistically significant association between the presence of PIM and patient's gender, number of diagnoses, health insurance schemes, inpatient admissions, prescriber's characteristics.

Conclusion: 28.1% of prescriptions had at least 1 PIM in the study year. A number of medications, patient's age, and outpatient visits had a strong association with PIM incident.

Keywords: Potentially Inappropriate Medication (PIM), prevalence, factors, elderly, Beers criteria

Incidence and Risk of Osteonecrosis of the Jaw (ONJ) among the Taiwan Osteoporosis Population

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Aim/Objective: Information of ONJ in Asian populations is lacking. Our study intended to compare the incidence and risk of ONJ between patients receiving alendronate and those receiving non-bisphosphonate osteoporosis medications in Taiwan.
Methods: From 2003-2006, Enrollees in the National Health Insurance Research Database (NHIRD) aged above 50 years, with vertebral/hip fracture and new to osteoporosis therapy were recruited. Patients had Paget's disease or cancer during baseline period were excluded. Patients were classified into alendronate or calcitonin/raloxifene (control) group according to the exposure after follow-up. Previous proposed possible ONJ diagnosis codes were adopted as potential ONJ cases, and these cases had to be with persisted ONJ symptoms for more than 8 weeks and no history of radiation to the jaws and ever received any broad-spectrum oral antibiotics. We used Cox modeling to compare the risk of ONJ between the alendronate and the control group, which was matched with the propensity score. Results were examined in series sensitivity analyses, including different cumulative doses group.
Results: A total of 16,003 patients were matched by propensity score, and over the 4-year follow-up period, no increased risk of ONJ in the alendronate group in the original (HR, 0.87; 95% CI, 0.47-1.58) and propensity score-matched cohorts (HR, 0.86; 95% CI, 0.44-1.69) was found. A similar incidence of ONJ was observed in all comparison groups, ranging from 6.9-8.2/10,000 person-year.
Conclusion: No excess risk for ONJ was found in osteoporosis patients >50 years old using alendronate as compared with patients using raloxifene or calcitonin under real-world conditions.
Keywords: pharmacoepidemiology; osteoporosis; alendronate; osteonecrosis of the jaw

Drug-drug interactions with antiepileptic drugs in elderly patients with epilepsy in Taiwan

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Aim/Objective: To evaluate the degree and associated risk factors of drug–drug interactions with antiepileptic drugs (AED-DDIs) in elderly patients with epilepsy in Taiwan.
Methods: A retrospective cohort study was conducted by using Taiwan's National Health Insurance Research Database (NHIRD). Patients aged 65 or older with epilepsy defined by ICD-9 code 345 from 2005 to 2009 were included. From the date of AEDs initiation, patients were followed until the end of one year, discontinuation, switch/add-on, or disenrollment. Medications with AED-DDIs were defined by Drug Interaction Facts 2013. DDI score were calculated as primary indicator of AED-DDIs degree, defining as days of medication with AED-DDIs supplied divided by follow-up days. Multivariate linear regression models were used to identify risk factors associated with AED-DDIs.
Results: A total of 5,785 elderly patients with epilepsy were identified with mean age was 76.61 (±7.15) years and 55.9% were male. The mean DDI score of all patients was 0.68 (±0.80), and the highest score were found in patient receiving phenytoin (0.94) and carbamazepine (0.99). Individuals receiving traditional AEDs [β=0.72; 95% CI: 0.65, 0.78], being cared by specialist other than neurologist [β=0.07; 95% CI: 0.03, 0.12], and receiving more than six chronic conditions drugs [β=0.20; 95% CI: 0.15, 0.25] were associated with higher AED-DDIs score.
Conclusion: A high degree of AED-DDIs in elderly patients with epilepsy warrants clinical attentions. Numbers of risk factors were identified and can be strong grounds for future investigations and policy decisions.
Keywords: elderly, epilepsy, drug-drug interaction, risk factors

Age differences in the use of guideline-recommended medication treatment and in-hospital mortality for acute myocardial infarction in China

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Aims/Objectives: To analyze the age differences in the use of these medications and in-hospital mortality of patients with AMI in China.

Methods: Use of aspirin, clopidogrel, β-Blockers, angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARB), and statins within 24h at presentation of 4,714 AMI patients were analyzed using a centralized data warehouse, which includes hospital information system (HIS) in 14 Chinese hospitals between 2005 and 2011. Hierarchical logistic regression was used to analyze the factors associated with medication use and in-hospital mortality.

Results: 2312 (49.0%) patients were aged 18 to 64 years, 1282 (27.2%) 65 to 74 years, 1120 (23.8%) older than 75 years. Older patients had higher prevalence of most comorbidities compared to younger patients, except for hyperlipidemia. Guideline-recommended medications were used less often among patients aged >/=75 and 65-74 years than among those aged <65 years (P<0.001 for all). In-hospital mortality in those three age subgroups were 24.1%, 12.3%, 4.7%, respectively (P<0.001). After multifactor adjustment, the mortality of older patients was substantially higher compared to younger patients (adjusted OR 2.23, 95% CI 1.63-3.06 for aged 65-74 years vs. <65 years; adjusted OR 3.95, 95% CI 2.92-5.34 for aged >/=75 years vs. <65 years).

Conclusion: Elderly patients have higher mortality than younger patients, however, they are less likely to receive guideline recommended medications. Clinicians should be encouraged to use some objective data to carefully weigh risks and benefits before withholding evidence-based therapies in these patients.

Keywords: acute myocardial infarction, guideline-recommended medications, in-hospital mortality

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Utilization pattern and healthcare resources evaluation of Japanese insulin initiators during their first year using DPC hospital claims database

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Aim/Objective: To describe the insulin utilization pattern and its associated healthcare resources use among Japanese type 2 diabetes patients initiating insulin.

Methods: Data from an administrative database consisting of 120 Diagnosis Procedure Combination (DPC) hospitals were used. Hospital claims between April 2008 and August 2012 were analyzed. Patients were diagnosed with type 2 diabetes and had at least three insulin claims (identified using International Classification of Diseases-10 code) during their first year of insulin therapy to be eligible for this study.

Results: The mean age of patients (n=4,814) was 69.3 years and 61% was male. Baseline mean HbA1c level was 7.4% (only available among 567 patients). Two thirds of patients (n=3,184) used non-intensive regimen (insulin monotherapy) during their first year of insulin treatment. 15.0% (n=723) of patients had a 100+ days gap between their insulin claims and half of them received oral diabetic medication during their break from insulin therapy.

88.0% (n=4,236) of patients were hospitalized when insulin therapy started and 47.5% of them (n=2,011) had re-admissions. The median length of stay per hospitalization was 28.0 days, insulin use covered 49.3% of their length of stay. The median cost per diabetic-related hospitalization was 619,814 JPY. Only 2.6% (n=124) of patients had emergency room visits (Median: 1.0 visit/year).

Conclusion: Majority of diabetic patients initiated insulin treatment in hospitals and almost half being readmitted within the year. They are more likely to receive non-intensive regimen. Further research is needed to understand what underlies the treatment pattern among insulin initiators.

Keywords: Japan, type 2 diabetes, insulin

Chemotherapy Treatment Patterns and Mortality of Lung Cancer Patients in Taiwan

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Aim/Objectives: To examine chemotherapy treatment patterns and mortality of lung cancer patients in Taiwan.

Methods: Medical and pharmacy claims 2000-2008 were analyzed of one million persons randomly taken from beneficiaries covered under Taiwan's national health insurance in 2000. The study identified newly diagnosed lung cancer patients between 2000 and 2008 based on medical claims with associated diagnoses (first observed diagnosis set as the index date). Patients were followed to the end of 2008 or until death, whichever comes first. Chemotherapy treatment patterns during the follow-up were examined and median survival was reported.

Results: This study included 3,343 lung cancer patients (mean age: 67.1 years; 34.5% female; 35.4% secondary lung cancer). Median survival was 8.1 months. Of the 1,952 patients who received chemotherapy, surgery, or radiation therapy, 71.7% received chemotherapy as the first-line treatment. Of the 1,633 patients who received chemotherapy during the follow-up, 375 received only one chemotherapy agent (gemcitabine 35.7%, vinorelbine 20.5%, platinum-based agents 20.3%, UFUR 8.3%, taxanes 7.7%, etoposide 7.5%). Among patients treated with chemotherapy, nearly three quarters (74.8%) of treated patients received combination therapy with platinum-based agents. Of the 1,221 patients treated with platinum-based therapy, the therapy was most commonly combined with gemcitabine (37.5%), taxanes (21.5%), and vinorelbine (18.2%), while 21.4% of patients received two or more other agents. We observed longer median survival in patients with a higher number of chemotherapy agents received.

Conclusions: More than half of lung cancer patients were treated with chemotherapy, in particular with multiple chemotherapy agents. Future research assessing comparative-effectiveness among different treatment options is warranted.

Effectiveness of respiratory syncytial virus immunoprophylaxis on bronchiolitis morbidity among high-risk infants

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Aim/Objective: Randomized clinical trials have demonstrated the efficacy of respiratory syncytial virus (RSV) immunoprophylaxis. Effectiveness of RSV immunoprophylaxis has not been well studied.

Methods: We conducted a population-based cohort study of 211,098 infants, a subset of the PRIMA cohort (Prevention of RSV: Impact on Morbidity and Asthma), who were continuously enrolled in Kaiser Permanente healthplan. RSV immunoprophylaxis administration was identified during the RSV season (November – March) of the first year of life. The RSV immunoprophylaxis "protected period" was assumed to last 30 days; the "unprotected period" was defined as all other days. Incidence rates of bronchiolitis hospitalization and any healthcare visits during the "protected" and "unprotected" periods were reported. Poisson regression and multivariable Cox regression were applied to estimate the effect of RSV immunoprophylaxis on bronchiolitis related morbidity.

Results and conclusions: Among 211,098 births, 3,444 (1.63%) infants were eligible for immunoprophylaxis based on the American Academy of Pediatrics guidelines. 3210 (1.52%) subjects, both eligible and ineligible, received at least one dose of RSV immunoprophylaxis. Infants who ever received immunoprophylaxis had a 35% decreased risk of bronchiolitis hospitalization (incidence rate ratio [IRR]: 0.65; 95% confidence interval [CI]: 0.46, 0.93), or a 37% decreased risk in a Cox model after adjusting for covariates (adjusted hazard ratio [aHR]: 0.63, 95%CI: 0.44, 0.91). Infants with chronic lung disease (CLD) had the highest risk reduction (IRR: 0.43, 95%CI: 0.23, 0.81; aHR: 0.50, 95%CI: 0.26, 0.96). RSV immunoprophylaxis was as effective as in clinical trials in a healthplan population, and infants with CLD benefited most.

Keywords: respiratory syncytial virus immunoprophylaxis, bronchiolitis morbidity, treatment effectiveness

The discrepancy of disease severity and medication use among patients diagnosed with moderate chronic obstructive pulmonary disease

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Aim/Objective: Upon 2009 guideline of Global Initiative for Chronic Obstructive Lung Disease (GOLD), the inhaled corticosteroids (ICS) were added whenever patients were diagnosed with severe or very severe Chronic Obstructive Pulmonary Diseases (COPDs). The aim of this study was to assess the discrepancy of disease severity and medication prescriptions among moderate COPD patients.
Methods: The in-house databases and electronic medical records in China Medical University Hospital, a 2000-bed medical center, were utilized. Those COPD outpatients aged greater than 40-year-old and were ever prescribed with any of respiratory medications in 2009 were evaluated for their lung functions, diagnosis and medications. Focusing on those moderate COPD patients categorized based upon 2009 GOLD guideline, those who were prescribed with bronchodilators only and combined with ICS were compared with their demographic data, disease severity recorded by physicians using inferential analysis approaches.
Results: There were 1,794 respiratory medications prescribed for 1,093 COPD patients in 2009. Of 180 patients categorized with moderate COPD, 98 ever received bronchodilator only and 82 received combined ICS. With no statistically significant differences in demographic information, 58.8% and 37.8% of them, respectively, had consistent disease severity upon physicians' diagnosis records, but 59.8% and 40%, respectively, were diagnosed with severe COPD.
Conclusion: With high inconsistent rates of COPD severity comparing 2009 GOLD classification with physicians' records, more moderate COPD patients were prescribed with combined ICS for severe COPDs diagnosed by physicians. Further evaluation would be warrant for outcomes for such discrepancies.
Keywords: diagnosis, medication treatments, chronic obstructive pulmonary disease

Patterns of respiratory medication regimen among chronic obstructive pulmonary disease patients in Taiwan

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Aim/Objectives: The respiratory medication regimens were various upon the disease severity and access of medications among patients with chronic obstructive pulmonary disease (COPD). The purpose of the current study was to explore the patterns of respiratory medication regimens across different levels of medical care settings among COPD patients in Taiwan.
Methods: A retrospective observational study was conducted using 2000 and 2005 Longitudinal Health Insurance Databases (two million random samples). Those national health insurance beneficiaries with any newly diagnosis for COPD in 2006 and aged greater than 40 year-old were examined for their one-year long respiratory medication regimens since the date of their first diagnosis of COPD.
Results: Of 7,838 newly-diagnosed COPD patients in 2006, 73.4% had been prescribed with any of respiratory medications. Of them, 65.6% were prescribed with any of controllers, whereas 12.5% were prescribed with inhaled controllers only. Regardless of disease severity, small-scale medical settings (community clinics and district hospitals) tended to prescribe with more rescue regiments than large-scale settings (regional hospitals and medical centers). About 40% were prescribed with oral theophylline alone across different medical settings.
Conclusion: The inhaled controllers were prescribed relatively less among COPD patients in small-scale medical settings than in large-scale settings, while oral theophylline was the primary choice across different settings in Taiwan. Further study is needed to explore the consequence of such phenomenon and its resolution.

Impact of Pneumococcal Conjugate Vaccines (PCV) on the incidence of community acquired pneumonia (CAP) in the UK

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Aims/Objectives: Heptavalent PCV (PCV7) was introduced into the UK vaccination schedule in September 2006 followed by 13-valent PCV (PCV13) in April 2010. In the US and Europe PCV7 reduced the incidence of invasive pneumococcal disease in children aged <5 years. Hospital pneumonia admission rates in England declined by 19% in the 2 years post-introduction (Koshy et al., 2010). We assessed the impact of PCVs on primary care diagnoses of CAP and associated antibiotic prescribing in children.
Methods: A descriptive cohort study was conducted using The Health Improvement Network database of anonymised patient health records for 5% of the UK population. The study population comprised children aged <16 years with ≥6 months' data and ≥1 pneumonia diagnosis recorded between 1 January 2002 and 31 December 2010. The duration of an episode of CAP was defined as 30 days. Annual incidences of CAP and antibiotic prescribing were calculated.
Results: CAP incidence declined by 13.3% for children aged <16 years between January 2006 and December 2010 from 1.07 episodes/1000 person-years (PY) to 0.92/1000 PY; the largest reductions were in younger age bands (28.3% in <2 years; 20.3% in 2-5 years; 27.8% in 6-10 years). Antibiotic prescribing decreased by 10.3% overall; however the steepest decline (44.2%) was seen in children aged <2 years from 0.74 treated-episodes/1000 PY in 2006 to 0.41/1000 PY in 2010.
Conclusion: PCVs have reduced the incidence of CAP diagnoses and antibiotic prescribing for CAP since their introduction; this is most evident in the main target group of young children <2 years.
Keywords: child, pneumococcal conjugate vaccine, respiratory tract infections, pneumococcal infections

Assessment on the combination therapy of inhaled corticosteroid and long-acting beta2 adrenergic agonist in asthma children in Taiwan

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Aim/Objective: This study was aimed to examine the appropriateness of initiation of inhaled corticosteroid and long-acting beta2 adrenergic agonist (ICS/LABA) combination therapy in asthma children in Taiwan.
Methods: We conducted a cross-sectional study by using National Health Insurance Research Database (NHIRD) 2007 in Taiwan. One-third of the children under 18 years of age were randomly selected from NHIRD, and children who had first prescription of fluticasone/salmeterol (FSC) or budesonide/formoterol (BFC) were included in this analysis. We retrieved patient's medical conditions in one year prior to the date of ICS/LABA initiation. Appropriate use of ICS/LABA was defined when met with one of the criteria: (1) use of ICS; (2) use of SABA (≥365 doses); (3) use of oral corticosteroids (OCS); (4) asthma-related emergency visit (use of OCS within 7 days after emergency visit); (5) asthma-related hospital admission during a 1-year period before ICS/LABA initiation. Multivariate logistic regression was used to examine factors associated with the appropriateness. Analyses were performed using the SAS statistical package.
Results: We identified 6,631 patients who met with the inclusion criteria with the mean age of 7.3 years (SD=4.31). 62.1% of the patients were male, 83.1% were prescribed with FSC therapy. Of the 6,631 patients, 4,137 (62.4%) met with 1 criterion for appropriate initiation of ICS/LABA therapy. Factors associated with appropriate use included age, prescriber specialty, comorbidity, region and hospital level.
Conclusion: Results from our study revealed that ICS/LABA therapy was initiated earlier than recommendation, which was inconsistent with GINA or NAEPP asthma guidelines.
Keywords: asthma, pediatric, appropriateness, ICS/LABA

Proportion of *staphylococcus aureus* and MRSA in patients with surgical site infections in mainland China: systematic review and meta-analysis

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Aim/Objective: We aimed to determine the proportion of *Staphylococcus Aureus* and MRSA in patients with surgical site infections in Mainland China.

Methods: We searched four Chinese electronic databases and PubMed to identify relevant studies. We assessed study quality using the revision of criteria by NICE and calculated the proportion of *S. aureus* and MRSA. Subgroup meta-analysis and Meta-regression were conducted to explore the sources of heterogeneity.

Results: Among 106 included studies, 39 studies were related to MRSA. Meta-analysis showed that S. aureus accounted for 19.1% (95% CI 17.3-21.1%) of all bacteria in SSIs. Subgroup analysis showed that the proportion of S. aureus in patients with thoracic surgery (41.1%, 95%CI 26.3-57.7%) was significantly higher than those with gynemetrics (20.1%, 15.6-25.6%) and abdominal surgery (14.9%, 9.3-22.9%). Meta-regression indicated that proportion of *S. aureus* was significantly lower in higher economic regions than lower ones (OR=0.753, 95%CI 0.577-0.983, P-value=0.037). MRSA accounted for 40.6% (95%CI 35.8-45.6%) of *S. aureus* isolates. MRSA resistant to vancomycin (0/513) or linezolid (0/70) were not found, while 79.9% (95%CI 67.4-88.4%) and 92.0% (95%CI 80.2-97.0%) of MRSA were resistant to clindamycin and erythromycin respectively.

Conclusion: The proportion of *S. aureus* SSIs in Mainland China is similar to North America. Nearly half of *S. aureus* were MRSA which were all sensitive to vancomycin or linezolid but mostly resistant to clindamycin and erythromycin.

Keywords: *S. Aureus*, MRSA, surgical site infections, proportion.

A score to identify stroke patients with poor functional outcome at discharge in the administrative database

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Aim/Objective: Functional outcome has been rarely assessed in stroke studies using administrative database. We aim to develop a risk score for identification of acute ischemic stroke (AIS) patients with poor functional outcome at discharge using claims data from Taiwan National Health Insurance Research Database.

Methods: Inpatient claims for AIS patients of a medical center were retrieved and matched with stroke registry data using sex, date of birth, admission, and discharge. A modified Rankin scale ≥ 3 in the registry data was considered the reference standard for poor outcome at discharge. Diagnostic and procedure claims codes selected from the logistic regression model were used to develop a score predicting poor outcome at discharge. The score of each candidate variable was determined by beta coefficient from the models with adjustment by age.

Results: Of the 1,555 AIS patients matched, 48% of them had poor outcome. The risk score derived for logistic models included per year increase of age (+1), male gender (-5), use of nasogastric (+30) and Foley (+25) tubes, diagnoses of cancer (+10), urinary tract infection (+15), and pneumonia (+10). A cutoff value of score 80 determined patients with and without poor functional outcome at discharge (c-statistic: 0.766).

Conclusion: Our risk score using variables of inpatient claims can be employed to determine AIS patients with poor functional outcome at discharge. It may be used in future effectiveness study of stroke treatment using NHIRD.

Keywords: acute ischemic stroke, functional outcome, administrative database, NHIRD

An investigation of the association between retinal detachment and oral fluoroquinolones: A self-controlled case series study

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Aim/Objective: To investigate the association between oral fluoroquinolones (FQ) and retinal detachment (RD) and to estimate the absolute risk of developing RD in patients exposed to oral FQ.

Methods: We performed a self-controlled case series study on Hong Kong, Taiwanese and British patients who had prescription(s) of oral FQ and RD procedure code(s) during 2001-2012; 2000-2010; and 1994-2012 respectively. Records were retrieved from the Hong Kong Clinical Data Analysis and Reporting System database, the Taiwan National Health Insurance Research Database and the United Kingdom IMS Disease Analyzer Database. Incidence rate ratios (IRR) are derived, by comparing the rate of RD during FQ exposed and non-exposed periods.

Results: A total of 1,516,566 FQ prescriptions were prescribed to 836,249 patients. There were 455, 1002, 861 cases in Hong Kong, Taiwan and United Kingdom respectively. A total of 13 events were found during the FQ exposed period; and 2,305 during the non-exposed period. The adjusted IRR for patients in Hong Kong, Taiwan and United Kingdom were 1.16 (95%CI 0.36-3.75), 1.70 (0.84-3.46) and 0.65 (0.16-2.63) respectively. In the combined model, there was no statistically significant association with an adjusted IRR of 1.27 (0.73-2.21). The crude absolute risk of RD whilst on oral FQ was approximately 1 per 150,000 prescriptions.

Conclusion: Our study does not support the association between the use of FQ and RD. Therefore, the use of FQ should not be precluded based on the current evidence on the risk of RD. However, a further study is warranted to investigate this controversial association.

Does preventively using hepatoprotectors in patients receiving anti-tuberculosis treatment effective and necessary?

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Aim/Objective: We aimed to explore effectiveness and safety of preventive hepatoprotectors usage in tuberculosis (TB) patients with anti-TB treatment.

Methods: With stratified cluster sampling strategy, a prospective cohort with 4488 sputum smears positive pulmonary TB patients were established from 52 counties of four regions in China. Blood routine, liver and renal functions were examined during anti-TB treatment. Prescriptions of hepatoprotectors and other drugs were documented in detail during treatment. ATLI was assessed based on liver function results following criteria of American Thoracic Society. The preventive effect of hepatoprotectors would be evaluated by using propensity score analysis.

Results: After 6-9 months monitoring, 4304 patients sustained in our cohort while 106 developed ATLI. 2751 patients preventively took hepatoprotectors with a median course of 183 days. Most frequently used drugs were liver-protecting tablet, silymarin, D-Glucurone and Creatinine. 51.0% patients took those drugs more than 6 months or during their whole anti-TB treatment course. Pre-existing diseases, Primary/re-treatment of TB, HBsAg status, family income per year and liver function before anti-TB treatment were proved to be affecting propensity of using hepatoprotectors. Statistical significances were not found by propensity score analysis for the association between using hepatoprotectors (OR=1.09, 95%CI: 0.71-1.67), using hepatoprotectors in the whole course (OR=1.03, 95%CI: 0.66-1.62), use silymarin, liver tablets and creatinine with ATLI occurrence. None adverse reactions induced by hepatoprotectors were spotted.

Conclusion: Although preventively using hepatoprotectors seems to be safe, the preventive effect was not observed in this study, which should be confirmed by large-scale randomized controlled trials.

Keywords: liver injury, tuberculosis, hepatoprotectors, cohort

Impact of concomitant use of proton pump inhibitors and dual antiplatelet therapy on recurrent myocardial infarction

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Aim/Objectives: To evaluate the association between concomitant use of proton pump inhibitors (PPIs) and risk of recurrent myocardial infarction in patients receiving dual antiplatelet therapy (DAPT) with aspirin and clopidogrel.

Methods: Using the Korean Health Insurance Review and Assessment Service database, a population-based retrospective cohort study was conducted in acute myocardial infarction (AMI, ICD-10; I21) patients aged 30 to 99 years old, received DAPT in ambulatory care setting from January 1, 2008 to December 31, 2010. The index date was defined as the first prescription date of DAPT within 90 days after discharge. Patients who received PPI treatment within DAPT duration were classified as PPI users. We matched each PPI user to one non-user using a propensity score. The Cox proportional hazards model was used to compare the risk of recurrent MI in users and nonusers of PPIs until December 31, 2011.

Results: We identified 43,822 AMI patients received DAPT with aspirin and clopidogrel, 16.7% of whom were PPI user and after matching by propensity score, 6,846 patients remained in each group. Compared to non-users, the adjusted hazard ratios (95% confidence interval) of PPI users for recurrent MI was aHR 1.26 (1.14-1.38). In patients with a proportion of days covered (PDC) lesser than 0.25, aHR was not significant (1.06, 0.95-1.19), while PDC greater than 0.75, aHR was higher (1.55, 1.33-1.81). In the subgroup analyses, there were no significant differences in risk of recurrent MI irrespective of gender, age, PCI performed, hypertension, diabetes mellitus and chronic renal failure.

Conclusion: The study result suggests a need for careful monitoring are needed when concomitant use of PPI in AMI patients receiving DAPT.

Keywords: acute myocardial infarction, proton pump inhibitor, antiplatelet drugs, drug interaction

Determinants of exposure to an evidence-based treatment of heart failure six months after diagnosis

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Aim/Objective: ndividuals with heart failure (HF) must use on one hand a beta-blocker and, on the other, an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker, or hydralazine + isosorbide dinitrate. We aimed to assess the proportion of HF elderly exposed to this evidence-based treatment six months after HF diagnosis and to identify determinants of exposure.

Methods: Using administrative data from the province of Quebec health insurance board we built a cohort of people aged 65 years + who were eligible to the public drug insurance plan during the twelve months preceding and the six months following their HF diagnosis. Were considered to be exposed to an evidence-based treatment those who had both a claim for a beta-blocker and a claim for one of the other drugs/combination covering the 6-month diagnosis anniversary date. Determinants of exposure were identified using a multivariate working-Poisson regression model.

Results: Out of 105,738 HF individuals, 28,619 (27.1%) were exposed to an evidence-based treatment six months after diagnosis. Were less likely to be exposed: women, the oldest, those who had their diagnosis at the beginning of the study period, those who used many drugs before diagnosis, had asthma, COPD, chronic kidney disease, dementia and non skin neoplasia. Were more likely to be exposed: individuals diagnosed at hospital, those who had ischemic heart disease, high blood pressure and diabetes.

Conclusion: Less than 1/3 of individuals with HF were exposed to an evidence-based treatment. Health characteristics seem to be major determinants of exposure to this treatment.

Keywords: heart failure, drug utilisation

Adoption of new molecular targeted drug among non-small lung cancer patients under National health insurance system in Taiwan

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Aim/Objective: Molecular targeted drugs (MTD), gefitinib and erlotinib, have been proven to provide clinical benefit to end-stage non-small cell lung cancer (NSCLC) patients. Therefore, access to such medical innovation in time is critical for patients who need it. The aim of this study is to explore determinants of adoption of MTD among NSCLC patients under Taiwan's National Health Insurance (NHI) system.

Methods: Using Taiwan's Longitudinal Health Insurance Database and Cancer Registry as data source, we identified 1,555 newly diagnosed NSCLC patients who initiated their cancer treatment between 2004 and 2009. Patients were categorized into "non-MTD adopters" and "MTD adopters" based on the cancer treatment they received. Logistic regression models were conducted to explore potential determinants associated with the adoption of MTD.

Results: Among 1,555 NSCLC patients, there were 562 (36.1%) "MTD adopters" and 993 (63.9%) "non-MTD adopters". Logistic regression shows that the elderly were less likely to receive MTD (OR=0.42; 95%CI: 0.29-0.61). In contrast, patients whose cancer stage was at end-stage (OR=1.44; 95%CI: 1.14-1.81) and whose cancer type was adenocarcinoma (OR=2.95; 95%CI: 2.10-4.16) were more likely to receive MTD. Those who went to private hospitals (OR=1.35; 95%CI: 1.03-1.78) and hospitals with big economic scale (OR=2.67; 95%: 1.79-3.98) were more likely to receive MTD as well.

Conclusion: Our findings suggest that both patient- and hospital-level characteristics significantly deterred the adoption of MTD among NSCLC patients.

Keywords: adoption, national health insurance research database (NHIRD), molecular targeted drug (MTD), non-small cell lung cancer (NSCLC)

Evaluation of counselling and booklet delivered by pharmacist impact to the treatment outcome of hypertension patients in Moeslim Private Hospital of Bantul, Yogyakarta

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Aim/Objective: The prevalence of hypertension in Indonesia is going increase. This phenomena could be caused by the increase of bad lifestyle such as, smoking, obesity, and psychosocial stress. The comprehensive treatment which are conducted by collaborative of health professional could show the better outcome of hypertension treatment. The role of pharmacist on medication counselling is expected to give the better control of blood pressure in hypertension patients. This study was aimed to explore the impact of counselling and booklet delivered by pharmacist to the patient's blood pressure in hypertension patients.

Methods: This study was designed as quasi-experimental study with prospective data taken during January to April 2013. We collected the data from 60 patients which were 30 patients as control group and 30 patients as intervention group. The patients who did not receive counselling and booklet from the pharmacist were categorized into control group and the patients who received counselling and booklet from the pharmacist were categorized into intervention group. This study was done in Moeslim Private Hospital of Bantul, Yogyakarta.

Results: The results showed that pharmacist counselling and booklet could decreased the systolic blood pressure (15.2 mmHg, p <0.05) and diastolic blood pressure (6 mmHg, p <0.05) in the intervention group. However, there was no decrease of the systolic blood pressure (1.27 mmHg, p=0.73) and diastolic blood pressure (0.43 mmHg, p=0.79) in the control group.

Conclusion: We concluded that the pharmacist counselling and booklet intervention can decrease blood pressure patients (p<0.05).

Keywords: counseling, booklet, hypertension

Impact of safety-related regulation on use of parenteral ketorolac in a nationally representative population

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Aim/Objective: Due to concerns on adverse events of ketorolac, the Taiwan Food and Drug Administration and Bureau of National Health Insurance issued a regulation for parenteral ketorolac, limiting its use for postoperative pain only, in July 2008. The objective of this study was to evaluate the impact of this regulatory action on use of parenteral ketorolac in a nationally representative population.

Methods: The data source of this study was the 2006-2010 Taiwan's National Health Insurance research database (NHIRD). The study employed a before-after design with a pre-regulation period consisting of a two-year control phase from July 1, 2006 through June 30, 2008 and a post-regulation period from July 1, 2008 through June 30, 2010. Monthly claim data on prescriptions of parenteral ketorolac two years before and after the regulatory action were analyzed. Demographics of patients who receive ketorolac and their prescribing physicians were examined.

Results: The proportion of non-compliance with the restriction among inpatient prescriptions of parenteral ketorolac decreased from 27.44% in the pre-regulation period to 24.63% in the post-regulation period. Half of inpatient prescriptions of parenteral ketorolac prescribed by physicians in the department of general medicine were non-compliant with the restriction in the pre- and post-regulation periods. Nevertheless, more than 90% of outpatient prescriptions of parenteral ketorolac in the pre- and post-regulation periods were non-compliant with the restriction.

Conclusions: Our study suggests that the impact of this safety-related regulation of parenteral ketorolac in Taiwan could be small. Further efforts are warranted to prompt the effectiveness of safety-related regulation.

Keywords: ketorolac, safety-related regulation

Taipei City household medical waste take-back station

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Aim/Objectives: Setting up "Taipei City Household Medical Waste Take-Back Station" is to promote the safe usage of medication, reduce medical resource waste, and provide channels for taking back medical waste.

Methods: The Department of Health of Taipei City Government are working with other local agencies to set up local take-back stations. Pharmacists at each station will classify the medical waste accordingly: solid medical waste, liquid medical waste, waste syringes and recyclable medical container waste. The pharmacists also provide educational information on the correct storage of medicine, and methods on how to self-inspect medicine, to improve medical safety knowledge.

Results: Over 360 "Household Medical Waste Take-Back Station" at community pharmacies, health centers and hospital pharmacies has been established. The program was initiated on April 2nd, 2010. Until 2012, 47,195 Kg of medical waste was taken back. The most is solid medical waste, and the next are liquid medical waste and waste syringes. If we sort medical waste by pharmacology, the majority are medicines for cardiovascular disease, common cold, and gastrointestinal upset.

Conclusion: The establishment of "Household Medical Waste Take-Back Station" in Taipei in the provision of pharmaceutical service is able to effectively reduce household medical waste and promote drug safety. The results demonstrate that it is promising to continue providing pharmaceutical services of taking back household medical waste in Taiwan.

Keywords: medical waste, take-back

Adherence and medication utilization patterns of fixed-dose and free combination of anti-hypertensive drugs among newly diagnosed hypertensive patients

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Aim/Objective: Adherence to anti-hypertensive medications, an important factor for hypertension control, was influenced by patients' co-morbidities, concurrent medications, ethnic populations, and insurance policy. This is a first study to compare the adherence and persistence among newly-diagnosed hypertensive patients using fixed-dose combination (FDC) and free combinations (FC) of angiotensin receptor blocker (ARB)/ thiazide in Taiwan population under nationwide health insurance coverage.

Methods: This is a retrospective cohort study using the National Health Insurance Research Database (NHIRD) in Taiwan. Newly-diagnosed hypertensive patients who initiated FDC or FC of ARB/thiazide diuretic between 2005 and 2008 were identified from the NHIRD. Adherence was measured by medication possession ratio (MPR) and persistence was defined as time from day of initiation to treatment discontinuation. General linear regression and Kaplan-Meier analyses were used to estimate the influence of FDC on adherence and persistence among hypertensive patients.

Results: We identified 7348 newly-diagnosed hypertensive patients. Among them, 77.9% use FDC and 28.1% use FC of ARB/ thiazide. Most demographic variables were balanced between the two groups, except for renal disease and anti-hypertensive prescriptions. After adjusting for covariates, FDC group demonstrated higher MPR (42.06% vs. 32.45%, p<0.0001) and lower likelihood of discontinuation at 2-year follow-up than FC group (HR=0.82, 95%CI=0.77-0.87).

Conclusion: Our findings suggest that use of FDC is associated with higher adherence and persistence rate than use of FC in newly-diagnosed hypertensive patients at 2-year follow-up period. Further studies are warranted to assess potential clinical benefits in terms of prevention of cardiovascular events associated with FDC of antihypertensive drugs.

Keywords: patient adherence, combination therapy, hypertension, fixed-dose combination, angiotensin receptor blocker, thiazide diuretic

Assessment of adverse drug reactions to anaesthetic agents in a tertiary care hospital

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Aim/Objective: To assess the prevalence, causality, severity, predictability, preventability; and to identify the risk factors for development of adverse drug reactions (ADRs) to anaesthetic agents.

Methods: Patients administered with pre-anaesthetics, local and general anaesthetics preceding to the surgery were enrolled into the study. The patients were monitored for occurrence of any ADRs during or after surgery. ADRs were coded according to WHO adverse reaction terminology. Causality of the reaction was assessed using WHO scale and Naranjo's algorithm. Severity was assessed by Modified Hartwig and Siegel scale and preventability by Modified Shumock and Thornton scale. Data was analysed by Chi square test. Risk factors for ADRs were identified by multiple logistic regression analysis.

Results: A total of 3,209 patients were enrolled into the study. 98 ADRs were observed in 75 patients [males 48 (53%) and females 50 (47%)] with a prevalence of 2.33%. Majority of ADRs were probable (79.6%) and moderate (66.3%) in severity. Amongst 98 ADRs, 46 (46.9%) were predictable and 57 (58.16%) were not preventable. Majority (40.8%) of ADRs were related to the system organ class skin and appendages. Local anaesthetics frequently caused ADRs (38.77%) followed by opioid analgesics (34.69%). The important risk factors for ADRs was found to be age >60 years [Odds Ratio (OR) 2.94, 95% Confidence Interval (CI) 1.81-4.71; p<0.0001] and one to two co-morbidities [OR 2.25, 95% CI 1.05-5.20; p=0.047].

Conclusion: Induction of anaesthesia presents highest risk of ADRs and it is important to monitor for ADRs, especially in elderly and patients with co-morbidities.

Keywords: adverse drug reactions, anaesthetic agents

Association analysis in adverse reactions of radiocontrast agent in regional pharmacovigilance Center

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Aim/Objective: Adverse reactions of radiocontrast agent probably involves direct cellular effects, enzyme induction, and activation of the complement, fibrinolytic, kinin, and other systems. In data mining, association rule learning is a popular and well researched method for discovering interesting relations between variables in large databases. The purpose of this study was to analyze the adverse reactions of radiocontrast agent using association rule mining (ARM).

Methods: The subjects were extracted from DSMD Regional Pharmacovigilance Center. A priori modeling of the ARM method was used to analyze subject data. Total subjects extracted 113 from DSMD Regional Pharmacovigilance Center from January to April 2013.

Results: As a result of ARM, If Age < 60 yrs and Itching then Urticaria (rule support, 23.89%; rule confidence, 79.41%; lift, 1.91). If Urticaria then Itching (rule support, 40.71%; rule confidence, 97.87%; lift, 1.78). If Itching then Urticaria (rule support, 40.71%; rule confidence, 74.19%; lift, 1.78). If Iopromide then male (rule support, 20.35%; rule confidence, 54.76%; lift, 1.17). If Urticaria then male (rule support, 22.12%; rule confidence, 53.19%; lift, 1.13). If Age < 60 yrs and Itching then male (rule support, 15.93%; rule confidence, 52.94%; lift, 1.13). If Urticaria and Itching then male (rule support, 21.24%; rule confidence, 52.17%; lift, 1.11). If male then Itching (rule support, 28.32%; rule confidence, 60.38%; lift, 1.10). If Itching then male (rule support, 28.32%; rule confidence, 51.61%; lift, 1.10). If Urticaria then Age < 60 yrs (rule support, 24.78%; rule confidence, 59.57%; lift, 1.04). If Urticaria and Itching then Age < 60 yrs (rule support, 23.89%; rule confidence, 58.70%; lift, 1.02).

Conclusion: On Lift's concepts showing, generated Lift's concepts of eleven in minimum support threshold 15%, minimum confidence threshold 50% level. All Lift's concepts suggested significant result.

Keywords: radiocontrast agent, adverse reaction, association rule mining, rule support, lift

Drug risk management in post marketing phase in Thailand

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Aim/Objective: The main objective is to describe risk management of medicinal products in process of risk minimization tools (Alert letters) released by Thai Food and Drug Administration (Thai FDA).

Methods: Retrospective study in alert letters or letters to healthcare professionals, released by the Drug Safety Advisory Committees was performed. They were elaborated to learn rate of releasing and drug-risk criteria.

Results: The alert letters or letters to healthcare professionals have been recommended by the Drug Safety Advisory Committees, Thailand. The releasing criteria have been evaluated. For the last 5 years, rate of using this tools have been increased as tool for mitigation of risk and public communication. Nearly 80% alert letters to healthcare professionals had information about drug-risk notification from changing safety profile to drug-risk decision or risk management in clinical setting in Thailand.

Conclusion: The risk minimization tools in releasing alert letters have been very effective to manage drug's risk before further evaluation of other safety measures. The mild action can be distributed directly to healthcare professionals. Many alert letters have been used to be one of drug risk management in clinical practice even they have not been legal applied for the whole system for using this risk minimization tools. Thai FDA should concern these tools to be one of drug risk management which are vastly affected to healthcare professionals.

Keywords: adverse drug reaction, drug risk management, post marketing surveillance

Poster Presentation

Drug therapeutic and adverse effects detecting system based on Taiwan national health insurance claims datasets

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Aim/Objective: To develop a user friendly information system that can rapidly detecting drug therapeutic and adverse effects based on Taiwan National Health Insurance (NHI) Claims Datasets.

Methods: The data source of this information system was one-million randomly sampled NHI enrollees in 2000, which include claims of all outpatient visits and inpatient hospitalization data between 1996 through 2011. We designed an information system that incorporated epidemiological study design and survival analysis modules, which can be easily accessed by the researchers.

Results: The user could enter the name of the drug of interest and the system would produce relative risk estimates such as hazard ratio (HR) of various disease categories or specific disease in relation to certain medication(s). The drug-outcome relationship can be determined by drug exposure of various measures. Level-1 measure: the scale of drug exposure was dichotomous (i.e., ever use versus never use). Level-2 measure: the scale of drug exposure was nominal (i.e., different level of exposure), which considers the duration and frequency of refills. Level-3 measure: the scale of drug exposure was interval which employed DDD (i.e., defined daily dose) to standardize the drug exposure and Cox proportion hazard model was used to compute the HRs. Level-4 design: confounding variables such as sex, age, comorbidities and co-medications would be entered into the hazard model to obtain the risk-set adjusted HR.

Conclusions: This risk detection system may rapidly and efficiently identify drugs that are potentially beneficial (relative risk estimate <1) or harmful (relative risk estimate <1) to health. While the preliminary risk estimation generated by this information system is not intended to draw firm conclusions regarding the therapeutic or side effects of drugs of interest, it can be used to call for further large-scale studies with detailed risk adjustment in order to substantiate or refute the preliminary results derived from the information system.

Keywords: drug therapeutic, drug adverse effect, Cox proportional hazard, data-driven analysis, population-based, information decision support system, administrative data

Frequency of causative drugs of severe cutaneous adverse reactions in the spontaneous report database of pharmacovigilance research network in Korea

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Aim/Objective: Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are diseases within the spectrum of severe cutaneous adverse reactions (SCARs) affecting skin and mucous membranes. The Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is another type of SCARs affecting internal organs with high mortality. There has been no nation-wide study for SCARs in Korea yet. Common causative drugs of SCARs in Korea were evaluated in this study.

Methods: Data collected in the Korean pharmacovigilance research network composed of 20 university hospitals all over the country from June 2009 to December 2010 were analyzed. Cases of SJS and TEN were extracted by diagnosis using WHO-ART 092 version. We sorted cases with eosinophilia and selected that reasonable to DRESS according to ResiSCAR scoring system to grade DRESS or physician's diagnosis. We analyzed reporters, age and gender of patients, route of administration and the number of cases according to causative drugs or ATC code categories.

Results: Total 100 cases of SJS (66 cases), TEN (7 cases) and DRESS (27 cases) were reported. Mean number of causative drugs per case was 1.6. Mean age of patients was 54.1±19.8 years. Total 81 kinds of drugs were reported as causative agents; SJS (61), TEN (16), and DRESS (29). The most commonly reported causative drug of SCARs was allopurinol (12 cases) followed by carbamazepine (6 cases), propionic acid derivatives (6 cases) and vancomycin (6 cases) in orders. Allopurinol was also the most commonly reported causative drug (8 cases) in SJS followed by carbamazepine (5 cases), lamotrigine (4 cases), paracetamol (4 cases) and propionic acid derivatives (4 cases) in orders. Levofloxacin (2 cases) was the most common causative agent in TEN. In DRESS, allopurinol (4 cases) and vancomycin (4 cases) were two most common causative drugs. Classified by ATC classification system, anti-infective drugs were the most common causative category (75 cases, 46.6%) including 24 cases related with beta-lactam antibiotics (32.0%).

Conclusion: Allopurinol was the most common single causative drug and the most common ATC category was anti-infective drugs in SJS, TEN, and DRESS in Korea.

Keywords: pharmacovigilance research network, SJS, TEN, DRESS

Pharmacoepidemiological researches in Hajj for pilgrimages; challenges and opportunities

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Aim/Objective: To determine pharmacoepidemiological studies and define the trend of drug use in Hajj period and to evaluate the adverse drug reactions as well as drug interactions monitoring using electronic medical record.

Methods: A systematic search from 1st January 2007 to 31 December 2012 of MEDLINE, ScienceDirect and World Health Organization databases was undertaken for relevant articles using the following terms combined with pharmacoepidemiology study (Hajj), (Pilgrimage), (Adverse drug reaction), (Electronic medical record, Pilgrimages) with inclusion criteria for only Hajj and excluded other studies for other events.

Results: No articles have been obtained using different keywords or demonstrated any data related to this aspect. Consequently, different articles have been speculated about the large number of population in Hajj period which has been estimated to be 2.5 million Muslims from over 160 countries travel to the same place and the risk of different health problem either illness or morbidity or eventually adverse drug reaction.

Conclusion: The Hajj pilgrimage in Mecca has been occurring at the same venue and at the same time and considered great opportunity for pharmacoepidemiological study of pattern of different diseases, monitoring adverse drug reactions of large population and prevent major health problem through electronic medical data base. Great attention should be given from the different governmental or international organizations to orient part of its fund to investigate the major health problem in the large number of population in order to improve the health services to pilgrimages during Hajj period.

Keyword: pharmacoepidemiology, Hajj, piligrimage, adverse drug reactions

Predicting relative risks from case-population data

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Background: The case-population approach in pharmacoepidemiology compares exposure in cases with exposure in the general population from which these cases originate. This implies identification of all cases, and accurate estimates of population exposure. Because this method may be used for rapid estimation of emerging risks, when exposure to a new drug is still low and events are rare, it is important to define how well the case-population ratio (CPR) estimates the relative risk (RR).

Methods: CPR is the ratio of exposure in cases to the exposure in the general population. CPR when divided by the ratio of non-exposure in cases to non-exposure in the population can be approximated to the Odds Ratio (OR). The Odds ratio is itself a good estimate of the RR when outcomes are rare. Results obtained using these calculations were compared in a case-population study of acute liver failure resulting in registration for transplantation (SALT).

Results: The CPR is all the better an estimate of RR when RR is closer to 1 and exposures low. Correcting CPR by the ratio of unexposed case rate to unexposed population rate results in exact RR. These computations are confirmed by the data from the SALT study.

Conclusion: When events are rare and exposures low, RR can be estimated by CPR (exposure rate in cases/exposure rate in the population), corrected when exposures are above 1% by (unexposed rate in cases/unexposed rate in population).

Psychiatric disorders associated with the treatment of multidrug-resistant tuberculosis: A systematic review and meta-analysis

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Aim/Objective: To systematically evaluate the incidence of psychiatric disorders in multi-drug resistant tuberculosis (MDR-TB) patients with the treatment of second-line anti-TB drugs.

Methods: MEDLINE, EMBASE and the Cochrane library were systematically searched from inception through October 1st, 2012 with the keywords including "Tuberculosis", "multidrug-resistant", "MDR-TB", "side effect", "adverse", "safety" and "tolerability" for the follow-up studies of MDR-TB patients with psychiatric disorders induced by second-line anti-TB drugs. Relevant information was extracted and data was analyzed using random-effects model. Subgroup and sensitivity analyses were performed based on diagnostic criteria, study population, study design, history of anti-TB treatment, HIV prevalence and treatment length.

Results: A total of 24 studies were included, and the weighted combined incidence of psychiatric disorders was 13.2% (95% CI: 9.9%-17.3%). There is a large degree of heterogeneity among the studies. Subgroup analyses showed that the incidence of psychiatric disorders was higher in groups with HIV prevalence> 0%, treatment length≥18 months and non-Asian populations, but there was no significant difference between groups (P>0.05). Among the 24 studies, only nine of them reported the diagnostic criteria of psychiatric disorders, while the criteria were not uniform.

Conclusion: The incidence of psychiatric disorders induced by second-line anti-TB drug in MDR-TB patients was high, and the diagnostic criteria were not uniform. We should pay attention to the prevention and treatment of psychiatric disorders, and develop standard diagnostic criteria for it.

Keywords: second-line anti-tuberculosis drugs, MDR-TB, psychiatric disorders, meta-analysis

Statins and the risk of liver injury: a population-based case-control study

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Aim/Objective: Using Taiwan's National Health Insurance Research Database (NHIRD), the aim of this study was to evaluate the association between statin use and liver injury in Taiwanese.

Methods: We conducted a case-control study. The cases were patients who had been admitted with a primary diagnosis of liver injury between 2002 and 2009, and the controls were patients who had not. The cases were matched with four controls by age, sex and index date. Multivariable conditional regression models were used to estimate odds of liver injury associated with statin use. Furthermore, we conducted stratified analyses to assess the impact of history of liver disease on this potential association.

Results: A total of 16,660 patients were included. Overall, users of statin was not associated with risk of liver injury (odds ratio (OR) 1.04; 95% confidence interval (CI) [0.90-1.19]) as compared to non-users. Increased cumulative duration (OR 1.07; 95% CI [0.91-1.27]) and dose (OR 1.14; 95% CI [0.95-2.11]) of statin were not associated with risk of liver injury. Nevertheless, a higher dose of statin (≥ 1 defined daily dose (DDD) (OR 1.55; 95% CI [1.14-2.11]) and use of rosuvastatin (OR 1.38; 95% CI [1.03-1.85]) were significantly associated with liver injury. There is no difference in the associations between statins and liver injury between patients with and without history of liver disease.

Conclusion: This population-based study extends previous evidence by exploring potential association between statin use and risk of liver injury. Our findings suggest that this risk may not exist.

Keywords: statin, liver injury, National Health Insurance Research Database (NHIRD), case-control study

The variation of psychopharmacological treatment for people with autistic spectrum disorder (ASD): an international study

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Aim/Objective: There is a variation of prescription for ASD treatment between countries. It has been suggested that many people with mental disorders in low/middle-income countries do not receive adequate treatment. This study aimed to investigate psychopharmacological treatment patterns in thirty countries which previously had no published data and the association between country's income and ASD treatment.

Methods: The IMS Prescribing Insights database was used to investigate the prescribing patterns for ASD treatment in 2007-2012. Data were obtained from countries in continents of Europe, Asia, Middle East, Australia, Central America, South America and Africa. The Gross Domestic Product (GDP) per capita was used to demonstrate each country's living standard. Spearman correlation was used to examine the association between prescription rates and GDP per capita.

Results: The highest prescription rate was found in Europe (1.3-36/10,000). Low prescription rates were found in Middle East (0.5-0.7/10,000) and some of the Asian countries such as Turkey, Indonesia and Pakistan (0.04-0.8/10,000). There was a significant positive relation between GDP per capita and prescription rate (Spearman ρ =0.59; p=0.002; 95%CI 0.26-0.80). The most common prescribed drug for ASD treatment was risperidone in most of the countries. Antidepressants and anti-epileptic drugs were also frequently prescribed for ASD treatment.

Conclusion: A large variation of psychopharmacological treatment for ASD treatment was demonstrated. As a moderate correlation between psychotropic drug use for ASD treatment and countries' income, future research should combine more detailed data for ASD treatment to have in-depth understanding of the disparity of psychopharmacological treatment between countries.

Keywords: psychopharmacological treatment, autistic spectrum disorder

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Examining the association between statin use and lung cancer incidence in patients with type 2 diabetes mellitus

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Aim/Objective: Diabetic patients are at higher risks for cancer and atherosclerosis and are usually indicated for statin use. We aimed to examine the relationship between statins, lung adenocarcinoma, and squamous cell carcinoma (SCC) incidence in diabetic patients.

Methods: A cohort of 596,812 type 2 diabetic patients was identified from the Taiwan National Health Insurance claims database in year 2000, and followed till the earliest of lung cancer diagnosis, death, or December 31, 2007. A Cox regression model with time-varying statin use was applied to estimate the hazard ratio (HR) of lung cancer incidence comparing statin ever use and nonuse. We further retrieved smoking information which was not recorded in the claims database from the National Health Interview Survey, quantified the imbalance in proportion of smokers between statin users and nonusers, and applied a sensitivity analysis to adjust for the potential confounding effect by smoking.

Results: In the diabetic cohort, 60,969 statin users and 535,843 statin nonusers were identified. In a median follow-up time of 7.9 years, a total of 1,182 incident SCC and 2,345 adenocarcinoma cases developed. Initial analysis showed a decreased risk of SCC for ever use of statins (HR: 0.69, 95% CI: 0.60-0.81). However, the relative risk would be 1.01 for statins after controlling for smoking effect. There was no association between statins and adenocarcinoma of the lung (HR: 0.97, 0.88-1.07).

Conclusion: There is no statistically significant association between statins and lung cancer incidence in the diabetic patients after adjustment for the confounding effect attributed to cigarette smoking.

Keywords: statins, lung neoplasms, diabetes mellitus, smoking

Poster Presentation

Hormone therapy and risk of venous thromboembolism among postmenopausal women in Taiwan – A nationwide population-based study

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Aim/Objective: We aimed to evaluate the venous thromboembolism (VTE) risk in postmenopausal women.
Methods: We used the Taiwanese National Health Insurance claims databases to established two cohorts (HT and non-HT users) including postmenopausal women aged $\geqq$50 years between 1998 and 2008. Using a nested case–control approach, all incident cases of VTE occurring during the study period were identified and matched with up to 10 controls selected from the cohort members. Adjusted odds ratios (OR) of VTE with non-use, current and past use of oral HRT were estimated using conditional logistic regression.
Results: We identified 394261 HT users and 477187 non-HT users in the cohorts. In the nested case-control analysis, we included 4140 cases of VTE matched with 82800 controls. The adjusted odds ratios of VTE associated with current use of oral HT was 2.36 (95% CI 1.99 to 2.80) relative to no use. The risk of VTE was also increased with recent use of oral HT (ORs 1.43; 95% CI, 1.12–1.83) and remote use (ORs 1.06; 95% CI, 0.90–1.25) relative to no use. By conditional logistic regression, oral HT users, history of varicose veins, heart failure, hypertension, and receiving major surgery were associated with higher risks of VTE events.
Conclusions: Although the incidence of VTE was low in Taiwanese postmenopausal women, oral HT was still associated with an increased risk of VTE. Therefore, physicians should take care of prescribing oral HT to postmenopausal women with other potential VTE risk factors.
Keywords: hormone, venous thromboembolism, postmenopausal, NHIRD, Taiwan

Long-term effectiveness of Lamivudine among Hepatitis B patients in Taiwan

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Aim/Objective: To evaluate the long-term effectiveness of lamivudine among patients with the hepatitis B virus (HBV).
Method: A population-based cohort was assembled using National Health Insurance claims data covering the period from 2004 to 2009. All patients included in the study were diagnosed with HBV and with prescriptions for lamivudine within a clinical setting. The outcomes were defined as all-causes mortality (ACM), liver-related mortality (LRM) and hepatocellular carcinoma incidence (HI). Results were analyzed using Cox proportional hazard model with inverse probability of treatment weighting (IPTW).
Result: A total of 86,648 patients were diagnosed HBV and included in the final analysis. Lamivudine therapy was administered to 9,586 patients (11.1%) and the median duration of treatment was 17.4 months (IQR: 11.6 to18.4 months). The adjusted hazard ratios (95% confidence interval) for lamivudine compared with untreated group were as follows: 0.62 (0.55-0.69) for ACM and 0.61 (0.54-0.68) for LRM, and 0.37 (0.32-0.42) for HI respectively.
Conclusion: Lamivudine use could decrease the risk of overall mortality, liver-related mortality and HCC incidence as compared untreated patients. This positive results support intensive efforts of antiviral treatment for HBV patients.
Key words: Lamivudine, HBV, long-term effectiveness

Retrospective cohort study of measles vaccine effectiveness among residents of isolated hill tribe communities, Thailand.

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Aim/Objective: The objective of this investigation was to study of vaccine effectiveness in resources limited area with measles outbreak.

Methods: We conducted retrospective cohort study in 2 villages on the hill which aimed to cover 100% of population. Cohort definition was the people under 15 years old lived in two villages during 7th July - 14th September 2011. Cases were person who had fever, rash and cough with at least one of: koplik spot, coryza or conjunctivitis. Vaccinated group was the person who able to obtain vaccination history from vaccine book, parents interviewed, recorded in their school or record in health facilities before September 2011. Non-vaccinated were the person who cannot obtain vaccination history from those sources or got first vaccination after 1 September 2011. Vaccine effectiveness will be calculate by attack rate in unvaccinated population minus attack rate in vaccinated population all divided by attack rate in unvaccinated population.

Results: 539 villagers were eligible in the cohort. The median age was 6 years old (IQR = 4-6 years). The vaccine coverage in this population was 17%. Since 7th July - 14th September 2011 there were 147 people (attack rate 27%) had measles sign and symptoms meet the case definition. 17 serum samples were drawn from eligible villagers to test for measles IgM with 16 samples gave positive result. Among the person who got vaccination, there were four percent of vaccination group and 32% of non-vaccinated group got sick. Vaccine effectiveness was 86.4% (95% CI, 71.01-93.24). Relative risk was 0.14 (95% CI, 0.07 - 0.29).

Conclusion: Vaccine effectiveness in this setting was quite lower than expected which may resulted from the distance from health facilities, cold chain problems or vaccine acceptability of villagers. Highly movement of the population made control and measure of communicable disease are more. We have done vaccine mop up which raised coverage up to 47% (another 28% infected already). The major limitations to interpretation this result was we have not done serological survey which may not practical due to above reasons. Additionally language was another limitation because most of villager cannot speak and understand Thai.

Keywords: measles, vaccine effectiveness, MMR vaccine, field epidemiology

What kind of pharmacoepidemiological information could be derived from Taiwan national health insurance claims datasets?

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Aim/Objective: To determine what kind of pharmacoepidemiological information could be derived from Taiwan National Health Insurance Databases (NHID).

Methods: We searched PubMed using terms [(insurance) OR (population-based study) AND (Taiwan)] and identified 1874 papers published between 2000 and 2012. After reviewing the abstract of each paper, we excluded 818 papers and identified 1156 empirical studies using NHID for analyses and 275 studies were drug related.

Results: We further classified drug-related studies into 1) Drug prescription (n=60); 2) drug utilization (n=65); 3) drug adverse effect and risk of disease (n=90); 4) drug therapeutic effect (n=57). There were 47 papers published in journals with impact factor higher than five and 23 papers were drug adverse effect and 20 papers were therapeutic effects and most of them used nested case-control design and Cox proportional hazard model. Drugs most often studied were Chinese herbal medicine (n=39), Statin (n=20), oral hypoglycemic agents (n=20 and 9 were on TZDs), antihypertensive agents (n=17 and 6 were on ARBs), NSAIDS (n=16), antipsychotic agents (n=12), antiplatelet agents (n=11), Benzodiazepine (n=11), influenza vaccine (n=10) and Bisphosphonates (n=9).

Conclusions: Using NHID could produce various and valuable pharmacoepidemiological information. The quantity and quality of papers published also increased. A user friendly information system could be developed to make these valuable information more easily accessed to those needed.

Keywords: insurance claims data, Population-based study, drug adverse effect; drug therapeutic effects

Association between pioglitazone and bladder cancer by a nested case-control study

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Aim/Objective: We tried to investigate the association between the use of pioglitazone and bladder cancer since it is still controversial although a meta-analysis was published recently.

Methods: A nested case-control design was applied to attain the objective. Cases were defined as a pathologically diagnosed bladder cancer and retrieved from diabetic patients at the Toyama University Hospital Database between 2005 and 2011. Controls were selected by matching with gender, age within 6 years, and visit date within 60 days. Conditional logistic regression provided an adjusted odds ratio of pioglitazone to incident bladder cancer for age, hemoglobin A1c, and other antidiabetic medications containing sulfonylureas, alpha-glucosidase inhibitors and insulin.

Results: We identified a total of 58 patients with bladder cancer. Since some cases contained missing data or failed to match with controls, there were 95 patients in matched analysis. Mean age was 69 years, 26% were women and mean hemoglobin A1c was 7.0%. Antidiabetic drug utilization was 6% for pioglitazone, 46% for sulfonylureas, 27% for alpha-glucosidase inhibitors and 38% for insulin. Use of pioglitazone was not associated with the risk of bladder cancer (adjusted odds ratio 0.90 [95% CI 0.09 to 8.89]; P=0.93). Insulin, sulfonylureas, alpha-glucosidase inhibitors revealed an adjusted odds ratio 1.41, 1.16, and 0.70, respectively.

Conclusion: Our finding has suggested that pioglitazone might not increase the risk of bladder cancer.

Keywords: Pioglitazone, diabetes, bladder cancer, nested case-control

Cilostazol uses in contraindicated conditions: A review from Taiwan adverse drug reporting system and health insurance database

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Aim/Objective: In March 2013, European Medicines Agency (EMA) has announced that cilostazol should not be given to patients who have unstable angina or who have had severe tachyarrhythmia, myocardial infarction or a recent coronary intervention nor to those receiving two or more antiplatelets or anticoagulants. In Asia, cilostazol is widely used in stroke patients, or added to aspirin and clopidogrel as triple therapy after stent implantation for coronary heart disease. This study is to evaluate the population at above risks in Taiwan.

Methods: (1) We reviewed all cilostazol-associated reports collected by Taiwan National Adverse Drug Reaction (ADR) Reporting System from 2003 to 2013. Cases with above contraindicated conditions were further analyzed. (2) We searched 2009 Taiwan National Longitudinal Health Insurance Database (LHID) for patients who received cilostazol prescriptions for over 30 days and further analyzed the risks mentioned above.

Results: (1) We identified 100 cilostazol associated ADR reports and of which, 12 (12.0%) were contraindicated with a mean age of 67. Congestive heart failure (25.0%), combination therapies and bypass surgery (16.7%) accounted for the top three contraindications. (2) In LHID, we identified 1943 cases combination antiplatelets therapies (2.93%), severe tachyarrhythmia (2.68%), and congestive heart failure (1.54%) represent the top three contraindications.

Conclusion: Our findings suggest that cilostazol were commonly prescribed in patients with above contraindications in clinical practice in Taiwan. Cautions should be addressed to health care professionals and further domestic regulatory actions should be taken for this potential risk.

Keywords: cilostazol, contraindication, drug safety

Reference:

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Poster Presentation

Clinical impact of P-glycoprotein inhibiting and non-inhibiting calcium channel blockers in acute myocardial infarction patients

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Aim/Objective: Some drugs of calcium channel blockers (CCBs) have strong inhibitory effects on the drug transporter P-glycoprotein (Pgp), which mediates antiplatelet drug's intestinal absorption. It was the aim of this study to evaluate the effect of co-prescription of Pgp-inhibiting and non-Pgp-inhibiting CCBs on antiplatelet drugs in acute myocardial infarction (AMI) patients undergoing percutaneous coronary intervention (PCI).

Methods: Using the Korean Health Insurance Review & Assessment Service data, we extracted the 14,980 patients whose main diagnostic codes include AMI and undergoing PCI during 2009 Jan 1 to 2009 Dec 31. And we checked off their prescribed drugs at discharge and their readmission during 1 year. And then we evaluated the readmission proportion by their prescribed drug types.

Results: 338 patients prescribed only aspirin and 36.7% of them were readmitted within 1 year, however 11.8% of 11,721 patients who was prescribed aspirin and clopidogrel were readmitted (OR=4.36, p<0.001). 74 patients was prescribed aspirin with Pgp inhibiting CCBs, and 52.7% of them were readmitted, but 33.8% of 65 patients who were prescribed aspirin and non-Pgp-inhibiting CCBs were readmitted (OR=2.2, p=0.023). 1,167 patients was prescribed aspirin, clopidogrel and Pgp inhibiting CCBs, and 15.8% of them were readmitted, and 15.7% of 510 patients who was prescribed aspirin, clopidogrel and non-Pgp-inhibiting CCBs were readmitted (OR=1.0, p=0.973).

Conclusion: This study demonstrates that concomitant use of Pgp-inhibiting CCBs with only aspirin may reduce the efficacy of aspirin. However using with non-Pgp-inhibiting CCBs or with clopidogrel, antiplatelet effect was not reduced.

Keywords: acute myocardial infarction, antiplatelet drug, calcium channel blockers, P-glycoprotein

Cost-effectiveness of Voriconazole therapeutic drug monitoring in the treatment of invasive aspergillosis

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Aim/Objective: Voriconazole is the drug of choice in the treatment of invasive aspergillosis (IA). Therapeutic drug monitoring (TDM) of voriconazole has been recognized as an effective way to improve clinical outcomes. However, the impact of TDM on the pharmacoeconomic aspect has not been studied. The objective of this study is to evaluate the cost-effectiveness of voriconazole TDM in a 2500 bed medical center in Taiwan.

Methods: New voriconazole users who underwent TDM in 2010 were enrolled in the TDM group. The historical control (HC) group consisted of new users in 2008 when pharmacists-managed TDM service was not established. Treatment of IA and clinical outcomes were collected from medical record. Direct medical costs were documented from insurance reimbursement profiles. Continuation of voriconazole for at least 3 months (recommended in treatment guidelines) and daily antifungal costs were compared between 2 groups.

Results: Demographic and clinical characteristics were similar between 71 patients (72 courses) in the TDM group and 69 patients (74 courses) in the HC group. Continuation of voriconazole for more than 3 months was 40% *vs.* 26% in TDM group and HC group respectively. The mean antifungal expenses were higher in TDM group (10,673 USD) compared with HC group (6857 USD) significantly. The daily costs, however, were similar between two groups (176.2 USD *vs.* 178.2 USD).

Conclusion: We found that voriconaole TDM can maintain the use of voriconazole in patient who need prolonged antifungal treatment course while antifungal medication cost didn't increase significantly.

Keywords: cost-effectiveness, voriconazole, therapeutic drug monitoring (TDM), invasive aspergillosis

Effect of nationwide computerized drug utilization review system on methylphenidate use in pediatrics

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Aim/Objective: Methylphenidate, which is a medication to treat attention deficit-hyperactivity disorder (ADHD), can cause serious cardiovascular events in children. In December 2009, Korea Ministry of Food and Drug Safety (MFDS) announced that methylphenidate should not be used in children under 5 years and informed physician and pharmacist through nationwide computerized drug utilization review (DUR) system. In this study, we determined whether implementation of regulatory action using national DUR system reduced the contraindicated use of methylphenidate

Methods: We conducted time series analysis using Korea Health Insurance Review & Assessment Service National Patients Sample (HIRA-NPS) database. Study subjects consisted of children under 18 years who were diagnosed with ADHD (ICD-10, F90) for 12 months before, and 24 months after regulatory implementation. Contraindicated use of methylphenidate was defined as use of methylphenidate at least one dose in children younger than 5 years. We calculated monthly percentage of methylphenidate prescriptions in children with ADHD younger than 5 years. The difference between the proportion for before and after years was estimated as the relative reduction in contraindicated use. We calculated 95% confidence intervals (CI) based on the sample-weight adjustment.

Results: Between 2009 and 2011, there were total 45,276 methylphenidate prescriptions among 5,550 pediatric patients (median age 10 [Interquartile range (IQR) 8-13 years]. The patient population was 17.0% female. During the 12-month period before the implementation, the percentage of contraindicated use of methylphenidate 1.46% (N=29). The monthly proportion of pediatrics receiving contraindicated prescription for methylphenidate was significantly decreased after the regulatory action. In the year after the regulatory action, 0.80% (N= 20) represented the contraindicated use of methylphenidate. Overall, there was 45.2% relative reduction (95% CI: 27.4%-74.5%) in contraindicated use of methylphenidate.

Conclusion: The Korea regulatory action regarding methylphenidate through nationwide DUR system had an effect of reduced use in pediatric population.

Keywords: methylphenidate, pediatrics, contraindication, regulatory action, drug utilization review

Follow-up results in patients with cephalosporin adverse events

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Aim/Objective: It is well known that there is cross-reactivity between the penicillin and cephalosporins hypersensitivity. However, cross-reactivity between cephalosporins is a field that had been rarely studied. We observed the response after re-exposure to cephalosporin in the patients with previous cephalosporin adverse events to evaluate the frequency of cross-reactivity between cephalosporins.

Methods: We searched patients with cephalosporin adverse events diagnosed from August to October 2009, and then examined electronic medical records of those patients until June 2013 in a tertiary hospital in South Korea.

Results: A total of 59 patients were classified as having cephalosporin adverse events. Cephalosporin was re-administered in 24 patients after previous adverse events. In the initial adverse events, 17, five, and two cases were caused by third, first, second generation cephalosporin, respectively. In the first generation cephalosporin group, there was no adverse reaction with same or different antibiotics. In the second generation group, one patient used third generation cephalosporin later and experienced same adverse event of first event, pancytopenia. In the third generation group, repeated leukocytopenia, generalized rash, respectively, developed with the same third generation cephalosporin, and one case of mild liver enzyme elevation with the different generation cephalosporin. We observed only four (16.7%) patients developed adverse events in the later cephalosporin exposure, and 50% (2/4) were used the different generation cephalosporins.

Conclusion: Only a small portion of patients may react to the cephalosporin re-exposure. Therefore, we think that it needs more cautious to contraindicate cephalosporin use to the patients with cephalosporin adverse events.

Keywords: cephalosporin, adverse event, cross-reactivity

Liver function monitoring among newly diagnosed tuberculosis patients who initiated their anti-tuberculosis treatments in Taiwan

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Aim/Objective: The objective of this study is to investigate the adherence to "Taiwan Guidelines for Tuberculosis (TB) Diagnosis and Treatment" issued by Center for Disease Control, Taiwan, in terms of liver function monitoring among newly diagnosed TB patients.
Methods: From Taiwan's National Health Insurance research database (NHIRD), we identified 11,397 newly diagnosed TB patients who initiated their TB treatments between 2000 and 2011. Patients were categorized into three groups as completely, partially and non- adherent groups based on their adherence rates of liver function monitoring suggested by the guideline. Logistic regression was used to explore potential determinants associated with the adherence rate.
Results: The completely adherent rate increased from 0.5% in 2000 to 9.2% in 2011 while the non-adherent rate decreased from 17.5% to 1.2%. Compared to non- adherent group, patients with prior history of liver disease (odds ratio (OR) 4.36 [95% confidence interval (CI) 1.92-9.87]) and viral hepatitis (OR 9.39 [1.47-60.19]) had a higher odds to be completely adherent to the guideline. In addition, patients whose prescribing physicians were from departments in chest medicine (OR 4.59 [1.91-11.05]), tuberculosis (OR 2.55 [1.01-6.40]) and infectious disease (OR 3.93 [1.08-14.31]) had a higher odds to be completely adherent to the guideline.
Conclusions: We found an increased adherent rate of liver function monitoring for newly diagnosed TB patients in the past decade in Taiwan. Our findings of potential determinants associated with completely adherent to the guideline could serve as an important reference for developing effective strategies to prompt compliance to the guideline.
Keywords: liver function tests, anti-tuberculosis drugs, adherence

Long-term outcome of patients with end stage chronic kidney disease taking low-dose aspirin

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Aim/Objective: There are some data indicated that low-dose of aspirin using to be ineffective for ischemic stroke prevention on end stage chronic kidney disease (ESRD) patients. Therefore, we try to investigative the association of low-dose aspirin in terms of preventing death and readmission of stroke.
Methods: This retrospective study identified cases of ESRD from the national health insurance database (NHIRD). Low-dose aspirin was administered for patients who had experienced a first ischemic stroke between 1998 and 2006. Outcome measurements were including death and readmission to hospital for stroke.
Results: 2406 patients experienced a first stroke. According to time-dependent analysis, the hazard ratio (HR) for mortality in patients treated with aspirin was 0.937 (95% CI: 0.933-0.941). In readmission outcomes, HR for readmission for stroke was 0.999 (95% CI: 0.998–0.999) in patients treated with aspirin.
Conclusion: This study includes the largest sample for evaluating outcomes of low-dose aspirin in ESRD patients for preventing recurrent stroke. The study results show that low-dose aspirin still offers safe and effective treatment for ischemic stroke prevention in patients with ESRD.
Keywords: ESRD, antiplatelet, clinical efficacy, safety

Preliminary model to establish the evidence-based database of safe Chinese herbal medicines use

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Aim/Objective: The use of Chinese herbal medicines (CHM) is prevalent in Chinese communities, as well as worldwide. With abundant items but limited consensus on safe medication use of CHM, the aim of this study was to establish a preliminary model to build the evidence database of safe CHM use.

Methods: Focusing on tertiary literature first, the comprehensive literature review and data extraction were performed using three common CHM books, including Taiwan Herbal Pharmacopeia, Chinese Materia Medica, and Chinese Pharmacopoeia Commission. All relevant information about safety matters, i.e., contraindications, precautions in pregnancy, and toxicity, were extracted using standardized form and cross-validated by hands.

Result: In the aforementioned three pharmacopoeias, the main records of safety information were retrieved from the 'Chinese Materia Medica' (n=513).There were 261, 106 and 190 records, respectively, related to CHM contraindications, precautions in pregnancy and potential toxicities. While the most contraindications were related to constitutional aspects (n=242), the remaining include aspects related to kidney, liver impairments and others.

Conclusion: Upon the available tertiary evidence, those CHM items with documented records about contraindications and/or toxicity concerns included those commonly used or easily misused CHM items. This preliminary approach will be expanded to retrieve information from websites, primary, and secondary literature in order to establish a more comprehensive and valid evidence database for clinical use.

Prescription patterns of topical corticosteroids in children and adolescents: Analyses of the Korea Health Insurance Review and Assessment Service-National Patients Sample (HIRA-NPS) 2009

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Aim/Objective: Topical corticosteroids (TC) are widely used in children and adolescents. However, pediatric population has a higher ratio of body surface area to their weight, they are particularly vulnerable to adverse events (AE). Especially, physicians should be very careful in prescribing TC-antibiotics/antiseptics combination agents (TC-combi) over TC alone. The objective of this study was to provide the usage patterns of TC in Korean children and adolescents using the the Korea Health Insurance Review and Assessment Service-National Patients Sample (HIRA-NPS 2009).

Methods: A cross-sectional study was conducted by analyzing data from HIRA-NPS for the year 2009. Study drugs included 67 TC (betamethasone, hydrocortisone, triamcinolone etc.). Among these agents, there were 12 combinations containing gentamicin, neomycin and econazole etc. We analyzed usage patterns by sex, TC indication (ICD-10 code), type of medical facilities (local clinic, general hospital and tertiary hospital), type of TC (combination with antibiotics or not). In subgroup analysis, we compared prescription rates between pediatric and dermatology.

Results: 71,504 children aged under 18 years had prescribed TC more than once. Of 71,504 patients, 53.9% were male. Of 158,121 prescriptions, the most indications for TC in study population were atopic dermatitis (L20) and allergic contact dermatitis (L23) (17.5% and 13.2%, respectively). 79.2%, 11.9% and 8.8% treated at a local clinic, tertiary hospitals, general hospitals, respectively. In subgroup analysis, prescription rates of TC-combi was 48.4%, 12.5% in the pediatric and dermatology, despite no significant differences of TC indications between two parts.

Conclusion: The prescription rates of TC-combi were higher for pediatricians than dermatologists. Further studies are needed to estimate the incidence and relative risks of AEs by TC prescribed each medical department in pediatrics.

Keywords: topical corticosteroids, prescription patterns, children, adolescents

Stevens-Johnson syndrome associated with carbamazepine therapy in psychiatric patients in Indonesia

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Aim/Objective: This study is aimed to investigate the incidence rate of stevens-johnson syndrome associated with carbamazepine therapy in psychiatric patients in Indonesia.

Methods: 320 inpatients data that received carbamazepine therapy from 2011-2012 was obtained. Incidence of Stevens-Johnson syndrome was rated by obtaining information from patients medical records.

Results: The result of this study shows that from 320 patients, age range from 23-70 years old (mean=2,93 years old), male 167 patients (52,30%), female 153 patients (47,70%), 4 patients (1,25%), 2 male and 2 female has experienced Stevens-Johnson syndrome. The onset of carbamazepine-induced Stevens-Johnson syndrome is range from 1-5 days (mean=4 days) since first therapy with carbamazepine.

Conclusion: Stevens-Johnson syndrome associated with carbamazepine therapy in psychiatric patients in Indonesia remain high. This need follow up for preventing this fatal side effect (genotyping test) when carbamazepine is still play as important medicine in psychiatric patients in Indonesia.

Keywords: carbamazepine, Stevens-Johnson syndrome, psychiatry, Indonesia.

Usage patterns of "over the counter" versus prescription-strength non-steroidal anti-inflammatory drugs in France

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Background: Most risks of non-steroidal anti-inflammatory drugs (NSAIDs) are pharmacological, dose and duration-dependent. Usage patterns of prescription-only (POM) or over-the-counter (OTC) NSAIDs may influence risks, but are not commonly described.

Methods: EGB, the permanent 1/97 representative sample from the French national healthcare insurance systems was queried over 2009-2010 to identify usage patterns, and concomitant chronic diseases and cardiovascular medication in OTC and POM NSAIDs users.

Results: Over two years, 229,477 of 526,108 patients had at least one NSAID dispensation: 44,484 patients (19%) were dispensed only OTC NSAIDs (93% ibuprofen), 121,208 (53%) only POM NSAIDs. OTC users were younger (39.9 vs. 47.4 years old) and more often female (57% vs. 53%); 69% of OTC users and 49% of POM users had only one dispensation. A mean of 14.6 defined daily doses (DDD) were dispensed over 2 years for OTC vs. 53 for POM; 93% OTC vs. 60% POM patients bought ≤ 30 DDD over 2 years, and 1.5% vs. 12% bought ≥ 90 DDD. Chronic comorbidities were found in 19% of OTC users vs. 28% of POM users; 24% vs. 37% had at least one dispensation of a cardiovascular drug over the two years.

Conclusions: Most of the use of NSAIDs appears to be short-term, especially for OTC-type NSAIDs such as ibuprofen. The validity of NSAIDs risk estimates extrapolated from clinical trials or from observational studies not including OTC-type usage may need to be revised,

Keywords: OTC NSAIDs, prescription NSAIDs, usage patterns, drug-related risks.

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Cost-effectiveness of granulocyte colony-stimulating factor prophylaxis in chemotherapy-induced febrile neutropenia among breast cancer and non-Hodgkin's Lymphoma patients under Taiwan's national health insurance reimbursement system

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Aim/Objective: The beneficial effects of granulocyte colony-stimulating factor (G-CSF) prophylaxis on reducing the risk of chemotherapy-induced febrile neutropenia (CIFN) were well-documented throughout the literature. However, its evidences of cost-effectiveness were conflicting. By analyzing the Taiwan's National Health Insurance research database (NHIRD) from year 2000 to 2010, this study estimated the cost-effectiveness of G-CSF prophylaxis in CIFN under Taiwan's National Health Insurance (NHI) reimbursement system.
Methods: Data on clinical outcomes and direct medical costs were derived for 5,179 newly diagnosed breast cancer and 629 non-Hodgkin's lymphoma (NHL) patients from the NHIRD. Patients were further categorized into three subgroups as "primary prophylaxis", "secondary prophylaxis" and "no prophylaxis" based on the patterns of G-CSF use. Generalized estimating equations (GEEs) were applied to estimate the impact of G-CSF use on the incidence of CIFN. The incremental cost-effectiveness ratios of primary and secondary prophylactic G-CSF were calculated and sensitivity analyses were performed.
Results: Primary prophylaxis of G-CSF decreased the incidence of CIFN by 28% and 83%, while secondary prophylaxis by 34% and 21% in breast cancer and NHL patients, respectively. Compared to those with no prophylaxis, the incremental cost per CIFN reduced in primary prophylaxis is NT$30,732 (currency: 1 US dollar=30 New Taiwan (NT) dollars) and NT$1,704 among patients with breast cancer and NHL, respectively. In contrast, secondary prophylaxis is dominated by no prophylaxis and primary prophylaxis in both cancer patients.
Conclusion: We found that primary prophylactic use of G-CSF, compared with secondary prophylactic use, was more cost-effective in CIFN.
Keywords: cost-effectiveness, national health insurance research database (NHIRD), granulocyte colony-stimulating factor (G-CSF), breast cancer, non-Hodgkin's lymphoma (NHL), chemotherapy-induced febrile neutropenia (CIFN)

What kind of clinical epidemiological information could be derived from Taiwan national health insurance database?

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Aim/Objective: To determine what kind of clinical epidemiological information could be derived from Taiwan National Health Insurance Database (NHID).
Methods: We searched PubMed using terms [(insurance) OR (population-based study) AND (Taiwan)] and identified 1874 papers published between 2000 and 2012. After reviewing the abstract of each paper, we excluded 818 papers and identified 1156 empirical studies using NHID for analyses.
Results: We classified the topics of papers into 13 categories: 1) prognosis and risk of disease (n=290, 25.1%); 2) healthcare utilization (n=172, 14.9%); 3) incidence/prevalence/mortality (n=157, 13.6%); 4) drug adverse effect and risk of disease (n=90, 7.8%); 5) cost-effectiveness analysis (n=70, 6.1%); 6) drug utilization (n=65, 5.6%); 7) Drug prescription (n=60, 5.2%); 8) Outcome of procedure (n=60, 5.2%); 9) drug therapeutic effect (n=57, 4.9%); 10) health services research (n=46,4.0%); 11) ecological association study (n=33, 2.9%); 12) methodology (n=32, 2.8%); 13) risk factor (n=24, 2.1%). With regard to the impact of the papers, there were only two papers published in journals with impact factor larger than 5 in 2003 and increased to 67 papers in 2012. Of 170 papers published in journals with impact factor larger than 5, 77 (42%) were related to prognosis and risk of disease and 23 (14%) were related to drug adverse effect and risk of disease.
Conclusions: Using NHID could produce various and valuable information. The quantity and quality of papers published also increased. Through the presentation of matrix by patients studied, exposure or interventions used and outcomes we could identified the gaps of studies needed.
Keywords: clinical epidemiology, insurance claims data, population-based study, systematic review

Poster Presentation

Five cases of Stevens-Johnson syndrome: May be associated with methazolamide treatment

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Aim/Objective: Recently, Stevens-Johnson syndrome associated with methazolamide has been reported in Koreans, more frequently. Methazolamide is a carbonic anhydrase inhibitor commonly used for lowering intraocular pressure in glaucoma and other ophthalmologic diseases. We reported five cases of Stevens-Johnson syndrome induced by methazolamide.

Methods: All patients showed atypical clinical manifestations, compared to classical Stevens-Johnson syndrome.

Results: Methazolamide induced Stevens-Johnson syndrome showed scattered or confluent maculopapular eruptions initially, which are similar to morbiliform drug eruption with mild lip erosion and palmar erythema. Even though without any skin erosion initially, it showed rapid progression to severe erosion on trunk and palmoplantar erythema within 5 to 7 days.

Conclusion: Therefore, our data indicated that methazolamide induced Stevens-Johnson syndrome should be checked for patient who has a history of ophthalmologic treatment with drug eruption like skin lesion.

Keywords: methazolamide, Stevens-Johnson syndrome

High-versus-low-dose histamine-2 antagonists for the prophylaxis of non-steroidal anti-inflammatory drug-associated gastrointestinal ulcers

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Aim/Objective: To compare the effectiveness of high-dose versus low-dose H2RAs in the primary prophylaxis of NSAID-associated clinical GIUs among NSAID new-users in Hong Kong during 2009-2012.

Methods: A retrospective cohort study was conducted using Hong Kong Hospital Authority Clinical Data Analysis & Reporting System. Both records of new adult patients (18 years or older) who had only one prescription of NSAID+H2RA (exposure) and diagnosis code(s) of GIUs (event) during study period (2009-2012) were retrieved. Patients who were ever diagnosed with at least one of: GIUs, Helicobacter pylori infection, or who had ever received NSAIDs+H2RAs or NSAIDs+PPIs or had gastrointestinal endoscopy procedures in the screening period (2007-2008) were excluded. The high dose of H2RAs was defined as double the standard dose or higher, and the low dose was defined as lower than double dose (according to British National Formulary 63). The adjusted relative risk of GIUs during NSAID+high-dose-H2RA versus NSAID+low-dose-H2RA treatment was calculated. Microsoft Excel and Statistical Analysis System (SAS) v9.3 (SAS Inc., United States) were used for data manipulation and analysis.

Results: A total of 102,042 patients had only one prescription of NSAIDs and were co-prescribed with H2RAs during 2009-2012. Among these patients, there were 77,509 patients on NSAID+low-dose-H2RA treatment and 24,533 patients on NSAID+high-dose-H2RA treatment. Of the total 70 GIUs events during study period, 65 GIUs events were found during NSAID+low-dose-H2RA treatment and 5 GIUs events were found during NSAID+high-dose-H2RA treatment. The adjusted relative risk for patients receiving NSAID+high-dose-H2RA versus NSAID+low-dose-H2RA was 0.32 (95%CI 0.13-0.79).

Conclusion: Our study support superior effectiveness of high-dose versus low-dose H2RAs in preventing NSAID-associated endoscopic GIUs. Further study involving international patient data will further inform on the place of high-dose H2RAs in clinical management.

Keywords: non-steroidal anti-inflammatory drugs (NSAIDs), histamine-2-receptor antagonists (H2RAs), gastrointestinal ulcers (GIUs)

Side Effects following Antiretroviral Therapy in Nepal

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Aim/Objectives: The objective of the study was to examine the incidence of side effects associated with ART intake as reported to the Nepal Drug and Poison Information Center (NDPIC).
Methods: We analyzed retrospectively all queries related to ART side effects to a NDPIC from 1st June 2006 to 30th May 2013.
Results: A total of 195 consecutive cases were reported to NDPIC. Seventy eight percentages of cases were males (n=152) and remaining were female (22%, n=43). Ages ranged from 22 to 56 years, mean 35 years ($\pm$ 10.00). Combinations of fatigue (n=48), nausea (n=33), vomiting (n=27) and headache (n=26) were the main complaints. Other effects were dry mouth, diarrhea, dizziness, skin rashes, confusion, fever, migraine, mood swing, insomnia, loss of appetite, sleeping disorders, and nightmares were the initial presenting symptoms. Time to onset of side effects ranged from 30 minutes to 8 hours after taking antiretroviral drugs. Treatment was symptomatic and supportive. In all cases, side effects were self limiting and patients were continued of ART therapy.
Conclusion: Patients can develop numerous side effects within a relatively short time of initiating ART therapy. In our experience, these reactions resolved with supportive and symptomatic treatments; however, larger and more systematic investigation would be helpful in delineating risk factors for severe reactions or discontinuation of ART medicines. This issue represents an important surveillance goal for drug and poison information centres, which are encouraged to coordinate with ART distribution centers and HIV researchers in developing countries.
Keywords: side effects, antiretroviral therapy, Nepal

Should metronidazole be routinely added to the first-line antimicrobial regimen in severe acute cholangitis?

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Prompt antimicrobial therapy is crucial to prevent rapidly-deteriorating courses of severe acute cholangitis. Since routine addition of metronidazole, which is related with common gastrointestinal side effects such as nausea or vomiting and resistance acquisition by *Helicobacter pylori*, to the first-line regimen is controversial, we intended this prospective study with historical controls. Patients with severe acute cholangitis who fulfilled the definition of severity by the Tokyo Guidelines were enrolled prospectively from January 2010 to December 2011. During that period, metronidazole wasn't added to third-generation cephalosporins which were used as the initial antimicrobials except for patients who were allergic to penicillin and received ciprofloxacin instead (no metronidazole group). Outcomes were compared with a historical cohort from March 2007 to December 2009 when metronidazole was added routinely (metronidazole group). Unified strategy was maintained throughout the whole period except the use of metronidazole. Outcomes between metronidazole group (n=338) and no metronidazole group (n=338) didn't differ in terms of the rate of successful biliary drainage by interventional procedures (93.2% vs. 94.7, $p = 0.88$), time elapsed for cholangitis to be controlled (10.4 $\pm$ 0.6 vs. 8.9 $\pm$ 1.2 days, $p = 0.38$) and mortality (1.2% vs. 0.6% with $p = 0.34$ for all causes and 0.9% vs. 0% with $p = 0.15$ for cholangitis-related respectively). Metronidazole, the routine addition of which didn't improve the outcomes, can be excluded from the first-line regimen if emergent biliary drainage can be performed efficiently.
Keywords: acute cholangitis, cephalosporin, metronidazole, drug resistance

2006-2009 Patterns of prescribed medications for elderly under national health insurance program in Taiwan

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Aim/Objectives: While National Health Insurance (NHI) program in Taiwan covered almost all prescribed medications for outpatient services, this study aimed to explore the patterns of covered medications prescribed for elderly patients in outpatient settings from 2006 to 2009.
Methods: This retrospective population-based cohort study was conducted using 2000 and 2005 Longitudinal Health Insurance Databases. Those elderly patients being prescribed with medications at any outpatient visits in 2006 to 2009 were evaluated for their NHI-covered prescriptions of Western Medication (WM) and Chinese Medication (CM) in that specific year. The medications with the same component name were classified as the same drugs and the descriptive analysis was performed to evaluate the prescription patterns.
Results: While the elderly accounted for up to 4.9% in NHI beneficiaries who ever utilized outpatient services or filled medications across four years, approximately 98% of them were prescribed with either WMs or CMs and up to 19% were prescribed with CMs. The symptoms relief WMs, e.g., cold preparation, antacid, pain killers, were listed in the top classes of prescribed WMs, where cardiac medications moved the ranking forward.
Conclusion: While the elderly accounted for small proportion of medical care users, relatively larger proportions were prescribed with WMs and symptom relief medications across four years. Further outcome assessments for such usage are necessary.

Drug related problems in chronic renal failure patients in Moeslim Private Hospital of Yogyakarta, Indonesia

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Aims/Objectives: Patients who suffered from chronic renal failure (CRF) have increased risk of toxicity and sensitivity for some drugs because the problem in elimination. Furthermore, many side effects are difficult to avoid due to chronic renal failure. Patients suffered from CRF mostly have a highly risk to suffer from DPRs. This study was aimed to understand the pattern of using drugs that cause DRPs for patients suffered from CRF in Moeslim Private Hospital of Yogyakarta in October-December 2011.
Methods: This study used observational method and the result was descriptively presented. The data was collected retrospectively based upon medical report data. The patient's data was analyzed due to DRPs based upon literature study (NFK/KDOQI 2007, JNC VII, Pharmacotherapy A Pathophysiologic Approach 2005. Drug Prescribing in Renal Failure (Dosing Guideline for Adults, 4th ed.), Drug Information Handbook, 20th ed., The Renal Drug Handbook, 3th ed, Drug Interaction Facts 2001).
Results: The mostly used drugs in patients suffered from CRF was folic acid, $CaCO_3$, furosemide, antihypertension, and antibiotic. DRPs percentages that were occurred in patients suffered from CRF were untreated indication (17.44%), drug use without indication (3.49%), improper drug selection (8.14%), over dosage (16.28%), side effect (26.74%) and drug interaction (27.91%).
Keywords: chronic renal failure, DRPs, Hospital

Impact of clinical pharmacist intervention on antibiotic use in outpatient clinics

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Aim/Objective: To describe the impact of clinical pharmacist on antibiotic use in community based outpatient clinics affiliated with Ministry of Health Malaysia (MOH).

Method: A total of six clinics have been selected for this study. Medications prescribed by health providers at these OPD clinics, often urgent medication that patients need to start in a more timely fashion such as antibiotics, can be filled by local pharmacies. A clinical pharmacist is available for consultation to the pharmacist or health providers for specific cases. Recommendations made are tracked for the documentation purposes without any patient-specific identifiers. We reviewed the types of recommendations and cost-avoidance provided by the clinical pharmacist from June 2009 to May 2013. Recommendations are categorized as: add drug, decrease dose, discontinue drug, increase dose, non-formulary drug approval and education.

Results: Over the 4 years period of reviewed, 622 therapeutic recommendations were made by the pharmacist. The most common recommendations were to education providers on Infectious disease topics (385), to discontinue chronic antibiotics (28%), and for non-formulary approvals (21%) with 40% of requests approved. A total of 260 antibiotic courses were avoided. It is not possible to determine if education provided helped avoid additional courses. These recommendations resulted in a net cost-avoidance of $39,000 for drug requisition cost alone.

Conclusion: A clinical pharmacist providing antibiotic related recommendations for OPD clinics decreased cost by about $9,750 per year and avoidance over 250 courses of unnecessary antibiotics over a four year period. A similar program could be adapted at other institutions with a pre-approval process in place.

Key words: clinical pharmacist, infectious disease, antibiotic, outpatients clinics.

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Prescribing and sensitivity patterns of antimicrobials in uncomplicated urinary tract infections in females

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Aim/Objective: The aim of this present study was to detect the causative agents of uncomplicated urinary tract infection in females, to assess the pattern of antimicrobial prescription with sensitivity pattern.

Methods: A prospective study was conducted in two hospitals viz. Charak Hospital and Research Centre and Western Regional Hospital, Kaski, Pokhara. Patient information was obtained by interviewing the patients and through their medical record files. Antimicrobials sensitivity testing was performed by disc diffusion.

Result: A total of 175 clean catched midstream urine samples of females who were clinically diagnosed to have UTI were collected, out of which 104 (75.4%) samples grew potential pathogens causing UTI. The study showed that UTI was mostly prevalent in females of age group 20-30. *Escherichia coli* were the predominant (64.4%) bacterial pathogen followed by Klebsiella species (13.3%), *Pseudomonas* species (3.8%) and others. Most of the strains of *E. coli* were resistant to cephalexin whereas sensitive to cefpodoxime, amikacin, gentamycin and nitrofurantoin. Most commonly prescribed antimicrobial was ofloxacin (28.8% in Charak Hospital and Research Centre and 21.8% in Western Regional Hospital) followed by nitrofurantoin (19.2%) and azithromycin(9.6%) in hospital A and cefixime (14.9%), amoxycillin (11.9%) and azithromycin (7.9%) in hospital B.

Conclusion: This study revealed that *E. coli* was the predominant bacterial pathogen of uncomplicated UTIs in both hospitals. It also demonstrated an increasing resistance.

Keywords: urinary tract infection, antimicrobial, resistance, sensitivity

Risk factors for surgical site infection in appendectomy in China: A systematic review and meta-analysis

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Aim/Objective: We conducted this systematic review to identify important risk factors for appendectomy SSI in China.
Methods: We searched four Chinese electronic databases and PubMed to identify case-control, or cohort studies identifying risk factors for appendectomy SSI. We conducted a quality assessment of all eligible studies according to Newcastle-Ottawa scale and performed a systematic review to report the crude and adjusted odds ratios (cOR and aOR) for all risk factors. Meta regression was used to assess effect modification by study quality and hospital level.
Results: We identified 48 eligible studies. Meta-analysis revealed that disease duration (>=24h) (cOR=5.34 3.48-8.18), prolonged operation time (cOR=4.76 3.65-6.20; aOR=2.41 1.53-3.81), exploratory incision (cOR=4.08 2.61-6.36), retrograde excision (cOR=4.11 2.98-5.66; aOR=2.56 1.54-4.27), complicated appendicitis (cOR=4.48 3.52-5.71; aOR=2.67 1.73-4.13), length of incision (>=4cm) (cOR=7.65 4.53-12.94), thickness of subcutaneous fat (>=2cm) (cOR=3.38 2.36-4.83; aOR=1.65 1.05-2.57) were significantly associated with appendectomy SSI. Compared with preoperative and perioperative antibiotic prophylaxis, patients with no antibiotic prophylaxis were more likely to have SSI after appendectomy. The risk estimates were (cOR=3.29 2.25-4.80; aOR=3.47 1.72-7.01) and (cOR=3.54 1.64-7.63) respectively. However, intraoperative irrigation (Metronidazole, Tinidazole, Gentamicin or Hydrogen peroxide) of wound can decrease the risk of appendectomy SSI (cOR=0.31 0.13-0.70).
Conclusion: Since these risk factors are potentially preventable, corresponding measures such as decreasing prehospital delay, improving surgical technique, antibiotic prophylaxis and intraoperative irrigation should be implemented to reduce SSI after appendectomy.
Keywords: appendectomy, surgical site infection, risk factors, meta-analysis.

Medication errors - pattern of occurrence and strategies for possible prevention in an Indian setting

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Aims/Objectives: Medication errors (ME) frequently contribute for patient's morbidity and mortality in health care settings. The present study was aimed to identify and assess the pattern of occurrence of MEs and to develop strategies to prevent these MEs.
Methods: It was a prospective study conducted in a teaching hospital over a period of 6 months. Trainee clinical pharmacists followed the patients admitted to general medicine (GM) and general surgery (GS) wards. MEs occurred and the cause for ME was identified by reviewing medical records, interviewing patients and concerned health care professionals (HCPs). Identified MEs were evaluated for its nature, extent, cause and outcome. Strategies for prevention of MEs were developed.
Results: Of the 3035 patients followed, 988 MEs were identified in 703 patients. Prescribing errors were observed highest, both in GM (71.45%) and GS wards (60.4%). The most common reasons for MEs were omission errors (25%), monitoring errors (18.52%), non-adherence to medication (15%), inappropriate drug selection (14%) and drug duplication (12.6%). Most of the MEs were due to inappropriate prescribing by clinicians (51%) followed by patient non-adherence to therapy (21%), improper follow up by ward clinical pharmacists (17%) and administration errors by nursing staff (11%). Strategies were designed to prevent commonly identified MEs. Majority of MEs that reached to patients were not harmful but 48% of them needed monitoring/intervention to ensure patient safety.
Conclusion: Most of the MEs can be prevented if patients are monitored correctly. Appropriate team work from all HCPs can certainly reduce the occurrence of MEs.
Keywords: medication errors, prescribing errors, general medicine wards, prevention of errors

Challenges to and the future of medication safety in Saudi Arabia: A qualitative study

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Objectives: To explored the perspectives of healthcare practitioners on current issues about medication safety in hospitals and community settings in Saudi Arabia in order to identify challenges to improving it and explore the future of medication safety practice.
Methods: A total of 65 healthcare professionals attended a one-day meeting. The participants were divided into nine round-table discussion sessions. Three major themes were explored; major factors contributing to medication safety problems, challenges to improving medication safety practice, and suggestions for improving medication safety. The discussion sessions were videotaped and transcribed verbatim and analyzed by two independent researchers.
Results: Major factors contributing to medication safety problems included unrestricted public access to medications from various hospitals and community pharmacies, communication gaps between healthcare institutions, limited use of important technologies, and the lack of medication safety programs in hospitals. Challenges to current medication safety practice included underreporting of medication errors and adverse drug reactions, multilingualism and differing backgrounds of healthcare professionals, lack of communication between healthcare providers and patients, and high workloads. Suggestions for improving medication safety practices included continuous education for healthcare professionals and competency assessment focusing on medication safety, development of medication errors and adverse drug reactions reporting culture, use of technology proven to decrease medication errors, and promotion and implementation of national patient safety initiatives.
Conclusions: Healthcare professionals have identified major challenges and opportunities for medication safety in Saudi Arabia. Policy makers and practitioners should consider these factors when designing future programs aimed at improving the safe use of medications.
Keywords: Medication safety, healthcare professionals, Saudi Arabia

Design, implementation and evaluation of a standardised inpatient prescription chart across five acute NHS trusts

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Aim/Objective: This project aimed to redesign the inpatient prescription chart to incorporate medication safety features for known risk areas such as allergy status documentation, anticoagulation and medicines reconciliation.
Methods: A prospective evaluation of the quality of documentation and a survey to determine user views about the chart design and its effect on medication safety. Ethics approval was not required.
Results: The evaluation involved 14 wards, 568 patients (255 before; 313 after) and 772 prescription charts (465 before; 307 after). Documentation of essential information was greater than 95% with the original chart but improved marginally with the new chart for most parameters except weight where a reduction was seen. Overall allergy status documentation was similar for both charts (95.1% before vs. 95.4% after), but for patients with known allergies there was an increase in documentation of the nature of the reaction from 40% to 61.3% ($p = 0.02$ X^2 test). Fewer patients required multiple charts following introduction of the new design (30/255; 11.8% compared to 96/313; 30.9%). The use of colour, pre-printed sections for specialist prescriptions and the cut-out section for allergy status documentation were considered to have a positive effect in improving patient safety as reported by 107 users (66 nurses, 23 doctors, 6 pharmacists, 1 pharmacy technician, 4 others and 13 profession not stated). Users identified other ways to enhance the new chart to improve usability and safety aspects.
Conclusion: A collaborative approach with involvement of relevant specialists and stakeholders resulted in the successful re-design, trial and implementation of a standard inpatient chart.
Keywords: medication safety

Medications knowledge and attitude among upper primary school students in Saudi Arabia

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Aim/Objective: To evaluate medications knowledge and attitude among upper primary school students in Riyadh, Saudi Arabia.

Methods: This was a cross-sectional survey distributed to grade 4, 5 and 6 primary school students. The questionnaire consisted of 14 close-ended questions and 10 pictogram measuring knowledge about medications. Students attitude were measured by asking 6 close-ended questions. A score of 1 was given to each correct answer and a score of zero to each wrong answer. The Statistical Package for Social Science (SPSS) version 20 was used to analyze the data.

Results: The questionnaire was distributed to 1500 students, 1306 completed questionnaires were received, response rate 87%. Most of the participants (73.5%) were in the age group 12-15 years; predominantly females (73.7%) and mostly studying in grade 6 (39.1%). 94.9% of the students know that medication is useful, 74.9% know that medications can also be harmful and more than half of the students or their guardian seek information on medications from physician (56.4). More than half 66.3% of the students had positive attitude toward the right steps to take if they forget taking their medications. The mean medications knowledge score was (6.37 ± 2.58) and the mean attitude total score was (1.99 ± 1.1). Male students had significantly better knowledge about medications compared to female (P value = 0.005).

Conclusions: Upper primary school students in Saudi Arabia have poor knowledge and negative attitude towards medications. Perhaps simple education about medications can be helpful to increase children knowledge and attitude regarding medications.

Keywords: upper primary school students, Saudi Arabia, medications, knowledge, attitude

Public perception and evaluation of ophthalmic medications educational booklet in Saudi Arabia

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Aim/Objectives: To assess public perception of safe use of ophthalmic medications; and to evaluate the usefulness of a booklet designed to guide patients on the proper way of administering ophthalmic medications.

Method: A cross-sectional survey was conducted among a convenient sample of general public in Riyadh, Saudi Arabia. A questionnaire consisted of six questions intended to measure participants' perception about the safe use of ophthalmic medications was prepared and validated. Another six questions was prepared to allow participants to evaluate the educational guide designed to help patients to safely administer ophthalmic medications.

Result: 298 people responded to the survey. The mean age of the participants was 28 and most of the participants had university level of education 158 (57.2%). 268 (91.2%) of the participants have ever used eye medications. Eye drops 244 (91%) was used by most of the participants, followed by eye ointment 87 (32.5%). Majority of the respondents 236 (87.4%) agreed that patient suffering from eye diseases need an educational booklet that explains the directions and instructions of ophthalmic medication use. After reading the booklet the explanation and the instructions given in the booklet were found to be very easy and full of useful information by most of the respondents 208 (78.2%). Majority of the respondents encouraged the distribution of the booklet by pharmacists along with the eye medications 241(90.6%).

Conclusion: An educational booklet that guide patient on the safe administration of ophthalmic medications is useful and might help patients to adhere to their medications.

Keywords: cross-sectional survey, ophthalmic medications, Saudi Arabia

The incidence, nature and defences against medication errors in general practice

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Aim and Objectives: The aim of this paper is to identify incidence, nature of medication errors and describe the defences against medication errors present in English general practice.

Method: A qualitative approach was taken, exploring defences against medication errors (specifically prescribing and monitoring errors) in 15 general practices from three Primary Care Trusts in England. Between October 2010 and May 2011, thirty-two GPs participated in audio-recorded interviews exploring their perspectives on the medicines management systems within their practice and the causes of specific errors. A broad range of general practice staff also participated in six audio-recorded focus groups exploring their perspectives on defences against medication errors within their practices.

Results: Errors happen in 1 in eight patients in general practice. The medicines management process within general practice is complex. Defences against medication errors were found at all stages, including issuing new prescriptions, supporting patients' ongoing decision making, dispensing prescriptions (in dispensing practices), repeat prescribing, monitoring patients, and amending prescriptions based on outside correspondence. In addition, there were a plethora of other activities which supported the medicines management process in general practice, including significant event reporting and staff training. Defences against medication errors were wide ranging and included practice-wide, health information technology (HIT) and personal strategies (which prescribers or other staff members could undertake).

Conclusion: General practices have a broad range of practice-wide, HIT and personal strategies to help avoid medication errors reaching patients. Pharmacists can help GPs to reduce errors by identifying patients at risk.

Keywords: prescribing, monitoring errors, general practice, defences

An evaluation of the long-term treatment outcomes of West syndrome

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Aim/Objectives: To compare the results of treatment of patients with West syndrome for more than two year follow-up.

Methods: We conducted a retrospective study of 65 patients (45 boys and 20 girls aged from 2.5 to 8 years) with West syndrome and calculated Risk Ratio (RR with Review Manager 5.2) for comparisons of therapeutic effects of antiepileptic drugs. Favorable outcome: remission lasting for more than two years.

Results: We separated all children with West syndrome into the 2 groups. First group included 45 children (73.8%) who received in treatment tetracosactide (synacthen depot). Different antiepileptic drugs as a mono-and combination therapy (valproic acid, topiramate, clonazepam, vigabatrin, ethosuximide, levetiracetam, lamotrigine) were used in the second group (16 children, 26.2%), but they did not receive tetracozactide. Thirty nine of the 45 patients (86.7%) achieved the linical remission (lack of seizures more than 2 years follow-up) in the first group. Only half of the patients (8/16, 50%) had a similar outcome in the second group. RR was 1.73; 95% CI [1.05 – 2.87], P=0.03.

Conclusion: long-term follow up shows higher effectiveness of tetracosactide for seizure control in patients with West syndrome than other antiepileptic drugs.

Conflicts of interest: – None.

Poster Presentation

Comparative risks of new onset diabetes according to combination of angiotensin system blockers

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Aim/Objective: Angiotensin system blockers including angiotensin converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB), as monotherapy, combination therapy, and fixed dose combination therapy are the most commonly prescribed antihypertensive medication in Korea. ACEIs or ARBs have been linked to reduced risk of new onset diabetes mellitus (DM) but evidence of combination therapy on risk of DM was insufficient. The aim of this study was to evaluate the comparative risks of new onset DM according to combination therapy of ACEIs or ARBs.

Methods: A retrospective analysis was conducted on patients diagnosed with hypertension from January 2007 to December 2011 using Korean Health Insurance Review and Assessment database. After excluding patients exposed to antihypertensive treatment with ACEIs or ARBs within the previous 6 months and had diagnosis of DM or antidiabetic medications, cohorts were defined by monotherapy with ACEIs or ARBs, combination therapy including ACEIs or ARBs +calcium channel blockers (CCB), ACEIs or ARBs+diuretics, and ACEIs or ARBs + beta-blockers. Reference group was monotherapy with calcium channel blockers, which is known to be neutral in risk of DM. Outcomes were defined by diagnosis of DM by International Classification of Disease 10th version (ICD-10, E10—E14) or prescription of antidiabetic medication. Comparative risks of new onset DM among different ARBs were also calculated. Analysis was performed using inverse probability weighted estimators with propensity score adjustment.

Results: Of total of 1,056,033 hypertensive patients, monotherapy with ACEIs or ARBs were 28.5%, most frequently prescribed, followed by monotherapy with CCBs (16.9%), and combination therapy with ACEI or ARB +CCBs (16.1%). When comparing with monotherapy with CCBs, monotherapy with ACEI or ARB were found to have lower risk of new onset DM (Hazard ratio, HR=0.78, 95% CI=0.77-0.79), but combination therapy with ACEI or ARB +CCB (HR=1.14, 95% CI= 1.12-1.16), ACEI or ARB + diuretics (HR=1.50, 95% CI= 1.47-1.54) and ACEI or ARB +beta blockers (HR=1.42, 95% CI=1.39-1.45) were having higher risk for new onset DM. Among different ARB therapy, valsartan was found to have lower risk of DM (HR=0.92, 95% CI=0.87-0.96) compared with losartan.

Conclusion: Compared with CCB monotherapy, ACEI or ARB monotherapy were associated with decreased risk of new onset DM, but combination therapy were increased risk for DM, highest in ACEI or ARB +diuretics followed by ACEI or ARB +beta blockers, and ACEI or ARB + CCBs.

Keywords: antihypertensive agents, angiotensin receptor antagonists, angiotensin-converting enzyme inhibitors, drug combinations, diabetes mellitus, propensity score

Concomitant use of cholinesterase inhibitors and anticholinergics in dementia elderly patients

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Aim/Objective: The effects of cholinesterase inhibitors for dementia may be compromised pharmacologically due to concurrent use of anticholinergic agents for common symptoms occurred in the elderly (i.e., urinary incontinence). While oxybutynin and imipramine are theoretically more influential on central nervous system (CNS) with better distribution, it is unknown how prevalent of such concomitant use in the elderly in Taiwan. This study aimed to explore the concomitant use pattern of cholinesterase inhibitors and anticholinergics.

Methods: A retroactive observational study was conducted in China Medical University Hospital (CMUH), a 2000-bed medical center. Those outpatients treated with two cholinesterase inhibitors in CMUH between January 2011 and December 2012 were evaluated for their prescriptions of anticholinergic agents. The descriptive analysis was performed to examine the concomitant prescription patterns of available cholinesterase inhibitors and anticholinergic agents (i.e., oxybutynin, imipramine, tolterodine, solifenacin succinate).

Results: In two years, 328 elderly dementia patients (Age: 78; 8.1 years-old; female: 60%) were ever prescribed with one of cholinesterase inhibitors. While more elderly were prescribed with Rivastigmine (52%) than donepezil, only twenty-nine elderly (8.8%) were prescribed with any of anticholinergic agents concomitantly. Although the two good CNS anticholinergics accounted for 65% of all concurrent use (oxybutynin ER: 45.3%, solifenacin succinate: 19.7%, tolterodine: 14.8%, imipramine: 20.2%), the majority were short-term use.

Conclusion: With less than 10% were concurrent use of cholinesterase inhibitors and anticholinergics among dementia elderly patients, the two CNS good penetration anticholinergics contributed to approximately two thirds of prescriptions. Further exploration is necessary to investigate the outcomes of such concurrent use.

Keywords: anticholinergic agents, dementia, elderly, cholinesterase inhibitors

Estimating patient drug regimens and regimen transitions from prescription supply data

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Aim/objectives: To estimate patterns of multiple medicine use on an individual patient basis using administrative medicines claim data in Australia.

Methods: The Australian Government collects Pharmaceutical Benefits Scheme (PBS) subsidised prescription data that includes information on the date of supply of each prescription. This presentation describes a method of estimating patient drug regimens (ie. sole therapy or co-administration) and drug regimen transitions (ie. initiating, switching, adding and ceasing drugs) using prescription supply data.

Results: The outcome is an estimated treatment regimen for each patient for every day in the data period. A key strength of the method is the ability to display the results graphically enabling the visualization of utilisation patterns. The presentation will contain examples of this output.

Conclusion: Estimation of patient drug regimens and regimen transitions has proven to be a valuable tool in the assessment of drug utilisation by the Pharmaceutical Evaluation Branch of the Australian Department of Health and Ageing. Patterns of drug use, including switching between treatments, co-administration and cessation, inform many aspects of public health policy and are of interest to researchers of utilisation.

Keywords: drug utilisation evaluation

Neighborhood material and social deprivation and use of antidepressants in depression

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Background: The Quebec's public drug plan aims to provide to residents equal access to medication. One would therefore assume that access of individuals suffering from depression to antidepressants (AD) and to guideline-recommended 1st-line (GR1)-AD, proposed by the Canadian Network for Mood and Anxiety Treatments, would not differ according to their material and social deprivation (M&SD) level.

Aims/Objectives: Among individuals suffering from depression with the most M&SD and those with the least: to describe the proportion exposed to ADs in the year following diagnosis; and among the latter, to describe the proportion who obtained a GR1-AD as the initial prescription.

Methods: Using Quebec administrative health data, we conducted a cohort study including individuals aged ≥18 years, newly diagnosed with depression between 1997/01/01 and 2006/12/31 and enrolled in the public drug plan 1-year before and 2-years following depression diagnosis. Neighborhood M&SD were measured using indices built and validated using the Quebec population. Individuals in the 1st and 5th quintiles were the least and most deprived, respectively. Individuals were considered exposed to an AD if they obtained such a drug in the 365 days following diagnosis. Difference in proportions between the most and the least deprived groups was tested using 95% confidence intervals (CI).

Results: Out of 100,455 individuals included, 65,453 (65%) were exposed to an AD in the year following diagnosis. Groups with the least (n=2000) and the most (n=7054) M&SD, 63.6% (95%CI=60.8-66.4) and 64.6% (63.21-66.2) were exposed to an AD, respectively. Among the 65,453 exposed to an AD, 58,204 (89%) obtained a GR1-AD as the initial prescription. The proportion of individuals initially exposed to a GR1-AD was 88.4% (83.6-93.2) in the least deprived group (n=1271) and 87.3% (84.8-89.8) in the most deprived one (n=4560).

Conclusions: Results suggest, Quebec drug plan achieves its goal as access to AD or GR1-AD treatment does not differ between the most and the least deprived groups.

Socioeconomic disparities in receiving long-acting insulin analogues under a universal healthcare system

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Aim/Objective: Explore whether the socioeconomic disparities in receiving long-acting insulin analogues persist in a universal healthcare setting with benefit coverage for the medication cost, such as that found in Taiwan.

Methods: A cross-sectional observational study design using Taiwan's population-based National Health Insurance claims data. Patients who first received intermediate human insulin, long-acting human insulin or either of the two long-acting insulin analogues: glargin or detemir, between 2007 and 2010 were included. Patients who had received intermediate human insulin or long-acting insulin before 2007 were excluded. The probability of receiving long-acting insulin analogues among the providers' geographic areas with different socioeconomic status (households of low-income families, persons with higher education) were estimated after controlling for age, gender, physician's specialty and types of provider: medical center, regional hospital, district hospital, local clinics.

Results: A total of 11167 patients received intermediate or long-acting human insulin (22.2%) and 39029 received long-acting insulin analogues (77.8%), and were included in this study. Physicians who were endocrinologists had a higher probability of prescribing insulin analogues (OR: 1.87). After controlling for patient-and provider-level factors, providers located at the areas with more low-income households had a lower probability prescribing insulin analogues (OR: 0.80). On the contrast, providers located at the areas which are the upper quartile of the percentage of high-education persons had a higher probability prescribing insulin analogues than those at the lower quartile (OR: 1.31).

Conclusion: Although the current National Health Insurance's benefit plan has increased a patient's accessibility to long-acting insulin analogues, the socioeconomic disparities remain.

Statin use in the elderly; Dose, potency and potential for harm

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Aim/Objective: To describe the prevalence and incidence of statin use in elderly patients and to determine whether initiation of statins is associated with an increased risk of initiation of medicines that may be used to treat myopathy.

Methods: Prescription sequence symmetry analyses were undertaken. PSSA assessed asymmetry in the distribution of incident dispensing of non-steroidal anti-inflammatory drugs (NSAIDs), indicative of treatment for myopathy, before and after incident dispensing of statins. Crude and adjusted sequence ratios (ASR) with 95% confidence intervals were calculated.

Results: Statin use increased in the population from 12% in 2001 to 33% in 2011. Statins were initiated in 4% per year in patients 85 or over compared to 5% in those aged less than 85. Of those patients on statins aged 85 or over, 60% were prescribed the medicine for primary prevention. High dose, high potency statins were used by one in four of those aged 85 years and older. Significant associations between initiation of statins and subsequent initiation of NSAIDs were found. ASRs ranged from 1.30 (95% confidence interval (CI) 1.11-1.52) for rosuvastatin to 1.67 (95% CI 1.56–1.78) for simvastatin.

Conclusion: Our study has highlighted that initiation of statins is common in the elderly. Initiation of statins was associated with initiation of NSAIDs which may be suggestive of myopathy. The effectiveness of statin use in the elderly population for primary prevention for which there is limited evidence must be weighed against the potential for adverse events in this population.

Keywords: statins, myopathy, prescription sequence symmetry analysis, drug utilization

Study of prescribing patterns of antihypertensive drugs and anti-diabetic drugs in tertiary care hospital

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Aim/Objective: To the study the prescribing patterns of antihypertensive drugs and anti-diabetic drugs in tertiary care hospital.

Methods: A cross-sectional study was conducted for the period of two months in an In-patient department at tertiary care hospital, Manipal. Patient's of the age >18 years and either gender with hypertension and diabetes. Patients prescribed with antihypertensive drugs and anti-diabetic drugs were included in the study. Data was obtained directly from the patient's medical records. The collected data was analyzed for the prescribing pattern of antihypertensive and anti-diabetic drugs used in the treatment of hypertension and diabetes.

Results: A total of 65 patient's medical records were analyzed for prescribing patterns of antihypertensive drugs and anti-diabetic drugs. Among them 38.46% (n=25) were Diabetes with Hypertension, 38.46% (n=25) were only diabetic and 23.07% (n=15) were only hypertensive patients. Out of sixty five patients 73.84% (n=48) of the patients were male followed by 26.15% (n=17) female and 30.76% (n=20) patients were in the age group of 45-60 years and >60 years followed by other age group. 55% of the patients were Pre-obese (25-29.9 mg/kg2) followed by 30% of normal weight and 15% were obese patients. In the present study 42.5% (n=17) of the patients were pre-hypertensive's (120–139 or 80–89 mmHg) followed by 35% (=14) were stage-2 and 22.5% (n=9) stage-1 hypertensive patients. 76.92% (n=20) of the patients of glycosylated hemoglobin (HbA1C >7%) followed by 23.07% (n=6) (HbA1C <7%).The most commonly prescribed antihypertensive drug class was 48% (n=24) of Calcium Channel Blockers followed by 16% (n=8) of Angiotensin II receptor antagonists, 12% (n=6) of β–Blockers, Diuretics and Centrally active alpha 2 receptor blockers. The most commonly prescribed anti-diabetic drugs were 44% (n=32) Insulin followed by 16% (n=8) Metformin, 12% (n= 6) Glimepiride and others.

Conclusion: In the present study Calcium channel blockers and Angiotensin II receptor antagonists were the most commonly prescribed antihypertensive drug class and Insulin followed by Metformin were most commonly prescribed drugs in diabetic patients.

Keywords: prescription, hypertension, drug utilization, diabetes.

The perceptions and attitude among community pharmacy patrons towards non-prescription medicines

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Aim/Objective: To explore the perceptions and attitude among community pharmacy patrons towards non-prescription medicines (NPM) and self-medication practices.

Methods: A face-to-face interview, using semi-structured questionnaire was conducted among community pharmacy patrons who purchased NPM. The principle saturation sampling was applied to determine the number of interviews required for gathering data. The data collected were transcribed verbatim and analysed using thematic analysis for theoretical constructs, themes, repeating ideas and relevant texts.

Results: Thirteen subjects were interviewed in which eight distinct theoretical constructs were identified. Most of these findings focused on the definition of NPM, cognition source of NPM, importance of NPM registration, factors affecting confidence in NPM usage and factors associated with patient's decision to self-medicate. Most subjects had their own definition of NPM. Source of information were self-exploration and healthcare personnel. The efficacy, safety and quality were the main concern in NPM registration. The decision to self-medicate or seek doctor depends on their perceptions of own health conditions, inherent knowledge and their confidence in healthcare professionals. Overall, subjects were receptive of NPM and self-medication, driven by confidence in healthcare professionals, influence of close social circles, role of past experiences, desire for a greater role in own health and also several advantages over conventional care from doctors in terms of cost, convenience and time factor.

Conclusion: The perception and attitude led to the high utilization of NPM even there are numbers of free healthcare institution served by Malaysian government. Therefore, the policies that promote the rational use of NPM should be implemented.

Keywords: non-prescription medicines, self-medication, qualitative

Poster Presentation

The use of analgesic agents among cancer patients receiving hospice care in Taiwan

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Introduction: Pain is one of the most common symptoms in cancer patients; most of cancer patients did not receive adequate pain management, especially for patients receiving hospice care. The aim of this study was to analyze the 8-year trends of using analgesic agents among cancer patients in Taiwan.

Methods: The longitudinal national health insurance research database from 2001 to 2008 was applied in this study. The cancer patients were identified by the records of catastrophic illness certification. The hospice ward care was according to the medical expenditure applications codes. The disease records were diagnosed by the format of International Classification of Diseases, Ninth Revision, Clinical Modification. The demographic characteristics and the use of analgesic agents were collected and analyzed. The descriptive statistics present the frequency and mean for categorical and continuous variables, respectively. The trend test was used to analyze the change during the study periods. All analyses were performed using SAS 9.3 (SAS Institute, Inc, Cary, NC).

Results: A total of 1059 cancer patients received the hospice care in our study. The mean age was 65.67 ± 14.50. Most patients stayed in medical center (68.37%) and distributed in northern (51.23%). The median of use of analgesic agents increased from 612.5mg in 2001 to 645mg in 2008.

Conclusion: The increasing trend of patients received hospice care would be a challenge for the medical team to manage the cancer pain. Using analgesic agents reducing pain during the end-of-life may be the easiest way, but the emotional support should be more important for patients in the hospice care.

Keywords: analgesic agents; hospice care; cancer patients; national health insurance research database

A systematic review of the causative drugs of Stevens-Johnson syndrome

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Aim/Objective: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are immune-complex–mediated hypersensitivity reactions with high mortalities that predominantly involve skin and mucous membranes. Although as many as half of cases are idiopathic, drugs have been implicated as main cause of SJS/TEN. This study aimed to identify drugs that were most associated with SJS/TEN and compare risks of the medications.

Methods: A comprehensive search was made of MEDLINE, Embase and 5 Korean databases. We defined study drugs as NSAIDs, antibiotics, antiepileptics, and allopurinol. Only epidemiologic studies investigating associations between the above drugs and drug-induced SJS/TEN were included. Two reviewers independently selected and assessed the quality of each study. The following information was extracted from each paper where possible: population, classes of drugs, follow-up period, odds ratios and incidences.

Results: Of 2,195, 8 case-control studies, 3 cohort studies and 1 RCT met our inclusion criteria. The ranges of adjusted ORs were 0.6-34.0 for NSAIDs, 1.6-302.0 for antiepileptics, 0.3-10.0 for antibiotics and 1.0-187.0 for allopurinol. The drug with the highest incidence of SJS/TEN was carbamazepine (40 persons/1,000 DDD). The risk was highest in first 8 weeks after onset of treatment in all drugs. Especially from the researches on HLA allele, the risk of carbamazepine and allopurinol induced SJS/TEN was significantly higher in Asian patients.

Conclusion: The results suggest that SJS/TEN represents a clinically important adverse drug reaction, and showed higher risk in Asian population. However, there were no studies on Korean population. Well-designed studies to estimate the prevalence of SJS/TEN and examine its characteristics are urgently required.

Keywords: adverse drug reaction, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), systematic review

Pharmacoepidemiological assessment of medication adherence rates among diabetic patients in South India

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Aim/Objective: The objective of the study was to assess the medication adherence among diabetic patients in South India.
Methods: A prospective observation study was conducted for a period of six months in both inpatients (n=43) and outpatients (n=97) of diabetic patients. Patient's of the age >18 years and either gender of diabetes were included in the study. Socio-demographics, duration of diabetes, co-morbidities, data and the prescribing pattern of anti-diabetic drugs in the treatment of diabetes were collected from the patient's medical records. The structured medication adherence questionnaires was framed and validated by committee of experts of health care providers. Same was administered to the diabetic patients and were assessed for medication adherence.
Results: A total of 140 patients were enrolled during the study period. Out of 140 patients, 79 (56.57%) were females and 61 (43.57%) were males. Among them 82 (58.56%) patients were in the age group of 40-60 years followed by 49 (35%) >60 years and others. In the present study 77 (55%) patients were illiterates, duration of diabetes was in the range of 1-5 years in 69 (49.28%) and hypertension 100 (71.42%) was the most common comorbid condition. One hundred and six (75.71%) patients were prescribed with combination of Oral hypoglycemic agent's, 17 (12.14%) were prescribed with insulin and oral hypoglycemic agents, 17 (12.14%) were prescribed only with Insulin and 5 (3.57%) patients were on oral hypoglycemic agents as monotherapy. The overall medication adherence rate was found to be 74.28%. The main factors for nonadherence was forgetfulness 19 (13.57%), easy inaccessibility 12 (8.57%), lack of finance 9 (6.42%) and others.
Conclusion: In the present study 74.28% of the patients were adherence to the prescribed medications. Most commonly prescribed oral hypoglycemic agents were Metformin and Glimepiride in 70 (50%) patients followed by Metformin and Glipizide in 15 (10.71%).
Keywords: medication adherence, diabetes, pharmacoepidemiology, prescription

Study of quality of life in psoriasis patients

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Aim/Objective: To assess the health-related QoL among patients with psoriasis
Methods: Psoriasis patients attending the Dermatology OPD were administered a quality of life questionnaire. The Dermatology life quality Index (DLQI) questionnaire was used. Socio-demographic variables like age, sex, education, occupation were collected. Based on DLQI questionnaire, QoL of patients was assessed.
Results: Total score of DLQI was calculated and the QoL was correlated with severity No association was obtained for total score and age or gender.

Taiwan birth cohort based on administrative datasets (TBCBA): Implications for life-course pharmacoepidemiological researches

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Aim/Objective: To establish a population-based birth cohort based on health-related administrative datasets in Taiwan for life-course pharmacoepidemiological researches.

Methods: As every citizen in Taiwan has a unique identification number, we used personal identification number to link the Birth Notification (2001-2011), the Birth Registry (2001-2009), the National Health Insurance (NHI) Claims (1998-2011), the Cancer Registry (2002-2009), and the Cause-of-Death Registry (1971-2011) to establish the Taiwan Birth Cohort Based on the Administrative Datasets (TBCBA). To assure the information security and to avoid the releasing of personal information, all of the analyses should be performed in the isolated restrict room in Collaborative Center for Value-Added Analysis run by the Office of Statistics, Department of Health, Taipei, Taiwan. The researchers could only bring out the statistics tables and could not bring out any of original datasets.

Conclusion: As there are drug prescription and refill information in NHI claims datasets, which include name and dose of the drug, duration and frequency of the drug, the TBCBA could provide a good opportunity to examine the short-term therapeutic effects and long-term adverse effects of drug use during the neonatal and early childhood period.

Keywords: administrative data; birth cohorts, life-course epidemiology, pharmacoepidemiology, Taiwan

Anti-diabetic drug uses and cost during inpatient care for patients with diabetes in West China Hospital: a cross-section study with a large Chinese electronic medical record database

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Objective: To investigate the use of oral hypoglycemic agents(OHAs) and insulin and cost of hospitalized patients with diabetes in a typical teaching hospital in China.

Methods: In this cross-sectional study, all patients with diabetes discharged from West China Hospital, Sichuan University from Jan 2009 to May 2013 were recruited via electronic medical records database. Demographic characteristics, prescription, and hospital cost were collected.

Results: A total of 42114 cases with diabetes (25133 men) were identified from the database. The median total hospital cost was 11857.83 (P25-P75, 6768.87-23830.97) RMB, of which 3716.89 (P25-P75, 1453.64-8928.47) RMB was pharmaceutical cost. There were 8679 (21%) patients received intravenous insulin infusion-pump during hospitalization. These patients had higher male/female ratio, greater age, longer length of stay, and higher total cost. Additionally, 27804 (66%) patients used subcutaneous insulin injection. Among them, 10279, 6916, and 10609 patients used one, two, and three types of insulin, respectively. Number of insulin types was positively correlated with both total cost and length of stay (P<0.05). For those who never use subcutaneous insulin, 5153 (36%), 2220 (16%), and 472 (3%) patients used one, two, and three types of OHA, respectively. However, number of OHA types used wasn't associated with either total cost or length of stay.

Conclusion: Insulin has being widely used in diabetic inpatients in China. The use of insulin was associated with higher cost and longer length of stay. (supported by Merck Sharp Dohme Corp)

Keywords: diabetes mellitus, economics, inpatient, electronic medical records

Poster Presentation

Iatrogenic aluminum and Moroccan children's memory

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Aim/Objective: The evaluation of the memory faculties among Moroccan schooled children (aged 6–8 years) living in the Gharb Plain (North-West of Morocco) and the study of the possible relationship between this faculty and the consumption of iatrogenic aluminum.
Methods: A cross-sectional study is conducted among 129 school-aged children living in the urban, periurban and rural region of the Gharb Plain (N-W of Morocco). The children suffering from cranial traumatism or neurologic disease are excluded. The memory faculties are measured by Memory Sub-test of WISC III (Wechsler Intelligence Scale for Children). The consumption of iatrogenic aluminum and the quality of children's life are evaluated by the questionnaire. Statistical analyses are realized by ANOVA 1, LSD and Pearson correlation coefficient.
Results: The obtained results show that the high rate of working memory impairments (66.67%) is registered among rural children. Significant correlations between performance of working memory ($p < 0.05$) and consumption of iatrogenic aluminum are also found.
Conclusion: The children's memory appear in connection with iatrogenic aluminum consumption. However, several factors (environmental, psychological, socio-economical, and nutritional factors) could influence this performance. So, deeper investigations are needed for studying all these factors.
Keywords: iatrogenic, aluminum, memory, children, Morocco.

Late initiation of insulin therapy in type 2 diabetes mellitus patients: observation from single teaching hospital in Taiwan

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Objectives: To investigate the status of type 2 diabetes mellitus (TTDM) patients when insulin therapy was initiated in clinical practice settings.
Methods: We performed a cross-sectional study by using electronic health records (EHR) from single hospital in Keelung, Taiwan. TTDM patients under oral antidiabetes medications (OADs) and newly received insulin therapy form July to December in 2012 were included. Patients without HbA1c test record during 6-month period before index date were excluded to ensure the baseline information on blood glucose was available. We excluded patients with single insulin prescription after index date to avoid temporal use of insulin therapy. Patients' baseline HbA1c, complications, and utilization of OADs were analyzed to evaluate the TTDM status of patients when insulin therapy was initiated.
Results: 41 patients with 46.3% male gender and age of 60.5±12.1 years were included. Baseline HbA1c of patients was 10.6±2.2%, and more than half of them (63.4%) received at least three kinds of OADs combination before insulin therapy initiation. 41.5, 19.5, 19.5, 7.3% of patients comorbided major vascular diseases, diabetes nephropathy, retinopathy and neuropathy respectively.
Conclusion: The baseline HbA1c of patients initiating insulin therapy was high; additionally, most of patients had received more than 3 kinds of OADs and had complications related to TTDM before insulin therapy initiation. The results indicated the status of TTDM was relatively severe and implicated the timing of insulin therapy was late based on guideline suggestions. Study to investigate the reason for the late initiation of insulin therapy was needed.
Keyword: insulin therapy, type 2 diabetes mellitus.

Self-poisoning with drugs: the past 11 years in Mali

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Aim/Objective: Voluntary poisoning is a major medical and social problem in developing countries and the most common method of attempted suicide. The aim of this study is to determine the frequency and the main characteristics of drug self-poisoning in Mali.
Methods: This is a retrospective analysis of voluntary poisoning cases, recorded between 2000 and 2010, in the medical records and the consultation register at 15 hospitals in Mali.
Results: There are 654 drug self-poisoning cases diagnosed, which is 75% of all voluntary poisoning cases reported during the study period. Of these, 558 (85.3%) are females and 79.2% are unmarried. Most victims are in their late teens or early twenties. The average age at diagnosis is 21.9±7.4 years. Suicide attempts and self-induced abortion are the most common forms of self-poisoning (59.3% and 38% of cases, respectively). The most commonly used drug for self-poisoning is chloroquine (67%). The poisoning effects vary depending on the type of drug consumed, the dose taken and the delay before treatment. Among the 648 cases for whom the evolution is known, 45 of them died. For other cases, the outcome is favourable with or without sequelae.
Conclusion: Drug self-poisoning remains a major public health problem in Mali. The number of victims is probably underestimated because of undiagnosed and unreported cases.
Keywords: drug, chloroquine, self-poisoning, Mali

Poster Presentation

Survey of pain syndrome in patients with pancreatic cancer in a medical center in Taiwan

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Aim/Objective: To assess pain and pain characteristics in advanced pancreatic adenocarcinoma patients.

Methods: A cross sectional study was conducted in a tertiary referral center. All advanced pancreatic cancer patients from September 2012 to January 2013 were invited. To assess pain, the pharmacist interviewed patients by a validated questionnaire, which is a short form of Brief Pain Inventory in Traditional Chinese.

Regarding neuropathic pain, Douleur Neuropathique 4 Questions (DN4) in Traditional Chinese was employed. Clinicians also independently evaluated if these patients had neuropathic pain.

We calculated the proportion of patient suffering pain as the number of patients reporting pain divided by the total number of observed patients. We estimated the proportion of patients with neuropathic pain by both DN4 and clinicians' assessment. We examined the bivariate association of DN4 and physician diagnosed depression with Fisher's exact test. Exact methods were used to calculate 95% CIs. All analyses were performed with SAS 9.3 software.

Results: In 50 eligible patients, 36 (74%) patients reported pain at the time of visit, while 28 reported no to mild average pain. 33 patients received pain relieving medication, 14 reported complete pain relief, 13 patients reported 50-90% pain relief, 4 reported less than 50% pain relief and 2 reported no change under current medication.

Among patients with pain, 17 (47.22%) were assessed as neuropathic pain by clinicians, 6 (16.67%) were identified by DN4. The concordance of clinicians' diagnosis and DN4 was 0.02 (p=0.33). None of the patients were taking or prescribed drugs for neuropathic pain at the time of interview.

Conclusion: More than 70% of advanced pancreatic adenocarcinoma patients in our observation reported pain. Among patients with pain, 16.67% and 47.22% were neuropathic pain as evaluated by DN4 and clinicians' assessment, respectively.

Keywords: pain, pancreatic cancer pain, neuropathic pain

Paediatric pharmacovigilance: Use of pharmacovigilance data mining algorithms for signal detection in a paediatric phase IIIb clinical trial safety dataset from 7 African countries

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Background: Pharmacovigilance programmes monitor and help ensuring the safe use of medicines which is critical to the success of public health programmes. The commonest method used for discovering previously unknown safety risks during post-marketing is spontaneous notifications. In this study we examine the use of data mining algorithms to identify signals from adverse events reported in a phase IIIb clinical trial evaluating the efficacy and safety of several artemisinin-based combination treatments (ACTs) in African children.

Methods: We used safety data from a randomized, open-label non-inferiority clinical trial conducted in 12 sites in seven African countries. Each site compared three out of four ACTs, namely amodiaquine-artesunate (ASAQ), dihydroartemisinin-piperaquine (DHAPQ), artemether-lumefantrine (AL) or chlorproguanil/dapsone and artesunate (CD+A). We applied and assessed two pharmacovigilance signal generation methods, namely the proportional reporting ratio and the Bayesian Confidence Propagation Neural Network.

Results: A total of 4,116 children (6-59 months old) with uncomplicated *P. falciparum* malaria were treated (1,226 to AL; 1,002 to ASAQ; 413 to CD+A, and 1,475 to DHAPQ), followed up actively until day 28 and then passively for the following six months. Patients who received CD+A were excluded from this analysis since the use of this drug was discontinued for safety reasons. A total of 6,238 adverse events were reported, resulting into 346 drug-event combinations. Nine signals were generated both by proportional reporting ratio and Bayesian Confidence Propagation Neural Network. A review of the manufacturer package leaflets or a Multi-Drug Symptom/Interaction Checker (DoubleCheckMD) and further by therapeutic area experts reduced the signals to five. The ranking of some of the drug-adverse drug reactions (ADRs) pairs on the basis of their signal index differed between the two methods.

Conclusions: The two data mining methods presented in this paper worked well in predicting signals. They could be used to analyse Phase IIIb clinical trials safety data to complement spontaneous reporting systems and validate previously reported ADRs.

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No.1 Anti-Allergic Rhinitis therapy in Hong Kong[4]

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