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

VYTORIN®
(ezetimibe/simvastatin)

High Efficacy, Low Dose

50% Mean LDL-C Reduction at a Usual Starting Dose[1a]

- Provided superior LDL-C reduction & brought more patients to goal[1b]
- Generally well tolerated in clinical trials[2]

Choose VYTORIN® to help patients achieve goal right from the start[c]

[a] Usual starting dose: VYTORIN 10/20mg

[b] NCEP ATP III LDL-C goal < 2.6 mmol/L

[c] Patient should be placed on a standard cholesterol-lowering diet as well as exercise before receiving VYTORIN and should continue on these life-style changes during treatment with VYTORIN. Reduction was shown in clinical trial as early as 6 weeks

The following excepts are from the Prescribing Information for VYTORIN.

INDICATIONS: Primary Hypercholesterolemia: ***VYTORIN*** is indicated as adjunctive therapy to diet for the reduction of elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and non-high-density lipoprotein cholesterol (non-HDL-C), and to increase high-density lipoprotein cholesterol (HDL-C) in patients with primary (heterozygous familial and non-familial) hypercholesterolemia or mixed hyperlipidemia. **Homozygous Familial Hypercholesterolemia (HoFH)** ***VYTORIN*** is indicated for the reduction of elevated total-C and LDL-C levels in patients with HoFH, as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable. **CONTRAINDICATIONS:** Hypersensitivity to the active substances or to any of the excipients. Active liver disease or unexplained persistent elevations of serum transaminases. Pregnancy and nursing. **PRECAUTIONS: Myopathy/Rhabdomyolysis:** Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. All patients starting therapy with ***VYTORIN***, or whose dose of ***VYTORIN*** is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. **Liver Effects:** In controlled coadministration trials in patients receiving ezetimibe with simvastatin, consecutive transaminase elevations (≥3 X ULN) have been observed. It is recommended that LFTs be performed before treatment with ***VYTORIN*** begins and thereafter when clinically indicated. Patients titrated to the 10/80-mg dose should receive an additional test prior to titration, 3 months after titration to the 10/80-mg dose, and periodically thereafter (e.g., semiannually) for the first year of treatment. In controlled clinical coadministration trials, the incidence of clinically important elevations in serum transaminases (ALT and/or AST 3 X ULN, consecutive) was 1.7% for patients treated with ***VYTORIN***. These elevations were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment. **Hepatic Impairment:** Treatment with ***VYTORIN*** is not recommended in patients with moderate (Child-Pugh score 7 to 9) or severe (Child-Pugh score >9) liver dysfunction. **Fibrates:** The safety and effectiveness of ezetimibe administered with fibrates have not been studied. Therefore, the combination of ***VYTORIN*** and fibrates should be avoided. **SIDE EFFECTS:** In clinical trials, the most comment (> 1%) adverse effects with ***VYTORIN*** were headache, flatulence, and myalgia. **DOSAGE AND ADMINISTRATION:** ***VYTORIN*** is not recommended for pediatric patients.

Before prescribing, please consult the full prescribing information.

References: 1. Ballantyne CM et al. Dose-comparison study of the combination of ezetimibe and simvastatin (Vytorin) versus atorvastatin in patients with hypercholesterolemia: The Vytorin Versus Atorvastatin (VYVA) study. Am Heart J. 2005; 149: 464-473. **2.** Hong Kong Product Circular (VYTORIN, MSD).

(There are other strengths available)

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Merck Sharp & Dohme (Asia) Ltd.
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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
- Drug & Therapeutics
- OTC & Health
- Pharmaceutical Technique & Technology
- Medication Safety
- Herbal Medicines & Nutraceuticals
- Society Activities
- 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.

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Society Activities

New Products

Get a Load and Proper Treatment of Fever

We have received several articles covering an issue relevant to the causes, problems and various treatments of abnormal body temperature as well as the quality control of therapeutics used for its treatment. Because of these contributions, it allows us to dedicate this issue specifically on fever. We hope that similar special issues could be met if more pharmacists would like to get involved and to share.

A fever means the body temperature has been elevated beyond the normal range. It is a natural response to reflect that something is wrong inside the body. An infection is the most common cause of fever. Other causes include too much exposure to the sun, an allergic reaction and an adverse reaction to an immunization. As explained by Baibado *et al* in page 110-116, it is often accompanied by unpleasant symptoms such as headaches, chill, muscle pain, nausea, vomiting and diarrhea.

When the body temperature increases or gets really hot, most people are tempted to take medication right away. This is actually a wrong practice. As fever is caused by body's attempt to return to its normal state, it is no need to apply medicines at the first sign. Contrary, it is more important to monitor the fever very closely. Be sure to take body temperature regularly to determine if it is worsening. If fever continues to increase or shows no signs of breaking, then take medicines that have the ingredient to help reduce it. This will also help alleviate some of the aches, pains and other uncomfortable symptoms associated with a fever.

Besides the most commonly used medicines such as aspirin, acetaminophen or ibuprofen, which are available over-the-counter in most drug stores, Asian people may opt to use herbs for eliminating the body heat or infections. One of the most popular herbs for this purpose is honeysuckle, or Jinyinhua in Chinese. Its distribution, biological features, applications and various aspect of its safety during use are the focus of a mini- review written by Yang and Cheung (p.123-129). Different aspects of its natural compounds and their beneficial effects are also addressed in this article.

Not only that the right drug should be used to treat fever, the contents of its main ingredient during and after drug manufacturing should also be properly monitored too. In this aspect, a study conducted by Lau *et al* using a liquid chromatographic method revealed that the amount of paracetamol in different brands produced in the greater China region and in the United States was satisfactory; the content fulfilled what have been put down on the label and met the requirements of the official compendium of the United States. Readers should turn to p117-121 for details of their findings.

Fever is not a symptom found merely in sick person who has been infected by microorganisms, it could also be referred to the attitude or morale of people towards an affair. In many occasions, it is a measure of enthusiastic or devotion to a movement. From the political point of view, fever of a society is protest and demonstration; both reflect some social problems or conflicts have been bred. For instance, a series of appeal followed by uprising more than a century ago during the Chin Dynasty reflected the strong desire for political reform before the fall of the dynasty. Historians describe these uprising, including the Xinhai Revolution in Wu Han as revolutionary fever. The uprising on October 10, 1911 spread very fast throughout the whole country and became a milestone in the Chinese history as it ended China's monarchy system. In the last eight months, people have witnessed countries in North Africa and the Middle East being hit by a wave of revolutionary fever with gutsy mass protests and sustained political demonstrations toppling regimes and causing chaos. The ousting of Egyptian President Hosni Mubarak, Tunisian President Zine El Abidine Ben Ali and more recently, the fall of Libyan dictator, Moammar Gadhafi make the whole world knows that only people are the real ruler of a country. Dictators, no matter how powerful they are, will be eventually pulled down if they do not devote their life wholeheartedly and unselfishness for their country with authority and power entrusted by their kinsmen.

For pharmacists, we may not be as powerful as many politicians. However, we have also been entrusted power according to law to use and dispense drugs, that would save life if they are used properly, based on our professional trainings. Hence, pharmacists are obliged and have a devotion fever to coach and to tell others how to use these compounds. It is glad to learn that an outreach service was launched by our students from the pharmacy school to give advices to senior citizens and to educate them how to use drug properly. Since the start of this service more than three years ago, they found that senior citizens have benefited a lot. It is concluded that pharmacy outreach service should be continued and encouraged. Readers are encouraged to turn to p133-135 for the whole story of this service fever. Our service fever should not be restricted to provide assistance for ordinary people but should also cover coaching services for junior or freshly graduated pharmacists so that they could be mature in their professional growth. Chong and NG explain to us why coaching is needed in these days and the first part of their article could be found in page 102-104.

To conclude, after going through most of the articles published in this current issue, the editor found that the symptoms of fever is a paradigm for everyone to learn. It is about the evolution of a problem, whether it is an infection, intention or behavior, they all share a similar pattern; requirement of some stimulating factors before some signs emerging to surface. The observed signs are not necessarily bad or good but they do reflect something is wrong inside. As long as they are properly controlled, handled and treated, the organic body will be back to its normal function. To overcome whatever problems that may arise, it requires wisdom rather merely relies on knowledge, skill or power.

Cheung Hon-Yeung
Editor-in-Chief
25th October, 2011

The Treatment with Angiotensin Receptor Blockers for High Blood Pressure Does Not Increase Risk of Cancer

Date: June 2, 2011

The U.S. Food and Drug Administration today announced that a group of medications used to control high blood *pressure, called angiotensin receptor blockers (ARBs), do not increase the risk of developing cancer in patients using the medications. In July 2010, the FDA reported that a safety review of ARBs would be performed after a published study found a small increased risk of cancer in patients taking an ARB compared to those patients not taking an ARB. For this safety review, the FDA evaluated 31 randomized clinical trials, comparing patients taking an ARB to patients not taking an ARB, looking for the incidence of cancer. The FDA has completed its review of controlled trial data on more than 155,000 patients randomized to ARBs or other treatments and finds no evidence of an increased risk of cancer in patients who take an ARB. The FDA has determined that any concern about a relationship between ARB use and development of cancer has been resolved by this analysis.*

Source:http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm257670.htm

Chinese Scientists Unravel the Highly Infectious and Toxic Strain of *E. coli*

Date: June 3, 2011

Chinese scientists have shed light on Europe's mystery killer *E. coli* outbreak which is caued by a new, highly infectious and toxic strain of bacteria that carries genes giving it resistance to a few classes of antibiotics. The mutant E coli strain has made more than 1,500 people ill, including 470 who develop a rare kidney failure complication, and kill 18, including one overnight in Germany, the country hit hardest. Researchers have been unable to pinpoint the cause of the illness, which has hit at least nine European countries, and prompted Russia to extend a ban on vegetables to the entire European Union.

"This *E. coli* is a new strain of bacteria that is highly infectious and toxic," said scientists at the Beijing Genomics Institute (BGI) in Shenzhen. The scientists, who are collaborating with Germany's University Medical Centre Hamburg-Eppendorf, completed sequencing the genome of the bacterium in three days after receiving DNA samples. They said the bacterium was closely related to another *E. coli* strain, EAEC 55989, which was previously isolated in Central Africa and know to cause serious diarrhea. "The analysis further showed that this deadly bacterium carries several antibiotic- resistant genes, all of which makes antibiotics treatment extremely difficult," the scientists said. Authorities are still hunting for the source of the new bacteria, which is believed to have contaminated raw vegetables. Some scientists suspect the deadly *E. coli* might have originated in contaminated manure used to fertilise vegetables.

Source: South China Morning Post

Canada: Antipsychotic Drugs Labelling Update Regarding the Risk of Abnormal Muscle Movements and Withdrawal Symptoms in Newborns Exposed during Pregnancy

Date: June 16, 2011

Health Canada is informing healthcare professionals and consumers that the prescribing information for the entire class of antipsychotic drugs is being updated. The updated labelling will contain safety information on the potential risk of abnormal muscle movements and withdrawal symptoms in newborns whose mothers were treated with these drugs during the third trimester of their pregnancy. Women taking an antipsychotic and who are pregnant or thinking of becoming pregnant should talk to their doctor about their treatment. Patients should not stop taking their medication without first speaking to a healthcare practitioner, as abruptly stopping an antipsychotic drug can cause serious adverse events.

In Hong Kong, the class of antipsychotic drugs are prescription medicines. The issue was discussed in the meeting of Registration Committee of the Pharmacy and Poisons Board on 11 May 2011. The Committee decided that the sales pack labels of products containing antipsychotic drugs should comply with the above warning requirements.

Source: http://www.psdh.gov.hk

European Union: European Medicines Agency Concludes Review of Systemic Nimesulide-containing Medic

Date: June 24, 2011

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that the benefits of systemic nimesulide-containing medicines continue to outweigh their risks in the treatment of patients with acute pain and primary dysmenorrhoea. However, these medicines should no longer be used for the symptomatic treatment of osteoarthritis. The Committee started a full assessment of the benefits and risks of nimesulide-containing medicines for systemic use at the request of the European Commission, because of ongoing concerns over their gastrointestinal and hepatic safety. The Committee had previously imposed several restrictions on the use of systemic nimesulide in order to reduce risks of liver injury. Having reviewed all available data, the CHMP is now recommending, as a further restriction, that systemic nimesulide should no longer be used for the treatment of painful osteoarthritis. The Committee considered that the use of systemic nimesulide for the treatment of this chronic condition, would increase the risk of the medicines being used for long-term treatment, with a consequent increase in the risk of liver injury.

Source: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2011/06/news_detail_001285.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c1

Level of LDL Cholesterol Could be Controlled by Simvastatin plus Ezetimibe in Patients with Chronic Kidney Disease

Date: June 25, 2011

The Study of Heart and Renal Protection (SHARP) concluded that around a quarter of all heart attacks, strokes, and operations to open blocked arteries could be avoided in people with chronic kidney disease by using the combination of ezetimibe and simvastatin to lower blood cholesterol levels. The SHARP study involved almost 9,500 volunteers aged 40 or over with chronic kidney disease recruited from 380 hospitals in 18 countries. Volunteers were randomly allocated to take either cholesterol-lowering therapy with a tablet containing ezetimibe 10mg daily and simvastatin 20mg daily, or matching dummy "placebo" tablets for an average of 5 years.

The major findings are summarized below: Taking the combination of ezetimibe and simvastatin long-term reduced the risk of heart attacks, strokes and operations to open blocked arteries by about one quarter in people with chronic kidney disease, irrespective of the severity of their disease. This combination treatment reduced risk safely, and may be particularly good for kidney patients as it avoids the possibility of side-effects with high statin doses. There was no support for previous concerns with ezetimibe about possible adverse effects on cancer, and no evidence of an increased risk of muscle or liver problems. The results of the trial have been published in the The Lancet, Vol. 377, Issue 9784, pages 2181-2192.

Source: http://www.sharpinfo.org/

New Website of Pharmacy and Poisons Board of Hong Kong Launched

Date: July 4, 2011

The Pharmacy and Poisons Board of Hong Kong is the local authority for the regulation of pharmaceutical products. The Board announced today the official launch of its new website at www.ppbhk.org.hk. To facilitate communication with stakeholders, pharmaceutical and healthcare professionals, the trade, academia, patient groups and members of the public, the Board put in place the designated website in order to provide an electronic means of access. The new website provides comprehensive information on the scope of work of the Board and its various committees, including information on the registration and discipline of registered pharmacists, manufacturers, importers and exporters, wholesalers and retailers of pharmaceutical products. Other information such as the lists of registered pharmacists and licensed drug dealers in Hong Kong is also provided. Interested parties and individuals are most welcome to visit the Board's website.

Source: http://www.psdh.gov.hk

European Union: European Medicines Agency Confirms Positive Benefit-risk Balance for Champix

Date: July 22, 2011

The European Medicines Agency has confirmed that the benefit-risk balance for Champix (varenicline) remains positive, despite the results of a recent meta-analysis of the medicine's side effects affecting the heart and blood vessels. The Agency's Committee for Medicinal Products for Human Use (CHMP) and Pharmacovigilance Working Party concluded that the slightly increased risk of cardiovascular events reported by the study's authors does not outweigh the benefits of Champix in helping people to stop smoking. The Committee has asked Pfizer, the marketing-authorisation holder for Champix, to submit a variation to include more information on cardiovascular events in the medicine's product information. Pfizer has informed the Agency that it will submit this application in early August this year. The Committee will review this application in an expedited fashion, aiming to conclude with a recommendation to the European Commission at its plenary meeting of 19-22 September 2011.

Source:http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2011/07/news_detail_001314.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c1&jsenabled=true

Community Care Fund (CCF) to Subsidise HA Patients in Financial Difficulty to Use Self-financed Cancer Drugs

Date: July 27, 2011

The Hospital Authority (HA) announced the details of the First Phase Programme of the Community Care Fund (CCF) Medical Assistance Programmes. From August 1, 2011, eligible patients can apply for financial assistance to use self-financed cancer drugs under the programme, which is expected to benefit 1,000 patients in the first year.

The Chairman of the Medical Sub-committee of the CCF and Chairman of HA, Mr Anthony Wu, officiated at a launch ceremony and press briefing on the programme today. He said, "The main objective of the CCF is to provide assistance to people facing economic difficulties, in particular those who fall outside the social safety net or those within the net but have special circumstances that are not covered.

"Having regard to the views from various sectors, two CCF Medical Assistance Programmes - the First Phase Programme and the Second Phase Programme - have been endorsed by the Steering Committee on the CCF after careful consideration. Both programmes are targeted at subsidising HA patients who have financial difficulties to use self-financed drugs."

The First Phase Programme will subsidise HA patients to use six specified self-financed cancer drugs that have not yet been brought into the Samaritan Fund (SF) safety net for seven specific cancer diseases. These are lung cancer, leukemia, colorectal cancer, renal cell carcinoma, gastrointestinal tumour, breast cancer and ovarian cancer.

"Drugs subsidised by the First Phase Programme are those that have been rapidly accumulating medical scientific evidence and with relatively high efficacy, though they are expensive. Although other related drugs and treatment are provided at HA's standard fees and charges, many patients may still choose to use these drugs at their own expense. The CCF will provide subsidy to eligible patients to facilitate their early access to these drugs," Mr Wu said.

To launch the First Phase Programme as early as possible, applications will be processed using the financial assessment mechanism of the existing SF operations with which patients, doctors and medical social workers are familiar, i.e. patients have to pass the means test conducted by medical social workers. In addition, patients are also required to fulfill specified clinical criteria. Patients in need can consult doctors or medical social workers for more details about the application procedure.

The Second Phase Programme will be rolled out in the first quarter of 2012 and will subsidise HA patients who marginally fall outside the SF safety net for use of SF subsidised drugs. Details will be announced when finalised.

The Steering Committee on the CCF announced earlier that 10 assistance programmes would be launched in 2011-12, and funds had also been set aside for three other programmes whose implementation details are being formulated.

Among them, two assistance programmes to help needy students, namely the lunch subsidy and the school-based fund to subsidise students in joining learning activities outside Hong Kong, were launched in June. The other assistance programmes will be rolled out in phases to benefit more groups.

Source: www.communitycarefund.hk or www.ha.org.hk

The United States: Diflucan (fluconazole): Long-term, High-dose Use during Pregnancy May be Associated with Birth Defects

Date: August 4, 2011

FDA is informing the public that treatment with chronic, high doses (400-800mg/day) of Diflucan (fluconazole) during the first trimester of pregnancy may be associated with a rare and distinct set of birth defects in infants. This risk does not appear to be associated with a single, low dose of fluconazole 150mg to treat vaginal yeast infection (candidiasis). Based on this information, the pregnancy category for fluconazole indications (other than vaginal candidiasis) has been changed from category C to category D. The pregnancy category for a single, low dose of fluconazole has not changed and remains category C.

Source:http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm266468.htm

Canada: Multaq (dronedarone) - Information on Increase in Heart-related Events in Patients with Permanent Atrial Fibrillation

Date: August 5, 2011

This is the update to the announcement made by Health Canada on 22 July 2011 regarding the review of Multaq (dronedarone) and the potential for an increased risk of cardiovascular events. Sanofi-aventis Canada Inc. in collaboration with Health Canada would like to inform you of important new safety information regarding Multaq which will be reflected on the Product Monograph. The information is based on preliminary data arising from the recently discontinued PALLAS trial such as: Multaq must not be prescribed in patients with permanent AF (duration for at least 6 months or duration unknown) and in whom an attempt to restore sinus rhythm is no longer considered, Multaq treatment should be stopped in patients with permanent AF, and it is recommended to closely monitor patients taking Multaq. If patients treated with Multaq develop permanent AF, treatment with Multaq should be discontinued.

Source: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2011/multaq_2_hpc-cps-eng.php

The United States: Actos (pioglitazone): Potential Increased Risk of Bladder Cancer

Date: August 5, 2011

Further to the announcement made by the U.S. Food and Drug Administration (FDA) on 15 June 2011, FDA is informing the public that the Agency has approved updated drug labels for the pioglitazone-containing medicines to include safety information that the use of pioglitazone for more than one year may be associated with an increased risk of bladder cancer. Information about this risk will be added to the Warnings and Precautions section of the label for pioglitazone-containing medicines. The patient Medication Guide for these medicines will also be revised to include information on the risk of bladder cancer.

The same new advise on bladder cancer have been added to the drug labels in the European Union, United Kingdom, Australia, Canada and Singapore in July 2011.

Source: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm226257.htm

The United States: FDA Alerts Health Care Professionals of Infection Risk from Repackaged Avastin Intravitreal Injections

Date: August 31, 2011

The U.S. Food and Drug Administration (FDA) is alerting health care professionals that repackaged intravitreal injections of Avastin (bevacizumab) have caused a cluster of serious eye infections in the Miami, Florida area. The Florida Department of Health (DOH) notified FDA of a cluster of Streptococcus endophthalmitis infections in three clinics following intravitreal injection of repackaged Avastin. Investigators traced the tainted injections to a single pharmacy located in Hollywood, Florida. The pharmacy repackaged the Avastin from sterile injectable 100 mg/4 mL, single-use, preservative-free vials into individual 1 mL single-use syringes. The pharmacy then distributed the Avastin to multiple eye clinics for use in treating patients. To date, FDA is aware of at least twelve patients in at least three of these clinics who had eye infection. The agency and Florida health officials continue to investigate the cause of the infection. While the investigation is not yet complete, the common link for the infections is the pharmacy that repackaged the Avastin and the single lot of Avastin used in the re-packaging. Health care professionals should be aware that repackaging sterile drugs without proper aseptic technique can compromise product sterility, potentially putting the patient at risk for microbial infections.

In Hong Kong, Avastin Roche Inj 100mg/4ml (HK-53549) is registered by Roche HK Ltd. and is a prescription-only medicine. In Hong Kong, repackaging of pharmaceutical products for the purpose of sale should only be carried out by the person who is the holder of a licence to manufacture pharmaceutical products. Department of Health will keep vigilance against any safety information related to the drug.

Source: http://www.psdh.gov.hk

The United States: Drug Labels for the Tumor Necrosis Factor-alpha (TNFα) Blockers now Include Warnings about Infection with Legionella and Listeria Bacteria

Date: September 8, 2011

FDA notified healthcare professionals that the Boxed Warning for the entire class of Tumor Necrosis Factor-alpha (TNFα) blockers has been updated to include the risk of infection from two bacterial pathogens, Legionella and Listeria. In addition, the Boxed Warning and Warnings and Precautions sections of the labels for all of the TNFα blockers have been revised so that they contain consistent information about the risk for serious infections and the associated disease-causing pathogens. Patients treated with TNFα blockers are at increased risk for developing serious infections involving multiple organ systems and sites that may lead to hospitalization or death due to bacterial, mycobacterial, fungal, viral, parasitic, and other opportunistic pathogens. Healthcare professionals are advised that the risks and the benefits of TNFα blockers should be considered prior to initiating therapy in patients with chronic or recurrent infection and patients with underlying conditions that may predispose them to infection.

Source:http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm270977.htm

The United Kingdom: Fluoxetine - May Slightly Increase Risk of Heart Defects in an Unborn Child if Taken During Pregnancy

Date: September 14, 2011

The Medicines and Healthcare Products Regulatory Agency (MHRA) announced that taking the antidepressant medicine fluoxetine in the first three months of pregnancy may cause a small increase in the risk of heart defects in the unborn child. Seven published clinical studies were identified which examined the risk of defects occurring in an unborn child with the use of fluoxetine during the first trimester of pregnancy. These data suggest that fluoxetine was not associated with non-cardiac congenital defects. However, cardiac defects were reported in five of these seven studies. Analysis of data from these five studies suggests that fluoxetine is associated with a small increased risk of cardiac congenital defects. In conclusion, use of the SSRI antidepressant fluoxetine in early pregnancy may cause a small increased risk of heart defects in the unborn child and there are insufficient data at present to conclude whether there is a similar risk with other SSRIs. On the basis of the results of the analysis, the warnings on the risk of congenital cardiac defects were included in the product information and patient information leaflets for all medicines containing fluoxetine in the UK.

Source: http://www.mhra.gov.uk/home/groups/pl-p/documents/drugsafetymessage/con129100.pdf

The United States: Zofran (ondansetron) - Rrisk of Abnormal Heart Rhythms

Date: September 16, 2011

FDA notified healthcare professionals and patients of an ongoing safety review and labeling changes for the anti-nausea drug Zofran (ondansetron and ondansetron hydrochloride). Ondansetron may increase the risk of developing prolongation of the QT interval of the electrocardiogram, which can lead to an abnormal and potentially fatal heart rhythm, including Torsade de Pointes. Patients at particular risk for developing Torsade de Pointes include those with underlying heart conditions, such as congenital long QT syndrome, those who are predisposed to low levels of potassium and magnesium in the blood, and those taking other medications that lead to QT prolongation. The labels are being revised to include a warning to avoid use in patients with congenital long QT syndrome because these patients are at particular risk for Torsade. Recommendations for ECG monitoring in patients with electrolyte abnormalities (e.g., hypokalemia or hypomagnesemia), congestive heart failure, bradyarrhythmias, or in patients taking other medications that can lead to QT prolongation, are being included in the labels.

Source:http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm272041.htm

Coaching for Pharmacists (1) – Introduction

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ABSTRACT

Due to the dynamic environment in the pharmacy profession, pharmacists, who are the forefront individuals of the profession, must be equipped with essential skills to overcome the many challenges faced. Above all, learning how to organize an effective and efficient team is a vital skill that will likely result in success. Coaching is essentially required to stimulate and support growth in an individual's performance. It is different from other development interventions. It provides directions for any individual, allowing one to utilize their potential to maximize their productivity and achieve their personal goals.

Keywords: *coaching; mentoring; personal development; skills for pharmacists.*

INTRODUCTION

Healthcare is a rapidly changing profession with ever increasing demands. In Hong Kong, nurses, practitioners, pharmacists and other health care professionals are surely feeling the crunch of decreasing dollars, increasing productivity, short staffing and downsizing. Working in this environment often means that the individual strengths we bring to the job are something that we may not be able to use frequently because of the focus on multitasking and other related factors. When people are using their unique character strengths, they are often very engaged with and challenged by their work. Multitasking actually prevents this type of fulfilling connection. Many healthcare professionals now feel that work is less fun and, also less meaningful, than it was a few years ago. Current research from the Gallup Organization indicates that there are better patient outcomes when healthcare professionals are engaged with their work. Also, there is a growing request for the improvement of the management of expenditures and clinical needs of the patients, which further burdens pharmacists. With the development of stricter regulatory requirements, the government demands further input from pharmacists in regards to both existing and developing drugs. All employees in the pharmaceutical world, especially pharmacists, are affected by these changes. It is clear that the roles of pharmacists are becoming much more important and strongly influential in many aspects of the field. Without a doubt, the role of a pharmacist must undergo an evolutionary redevelopment to strengthen and improve vital skills.[1-3]

The following sections will be highlighting the importance of coaching in the pharmacy profession. After a brief introduction into the critical concepts of coaching, there will be a chronological guide on the process of incorporating coaching into development intervention and followed by comparisons between coaching and other disciplines such as mentoring, counseling, etc.

LEADERSHIP IN PHARMACY

The complexity of today's medical world is evident in the continuous changes occurring within each successful health care service that constantly requires improvement in their health-care professionals and all supportive staffs. The same situation is happening along the health-care-chain, which includes the government, pharmacies, as well as pharmaceutical industry.

Pharmacists is one of the centre of focuses in the health-care reformation, as many of the up-coming challenges will lead to the integration and redevelopment of responsibilities, possibilities, and opportunities providing new direction in the pharmacy profession. However, there are always uncertainties in the approaches pharmacists take to engage the dynamics of the pharmaceutical sciences. An ability essential to all pharmacists is adaptability. The profession and the demand of the market are ceaselessly changing bringing with them the inevitability that all pharmacists must pursue new concepts and skills to perform well in these changes **(Figure 1)**.[1-3]

As leaders, pharmacists of this newer generation should not be limited

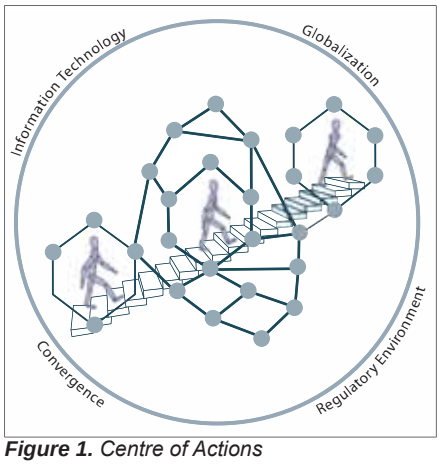

Figure 1. *Centre of Actions*

to the application of technical skills and knowledge, but also the remodeling of acceptable behaviors and values. Coaching is a way to demonstrate one's approach towards problem solving, interaction with patients, and one's general ability to communicate. Naturally, people always tend to perform well in their roles which they are most suitable at, and eventually wish to pursue goals of greater value. However, it is always difficult to ensure a satisfactory outcome for all individuals in their pursuits and in their present roles. Through coaching, coaches can help them to take hold of job responsibilities, overcome poor performance, establish new skills and excel to a higher career level. Since both the coach and coachee will develop and benefit through the experience, it is imperative for the two parties to participate equally in this collaborative effort.

In Hong Kong, only the Chinese University of Hong Kong and the Hong Kong University offer Bachelor of Pharmacy program. The curricula of the two programs focus on knowledge of pharmacy and do not provide courses in leadership or coaching skills to prepare for students' future work. Furthermore, different work settings, such as the Hospital Authority, community chain pharmacies or pharmaceutical companies, seldom provide training on leadership or coaching. In fact, leadership should not be considered an inherent part of an individual's make up. It is also a shill that

can be learnt, nurtured and cultivated. Education and experience are the cornerstones of leadership development. It is important that pharmacy student and young pharmacists who will be the leaders of tomorrow, be given the opportunity to receive leadership and coaching training as early as possible. Their sense of commitment and passion to lead and coach must be encouraged and nurtured to ensure that they look to the future with the confidence to face challenges and change.

WHAT IS COACHING

The Concise Oxford Dictionary defines the verb "coach" as "tutor, train, give hints to and prime with facts". However, this definition does not directly reflect upon what a coach actually does. Coaching should be more focused on the way of doing these things rather than what is being done. There are various interpretations of coaching, yet all these explain what coaching is and where a good coach can help: [4, 5]

1. Partnership between a manager and an individual, where the manager helps the individual to learn.
2. An ongoing professional relationship that helps people achieve extraordinary results;
3. Helping people to unlock their potential;
4. Accelerate an individual's progress to achieve personal and organizational goals;

Early in the 1960s, "coaching" was described by Paul Hersey and Ken Blanchard through the "Situational Leadership Model" **(Figure 2)**. The simple model comprises of four quadrants, depicting the concepts of four different styles of leadership. "Coaching" was stated to be highly directive and supportive, which is superior to that of the other three skills including "delegating", "supporting" and "directing".

It is stated in the model that coaching involves the explanation of specific task directions in a supportive and persuasive way, which implicates a high-task, high-relationship style of focus in that type of leadership. Therefore, it is clear that a coach's job primarily involves the utilization of knowledge and the potential of the coachee to direct the coachee towards a more effective way of operating. [4, 6]

Coaching enables employees to identify their individual strengths and weaknesses, and then be able to link them to their personal and career aspirations. Coachers play roles in the way to encourage employees (pharmacists) to establish long-term developmental goals and help them conceptualize a strategy to attain them; they also make agreements with their coachees about their role and responsibilities in the development plans; they may also give some instruction and feedback. Generally speaking, coaching is forward-looking and direction-oriented with the purpose of helping individuals define themselves, create awareness of different solutions and achieve set goals.

APPROPRIATE USE OF COACHING

Since the term "coaching" has been popularized and made confused with many other development interventions, misperception and misrepresentation is common. Some practitioners attempt to take the advantage of this new popular term and apply to their general services. It is ill-advised to use "coaching" without a clear understanding on the situations coaching should be used. Here are some characteristics of coaching: [7]

1. One-on-one discussions;
2. Provides individuals with feedback on both their strengths and weaknesses;
3. Targets specific issues / areas;
4. Relatively short-term activity compared to counseling, mentoring etc;
5. Essentially a non-directive form of development;
6. Focuses on improving performance and developing/enhancing individual skills;
7. Coaching activities have both organizational and individual goals;
8. Works on the assumption that clients are self-aware, and have motivation to improve;
9. Personal issues may be discussed but the emphasis is work performance.

Coaching is focused on supporting growth in a person's skills and knowledge so that their job performance can improve, which ultimately results with the achievement of organizational objectives. Identifying the developmental need of an individual who could benefit from coaching can happen in a variety of organizational settings. Once that need has been determined, the next step is to arrive at the must appropriate development intervention. The merits of coaching should be considered alongside with other interventions where the trainee's preferences should be borne in mind. Decisions as to whether coaching is an appropriate approach are illustrated in **Figure 3**.

To decide whether coaching is the most appropriate course of action, one must be clear what coaching is and how it can help. Before making the decision, one should first ask himself / herself: what will happen if no coaching occurs? What is the expected impact of coaching ? Are there any other development options that can deliver the same results? All these questions should be addressed before deciding to use "coaching" as the development intervention. Therefore, understanding the differences between coaching and other development interventions is essential to making a correct choice.

COACHING VS OTHER DISCIPLINES

Coaching may occur in conjunction with other disciplines and managing skills,

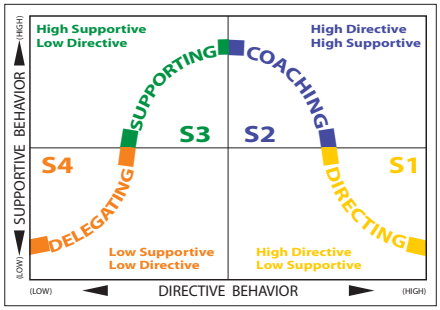

Figure 2. *The "Situational Leadership Model"*

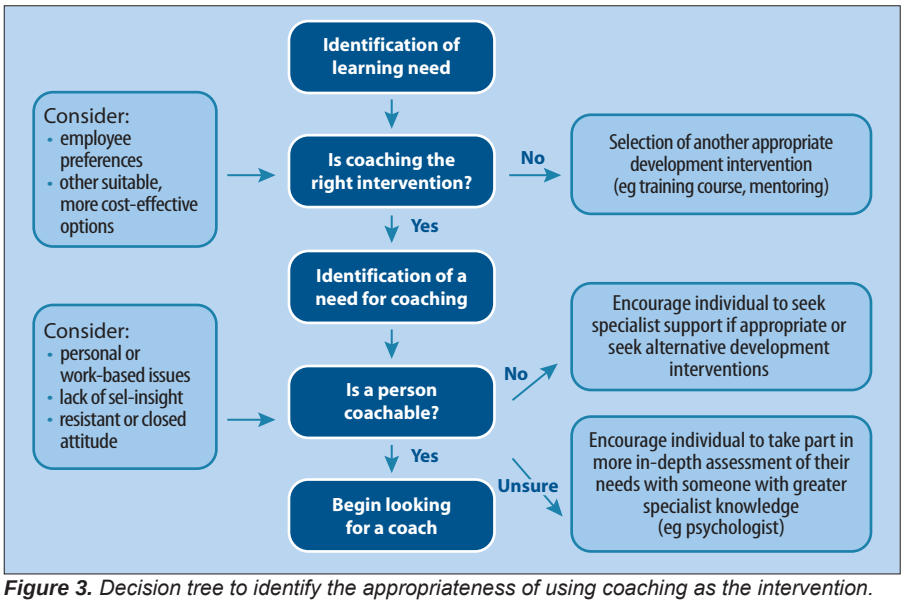

Figure 3. *Decision tree to identify the appropriateness of using coaching as the intervention.*

including feedbacks, trainings, counseling and mentoring. Although these skills and approaches are complementary parts, they may be confused when a specific technique is required. These terms are different in various dimensions, which will be discussed and compared in the following paragraphs and tables.

Coaching is different from training as the latter involves teaching something, usually a skill or knowledge. On the other hand, the coaching process assumes that the coachee has the ability to be resourceful and achieve their goal independently. Therefore, coaching is about assisting people through a process to learn, to provide guidance and to inspire, rather than teach them concrete techniques or knowledge **(Table 1)**.[8]

Coaching is also different from counseling in the sense that coaching is forward focused and goal oriented, whereas counseling tends to focus on the past. Counseling typically helps people to resolve problems through their past which maybe impacting their current performance. Counseling is a highly skilled intervention method but usually deals with psychological problems with significant differences in the way of implementation **(Table 2)**.[3]

Coaching distinguishes from mentoring in the way that mentoring involves a more experienced person offering advice and acting as a role model to others; however, in coaching the coach does not have to know the answers as their role is to work alongside the coachee to find his/her own way **(Table 3)**.[9, 10]

Feedback refers to the information provided as an overview of an individual's performance and how it has met or fallen short of the expectations, but it can simply be the manager's perception of the performance. It is an integral part of effective coaching, and a critical element in the developmental and learning process. Feedback also includes evaluation of the coaching, so that it is possible to project future plans for the coacher and coachee to improve upon.[2, 10]

Coaching is unique as it involves the management of people rather than monitoring specific tasks. Through coaching, pharmacists and managers can contribute to the independent development individuals and encourage improvement through self learning. Once the potentials of an employee are understood and reached, job delegation is much easier, which is an important way to maximize productivity and bring additional benefits to the organization.

CONCLUSION

Pharmacists have responsibilities in a leadership role, due to the dynamic environment of the pharmacist operates within as there are numerous and varying challenges emerging each and every day. People continue to expect more in terms of job satisfaction, knowledge / skill enhancements and career progression. All these expectations demand that the leader to become more proactive in the management position and being able to provide guidance through coaching activities.

Coaching is undoubtedly more than a tool that pharmacy managers can use in a variety of situations such as planning, delegation or problem solving. It offers a different and personal look on individuals with optimism. And thus it results in a various developing yet unique approaches to treating different people. Good coaching requires coach to suspend beliefs regarding people, including themselves, as they may have impeding effects along with old habits and traditional methods of thinking as they do not support continuous growth.

Coaching is an activity with a forward outlook with little consideration for the past, by providing guidance focuses on a specific goal. The process of coaching involves the evaluation and identification of suitable approaches to achieve the set target through the implementation of a robust strategy. It stimulates thinking and planning which can bring out best performance of a coachee, helping them to focus, breaking down tasks and clarifying their values. Without doubt, coaching is a vital element in establishing good management and utilizing available human resources with efficiency in an organization. Coaching, specially for nurses, practitioners, pharmacists and other healthcare workers, will make a difference. Through coaching, healthcare professionals are empowered to recognize their unique strengths and to modify their career (within or outside of the healthcare professionals). The goal is to create the joy and satisfaction we all desire from our work.

Table 1. Comparison between coaching and training.

	Coaching	Training
Purpose	To "guide" something	To "teach" something
Situation	Any time	Training session
Target	Usually one to one	Usually a group of people
Topic	Personal or job issues	Specific skill or knowledge
Progress monitoring	With follow-ups	Generally no follow-ups

Table 2. Comparison between coaching and counseling.

	Coaching	Counseling
Situation	A goal	A difficulty / problem
Purpose	Achieve the goal	Overcome the difficulty
Focus	Future-focused	Focus on the past
Problem	Personal / working issues	Psycho-social problems
Discussion	Around possibilities	Around problems
Direction	Move towards a solution	Move away from a problem

Table 3. Comparison between coaching and mentoring.

	Coaching	Mentoring
Relationship	Relationship generally has a set duration	Ongoing relationship which can last for a long period of time
Structure	More structured and meetings are scheduled	More informal and meetings can take place any time
Focus	Short term and focus on specific development areas	More long term and broader view of the person
Job-related experience	Coacher directs experience of their clients	Mentor provides advices through their experience
Method	More on asking questions	More on providing instructions.
Development	Specific development areas/issues	Life-long development

Author's background

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HPV types 16, 18, 31, 33 & 45 are the 5 most common high-risk HPV types.[4]

Vaccination against HPV 16 & 18 alongside regular Pap smear screening is the best preventive measure for women against cervical cancer.[5-7]

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Case Study and Treatment of Acute Iritis

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ABSTRACT

Iritis is an inflammatory ocular condition affecting the iris. The presentation frequently involves a red painful eye with inflammatory debris in the anterior chamber. Whilst the aetiology of iritis is often idiopathic, there are some associations with underlying systemic conditions. The most common association is with human leukocyte antigen B27 (HLA-B27). Treatment of iritis involves controlling the inflammation with aggressive steroid therapy possibly combined with an anti-infective agent. This case study presents an episode of HLA-B27 associated acute iritis in a middle-aged female. Treatment was successful with topical steroids. Disease classification, differential diagnoses, potential complication and treatment option are considered and discussed.

Keywords: *Iritis, eye inflammation, drug therapy, leukocyte antigen, infectious causes, acute anterior uveitis*

INTRODUCTION

The uvea or uveal tract is the vascular middle layer of the eye consisting of the iris, ciliary body and choroid. Inflammation involving one or more of these ocular structures is termed uveitis (Fig. 1). The disease is further divided into subclasses depending on anatomical location, duration and onset of disease. Inflammation confined to the iris and ciliary body is termed anterior uveitis. Furthermore, if the iris alone is affected, it is referred to as iritis. Inflammation lasting less than 3 months with a sudden onset is termed as acute.[1]

Acute iritis is a relatively common condition.[2] Its presentation is typically with a red, watery and painful eye with photophobia and occasionally, mildly blurred vision. Critical signs include circum-limbal flush, anterior chamber reaction and keratic precipitates on the corneal endothelium.[3-5] Although most cases of acute iritis are idiopathic, there are potential links with underlying systemic diseases or associations. Of the known aetiologies of anterior uveitis, HLA-B27-associated uveitis is the most common.[6]

The primary goals of treatment are to control the inflammation, reduce ocular complications and provide symptomatic relief. This is generally achieved using corticosteroids and cycloplegia. With appropriate and timely treatment, the prognosis of acute iritis is generally good. In addition to treating the iritis, any identified underlying systemic causes must be treated or referred for the appropriate care.

This case report discusses the medical treatment of recurrent HLA-B27 positive acute iritis in a middle-aged female. Potential complications of untreated inflammation and side effects of anti-inflammatory treatment are also considered.

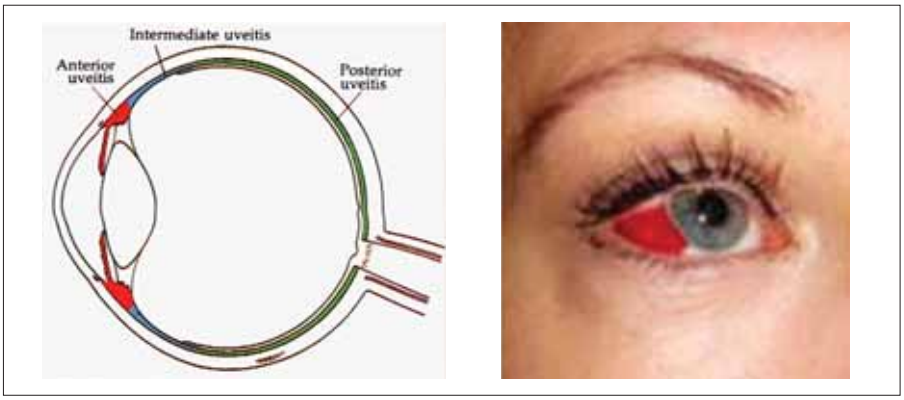

Figure 1. *Anatomical classification of iritis (uveitis) (left) and a female patient with an anterior uveitis (right)*

CASE REPORT

A 38 year old Caucasian female, LS, first presented to a private ophthalmology clinic on the 6th September 2010 with a referral from an optometrist for recurrent iritis (reportedly 3 times in the last 3 months) in the right eye. Incidentally, she has a 20 year history of contact lens wear.

On initial presentation to the optometrist, 8 days after onset of symptoms, LS complained of a red, throbbing-painful and photophobic right eye with marked epiphora. The optometrist had noted anisocoria with the right pupil smaller than the left. Visual acuities measured R: 6/6 and L: 6/6^{2+}. She was given Pred Forte 1% tds and Homatropine qid by her optometrist and contact lens wear was ceased.

Ophthalmologist examination on the 6th September 2010 revealed inferior SPK in the right cornea and grade 2+ cells in the right anterior chamber. Intraocular pressures measured 16mmHg R and L. A prescription for Pred Forte 1% drops was given q2h.

LS was reviewed on the 14th September 2010 with marked improvement. She had stopped the steroid drops for 4 days. Visual acuities

measured R: 6/9 and L: 6/6. Intraocular pressures measured R: 16 mmHg and L: 17 mmHg. Cornea was clear with only grade 1+ cells in the right anterior chamber. Pupils were even and responsive.

Pred Forte 1% drops were resumed q2h for 1 day and then tapered to qid until review. A battery of laboratory tests was ordered to further investigate underlying associations.

A final review was organised on the 30th September 2010. Acuities measured R and L 6/6. Intraocular pressures measured R and L 17mmHg. Cornea was clear and no cells were found in the anterior chamber. Therapy was ceased. Laboratory testing returned positive for HLA B27 gene.

DIAGNOSIS

LS was diagnosed with HLA-B27-positive acute iritis. Diagnosis of iritis is dependent on the presence of clinical signs and symptoms. Signs and symptoms vary depending on the severity of the attack and the duration of disease before initial presentation.

Classical signs and symptoms of acute iritis have been well described (see Table 1). They typically include unilateral pain, redness, direct and consensual photophobia, lacrimation and little or no effect on vision. Clinically critical signs include cells and flare in the anterior chamber (AC), ciliary flush and keratic precipitates (KP). Other possible signs include a miotic pupil with sluggish and irregular response, pain on or reduction in accommodation and a reduced intraocular pressure (IOP) (in some cases a raised IOP). In more severe attacks synechiae, corneal oedema, vitritis and macula oedema may be observed.

The diagnosis of acute anterior uveitis becomes more straightforward in advanced attacks, recurrent episodes and later presentations.[2] However, there are important mimicking diseases which require an extensive history and thorough eye examination to differentiate and rule out.

The differential diagnosis of anterior segment inflammation can be classed under 4 broad categories:

1. As a result of anterior segment disease
2. As a result of posterior segment disease
3. Chronic anterior uveitis
4. Non inflammatory disease mimicking iritis

Each of the above can be ruled out by carefully examining clinical features and comprehensive history taking. Important mimicking conditions include: keratitis, conjunctivitis, corneal trauma, corneal foreign bodies, acute forms of glaucoma, scleritis and episcleritis.[5] Table 2 shows some features of certain acute eye disorders for their differentiation.

Table 2. Differential Diagnosis of Certain Acute Eye Disorders

Acute Iritis	Acute Glaucoma	Acute Conjunctivitis
Small irregular pupil	Dilated pupil	Normal pupil
Circumcorneal injection	Circumcorneal and episcleral injection	Superficial conjunctival injection
Iritis muddy and swollen	Iris congested and bulging	Iris normal
Lacrimation	Lacrimation	Mucous or mucopurulent discharge
Moderately severe pain	Very severe pain	Burning, but no severe pain
Anterior chamber normal depth	Anterior chamber very shallow	Anterior chamber normal
Eyeball tension usually normal	Tension increased	No change in tension
Cornea transparent, precipitates may be present on posterior surface	Cornea appears steammy	Cornea normal
Moderately decreased vision	Considerably decreased vision	Normal vision

DISCUSSION

Epidemiology

There have been several studies surveying the epidemiology of uveitis, each producing varying prevalence and incidences. Despite these variations, these studies generally suggest that uveitis is a relatively common condition. Annual incidences of uveitis have been reported to range from 17 to 52.4 per 100,000 person and prevalence ranges from 38 to 370 per 100,000 population.[6] In 1991, a Dutch study found a lifetime incidence (indicating the number of people who had ever had AAU in their life) of AAU to be 0.23 per cent of the population.[7]

Uveitis is most likely to affect those between the ages of 20 and 50 years. It is rarely found among the very young (under 10 years of age) and the very old (over 70 years of age).[6] One recent study has found an average age of onset to be 36 years of age.[8] Several studies suggest that idiopathic AAU does not show any sex preference.[6] In contrast others have reported that HLA-B27 AAU predominantly affects males, occurring 1.5 to 2.5 times more in males than females.[6]

Anterior uveitis has been shown to be the most common form of uveitis. There has been some discussion regarding the bias towards posterior and intermediate uveitis in studies based on tertiary referral centres. However, anterior uveitis is consistently the most frequent presentation of uveitis with reports ranging from 60 to 90 per cent of all uveitis cases.[2] Lower proportions were noted in tertiary referral clinics, suggesting a generally higher proportion of anterior uveitis in the general population.[2,6]

Causes

There are several factors and associations that have been linked with AAU (Table 3), however the majority of AAU is the result of undetermined aetiology. Wakefield et al. (1986) found 52% of cases of anterior uveitis were idiopathic.[9] Of the known aetiologies, HLA-B27 associated AAU is the most common.[6] The majority of HLA-B27 associated AAU will have ankylosing spondylitis.[9] AAU can also arise from other systemic diseases or infection such as Sarcoidosis or herpetic keratitis.

Table 1. Signs and Symptoms of Anterior Uveitis.[2-4,6]

Symptoms Vary Depending on Severity	Critical Signs	Possible Signs	Signs in Severe Attacks
Unilateral pain Photophobia Consensual photophobia Redness Hyperlacrimation Mild/no effect on vision	AC cells and flare Ciliary flush Small, fine KP	Miotic pupil Pain on accommodation Reduced accommodation Low IOP Elevated IOP	Synechiae (Posterior and peripheral anterior) Corneal oedema Vitritis Macula oedema

Table 3. Causes of Anterior Uveitis [6]		
Non-Infectious Causes		**Infectious Causes**
Ocular Involvement only	Underlying Systemic Disease	
HLA-B27 AAU	HLA-B27 AAU	Endophthalmitis
Idiopathic HLA-B27 negative AAU	- Ankylosing spondylitis	- bacterial
Fuch's heterochromic iridocyclitis	- Reactive arthritis / Reiter's syndrome	- fungal
Posner-Schlossman syndrome	- Inflammatory bowel disease	Herpetic uveitis
Lens-associated uveitis	- Psoriatic arthropathy	- Herpes simplex virus
	- Undifferentiated spondyloarthropathy	- Varicella zoster virus Epstein-Bar virus Cytomegalovirus
	Juvenile rheumatoid arthritis (JRA) / Huvenile chronic arthritis (JCA)	HIV HTLV-1 Onchocerciasis (Onchocerca volvulus)
	Sarcoidosis	
	Behcet's disease	
	Kawasaki disease	

There have been some studies to consider the link between stress and AAU, however a recent study in England found no significant correlation.[10]

Sequelae and complications

In general with accurate diagnosis and timely and sufficient treatment AAU resolves without any serious complications. However, there is potential for visually threatening sequelae and permanent anatomical damage to arise as a result of the inflammation or the treatment regime. There is also the potential to develop chronic anterior uveitis.[6]

Ocular complications which can occur in the anterior segment include: posterior or anterior synechiae, raised IOP leading to secondary glaucoma, cataract and corneal oedema. In the posterior segment there is the potential to develop vitritis, macular oedema and disc oedema.[5]

The most common ocular complication of AAU is posterior synechiae with frequencies reported from 13 to 91 per cent.[6] Permanent vision loss in AAU is relatively rare, with most cases arising as a result of cystoid macular oedema.[11]

LS did not have any significant ocular complications or sequelae.

Drug Treatment

In this case of acute iritis, LS was initially treated with Pred Forte 1% tds and Homatropine qid. In the absence of synechiae, the consulting ophthalmologist ceased the cycloplegia and increased the steroids to q2h for 1 week. On 1 week review LS had already ceased drops for 4 days after subjective improvement of symptoms. Clinical signs suggested residual inflammation and Pred Forte was resumed q2h for 1 day and then tapered to qid until 2 week review. On the final review, inflammation had completely resolved and therapy was ceased.

The chief aims of iritis treatment are to:

1. Control the inflammation
2. Provide symptomatic relief
3. Prevent ocular complications
4. Identify and manage underlying systemic diseases if appropriate.[2]

The main therapeutic agents used to achieve these goals are:

1. Corticosteroids
2. Cycloplegics

Corticosteroids

The mainstay of intraocular inflammation control is the aggressive use of topical corticosteroids.[2] Corneal penetration and potency in the AC are important factors to consider in the efficiency of treatment. These are influenced by the composition of the steroid, frequency of dosage and the state of the corneal epithelium.[2] As such, the steroid choice and prescribed dosage regime must be adequate to ensure sufficient control of the inflammation. The most effective topical steroids have been found to be Pred Forte 1% (prednisolone acetate), Flarex 0.1% (fluorometholone acetate) and Maxidex 0.1% (dexamethasone).[2] Aggressive initial dosage is important to quickly control the inflammation. Typically an hourly dosage for the first few days is adopted and occasionally an initial loading dose is appropriate. It is essential to ensure that steroid treatment is maintained sufficiently to suppress the inflammation even after initial improvement. Once inflammation is under control, steroid dosage is slowly tapered over several weeks to months to ensure rebound inflammation does not occur.[5]

In this case, LS was initially prescribed Pred Forte with a conservative dosage. This treatment may have been inadequate to suppress inflammation, leading to her frequent recurrences or rebound inflammation. Patient compliance was also an issue with LS as she ceased treatment without a taper. Eventually patient compliance was reinforced and inflammation was well controlled.

Cyclyoplegia

There are two main reasons to use cycloplegia in the treatment of iritis. First, cycloplegia reduces pain and photophobia by immobilising the ciliary body and reducing iris spasm. Second, cycloplegia prevents or breaks posterior synechiae and reduces the risk of pupillary block.[2]

Atropine 1% or homatropine (2%, 5%) are the most common cycloplegics used. Drug selection is dependent on the severity of the attack, with atropine 1% providing the strongest choice.[2] The inflamed eye can lead to rapid deactivation warranting a frequent dosage such as four times per day.

In milder cases of iritis with no synechiae treatment may exclude the use of cycloplegia and solely consist of topical steroid.[2] In this case synechiae was absent and the ophthalmologist chose not to use cycloplegia.

TREATMENT REVIEW

It is recommended that iritis patients are reviewed on the first or second day after commencement of treatment.[2] This is to ensure the correct diagnosis and adequate level of treatment. On the first review, clinical signs are expected to be no worse than at initial presentation and there should be subjective symptomatic relief.[2]

The diagnosis of iritis must be reassessed if inflammation shows no signs of improvement on review. Patient compliance can also be a factor contributing to unexpected poor response. A definite iritis which responds

poorly to initial treatment will require an increase in steroid level. This is achieved by increasing the frequency or strength of the topical steroid or by changing the means of delivery with a subconjunctival dexamethasone injection or with oral prednisolone.[5]

The frequency of subsequent reviews can vary depending on the severity, risk of side effects, experience of the clinician and patient compliance. In most cases topical steroids are maintained for six to eight weeks with a slow taper. Cycloplegia is usually stopped earlier when the inflammation is adequately controlled and the risk of synechiae is minimal.[2]

Finally, patients should be followed until complete resolution of the inflammation. Furthermore, patients should be warned of the potential for recurrent attacks.

Complications arising from steroid therapy

There are several potential unwanted side-effects that can arise as a result of prolonged steroid therapy. Steroid use can cause a rise in IOP in a proportion of patients.[2] This can cause subsequent optic nerve damage particularly in patients who are already at risk of glaucoma. IOP must be controlled without altering steroid treatment levels by adding topical medications such as B-antagonists or A-agonists. Prostaglandin analogues are avoided due to their pro-inflammatory action. In some cases a small IOP rise can be simply monitored.[2]

Other complications arising from steroid use include reactivation or exacerbation of existing viral infection, corneal epitheliopathy and cataract development. Viral infections such as herpetic uveitis treated with steroids often require additional prophylactic antiviral treatment such as acyclovir. In the instance of corneal epitheliopathy, the type of steroid may need to be re-evaluated.[2]

In other instances, the use of a combination steroid with an anti-infective component, i.e TOBRADEX Ophthalmic Suspension and Ointment, is also necessary where the risk of superficial ocular infection is high or where there is an expectation that potentially dangerous numbers of bacteria are present in the eye.

Identifying underlying conditions

Whilst identifying underlying conditions may not affect the treatment of the iritis, it is important for the patient's general health to identify these and refer them on for appropriate follow-up. Braakenburg et al (2008) concluded from their studies that systemic conditions can be precluded by the onset of AAU particularly in females.[8] Therefore, it is important to investigate any recurrent or new cases of AAU.

Table 4 shows some diagnostic tests that are useful tools to identify any underlying systemic conditions and also confirm the diagnosis of iritis. These useful laboratory tests include:

1. Full blood examination including an erythrocyte sedimentation rate
2. Antinuclear antibody (ANA)
3. Angiotensin-converting enzyme (ACE)
4. Syphilis serology
5. Chest X-ray
6. HLA-B27

Prognosis

Acute irities usually lasts a number of weeks. HLA-B27 associated AAU has been shown to have a high frequency of recurrence with a mean number of 0.6-3.3 attacks per patient, per year with a mean duration of each episode of 4-6 weeks.[6] Despite the frequency of attacks, Braakenburg et al. (2008) showed a good visual prognosis over the first 10 years of disease.[8] It is expected that with each recurring attack, patients will learn to recognise symptoms earlier and seek medical attention, preventing severe inflammatory episodes.

Table 4. Uveitis associated conditions and relevant investigations [2]

Underlying Condition	Relevant Diagnostic Tests
HLA-B27 Positive AAU	HLA-B27
Ankylosing Spondylitis	HLA-B27, Erythrocyte sedmentation rate, X-ray: sacroiliac / spine:
Reiter's Syndrome	HLA-B27, Erythrocyte sedimentation rate, Anti-nuclear antibodies
Psoriasis/Psoriatic arthritis	HLA-B27
Inflammatory Bowel Disease	HLA-B27, Endoscopy
Behcet's Disease	HLA-B5
Sarcoidosis	X-ray / CT:chest, Angiotensin converting enzyme
Tuberculosis	Quantiferon – interferon based blood test of *M. tuberculosis*, X-ray: chest, Erythrocyte sedimentation rate
Syphilis	Fluorescent trepinemal antibody absorption test, Venereal disease research laboratory test

CONCLUSION

Due to her positive HLA-B27 status, we expect that LS will have future recurrences of iritis. She will also need to be watched closely for the development of any other HLA-B27 associated disease.

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Non-Prescription Antipyretics

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ABSTRACT

Fever is a common manifestation of both infectious and non-infectious diseases. To alleviate signs and symptoms of fever, antipyretic agents at the right dose are effective. Inhibition of the release of prostaglandin is the common mechanism of action that many antipyretics work. The most commonly used non-prescription antipyretics available in drug store are either salicylates or acetaminophen, although cooling patch and some Traditional Chinese Medicines may also serve the same purposes. However, there are various types of fever due to different reasons. Risk of adverse effects or delay of proper treatment may happen if the use of non-prescription antipyretics is not supervised by doctor or pharmacist.

Keywords: *Fever, antipyretics, Chinese medicines, over-the-counter, etiology, thermoregulation*

INTRODUCTION

Fever, sometimes referred as pyrexia, is the temporary elevation of body temperature above the normal range 36.5-37.5ºC (98-100ºF) due to alteration of the body's thermoregulatory set point.[1-2] It is a common natural body response to physiological stress as ovulation, vigorous exercise, or emotional stress, to infection by microorganisms, or to a host of noninfectious process, as that accompanying inflammation or resulting from release of pyrogenic materials, as in leukemia. It alarms people that they are sick leading them to visit the doctor.

Elevation of temperature may be varied slightly depending on the site where the body temperature is measured. Fever is present when it is elevated in the oral region over 37.7ºC (99.9ºF); over 37.5-38.3ºC (99.5-100.0ºF) in the rectal region; and 37.2ºC (99.0ºF) in the otic and axillary regions.[3-5] It is otherwise known as pyrexia or controlled hyperthermia. It is a physiologic response facilitated by the release of pyrogens leading to an increase in the core temperature, phase reactant activation, and immune responses.[6] It helps the body fight against infection.

However, sometimes fever can become life threatening if it is continuously elevated leading to serious complications. It is not necessary to lower the fever down if it is mild because it is part of our nonspecific immunity neutralizing the infectious agents like viruses, bacteria, parasites, and fungi. Antipyretics are recommended if fever is severe and exceeding 39.4ºC.

SIGNS AND SYMPTOMS OF FEVER

There are other responses and symptoms associated with fever. They include sweating, sleepiness, lethargy, hyperalgesia, arthralgia, myalgia, depression, dehydration, shivering, anorexia, inability to concentrate and feeling cold.[7-9]

THERMOREGULATORY MECHANISMS LEADING TO FEVER[2,10-12]

Homeothermic organisms including humans and other mammals are able to maintain a relatively constant body temperature despite wide variation in environmental temperatures. The average normal body temperature (36.7ºC or 98.2ºF) varies depending on time of the day, individual differences, the ovulatory cycle in women and the stage of sleep. The balance between heat production mechanisms and heat loss mechanisms that occur to maintain a constant body temperature is termed thermoregulation.

The direction of heat flow is from higher temperature to lower temperature. The transfer of heat between objects that are in direct contact with each other is called conduction. For example, heat moves from the body to the cold ground when a person sits on the cold ground. The transfer of heat by the movement of air or liquid moving past the body is through convection. This is the reason why trapping air inside clothing keeps the body warm and why there is a cooling effect from a breeze across the skin. The transfer of heat energy via electromagnetic waves is called radiation. A reptile sunning on the sand in a summer day is an example, and the infrared signature of a human body seen at night with special glasses is another.

The heat transfer mechanisms can cause both heat loss and heat gain to the body. On the other hand, evaporation is a mechanism in which a liquid is converted to a gas. It involves heat loss only due to the latent heat of evaporation. An example of this heat loss mechanism is perspiration evaporating off the skin.

Decreases in heat production and increases in heat loss are manifested when the body is too hot. Peripheral vasodilation, the dilation of blood vessels in the skin is one way of increasing heat loss. Heat loss may occur via conduction, radiation, and convection. Large quantities of warmed blood from the core of the body are carried to the skin where these vessels dilate. Heat loss can also be caused by evaporation of fluids from the body in exhaled air and from the skin. Insensible perspiration is the unconscious loss of fluid.

The sympathetic nervous system controls and stimulates secretion of up to 4 liters (4.22 liquid US quarts) of perspiration per hour. However, the body has no active control over insensible perspiration. The environmental air must have a relatively low humidity level in

order for the sweat to evaporate and cool the body.

Increases in heat production and decreases in heat loss are exhibited when the body is too cold. Heat loss is prevented through vasoconstriction of the blood vessels of the skin. Heat production can be enhanced by shivering, which is a rhythmic contraction of skeletal muscles that usually starts around vital organs. An increase in metabolic heat production called non-shivering thermogenesis can also facilitate heat production.

Hormonal regulation can also facilitate temperature regulation. Hormones such as adrenaline (epinephrine), noradrenaline (norepinephrine), and thyroid hormones, increase the metabolic rate by stimulating lipolysis. To adjust for fluctuations in temperature, humans also change activity, clothing, posture, and even shelter. Another sign that the body is trying to prevent heat loss is the goose bumps that arise on the skin when the environment is cold. They are due to the contraction of the arrector pili muscles around hair follicles in the skin resulting in erection of the hair follicles in a process called piloerection. Thus, the air is trapped amongst the erect hairs and the heat is retained.

The thermoregulatory mechanism of the body involves a system of sensors and controllers across the body. Signals regarding body temperature from the nerves in the skin and the blood are brought to the hypothalamus. The hypothalamus coordinates thermoregulation in the body. It sends signals to control the sympathetic nervous system, which is responsible for shivering, sweating, hormonal controls over temperature, vasoconstriction, and metabolism. Generally, the anterior hypothalamus controls responses to heat while the posterior hypothalamus controls responses to cold.

Prolonged exposure to cold would result to hypothermia or low body temperature. All metabolic processes begin to slow with a decrease in body temperature. This can be life-threatening.

A body temperature that is higher than normal is called hyperthermia. This is not due to illness or infection but due to overexposure to hot environment. This is characterized by an overshoot in the thermoregulatory set point of the body due to the body's inability to regulate its temperature. This is manifested in heat exhaustion and heat stroke that occurs when heat production exceeds the evaporative capabilities of the environment. It may be fatal if untreated.

Hyperthermia differs from fever. A fever (controlled hyperthermia) is generally considered to be a body temperature over 38ºC (100.4ºF). In fever, the thermoregulatory set point has risen and caused the normal body temperature to be considered hypothermic. It is part of the body's natural defense to an infection by a pathogen. It functions to eliminate an invading organism. It may even make the immune system work more effectively.

FEVER ETIOLOGY

Bacterial products and other fever producing substances (exogenous pyrogens) cause fever through production of endogenous pyrogens (EPs) by the host. Interleukin-1 (IL-1), an endogenous pyrogen can be induced by lipopolysaccharides (LPSs) and other microbial products *in vivo* and *in vitro*.[13] It was found that pure, recombinant IL-1 produced fever in humans and in animals at sub-nanomolar concentrations.[13] Subsequently, other cytokines like IL-6 and recombinant tumor necrosis factor-alpha (TNF-alpha) were also shown to cause fever.[13-16] Recently, these endogenous pyrogens (EPs) have been renamed pyrogenic cytokines.[13-17] Fever can occur independently of IL-1 or TNF activity during infection.[13] Any microbial product can cause fever by engaging its specific Toll-like receptor (TLR) on the vascular network supplying the thermoregulatory center in the anterior hypothalamus because of the cytokine-like property of TLR signal transduction.[13] Cyclooxygenase-2 is required to cause fever induced by IL-1, TNF-alpha, IL-6 or TLR ligands.[13] Harden *et al*. (2006) found that peripherally released IL-6 and leptin appear to be important in regulating LPS-induced fever and sickness behavior.[18-19] The synergistic effects of IL-6 and IL-1 beta to decrease voluntary activity and to induce anorexia and fever was demonstrated by Harden *et al*. (2008).[20] The mechanism of fever production by both exogenous and endogenous pyrogens is a unified mechanism that resulted from the production of prostaglandin E2 (PGE2) and activation of hypothalamic PGE2 receptors.[13-16] Thus, according to Dinarello (2004), fever is the result of either TLR trigerring or cytokine receptors.[13] During infection, both cytokine and TLR account for fever, whereas in autoimmune diseases, fever is mostly cytokine mediated.[13] The systemic effects of IL-1β in fever production was demonstrated by Dinarello (2005; Fig 1).[21] Many cell types including monocytes and macrophages secrete active IL-1β.[21] Upon entrance to the circulation, it triggers IL-1 receptors on the hypothalamic vascular network to facilitate synthesis of cyclooxygenase-2.[21] This will induce elevation of brain levels of prostaglandin E2, thereby activating the thermoregulatory center for fever production.[21] Indeed, PG2 has diverse actions (Fig.2). Thus, success of prostaglandin E2-function is a challenge for structure based therapeutics.[22]

TYPES OF FEVER[23-31]

Fever can be classified according to the pattern of the changes in the body temperature. Figure 3 shows the pattern of temperature change of various types of fever.

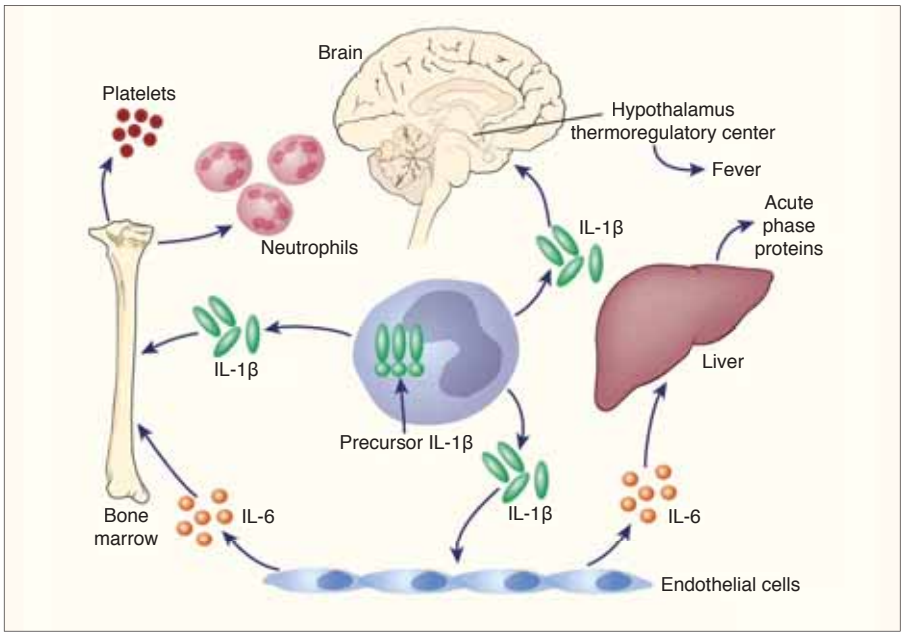

Figure 1. *Systemic manifestations of IL-1β and fever induction.*[21]

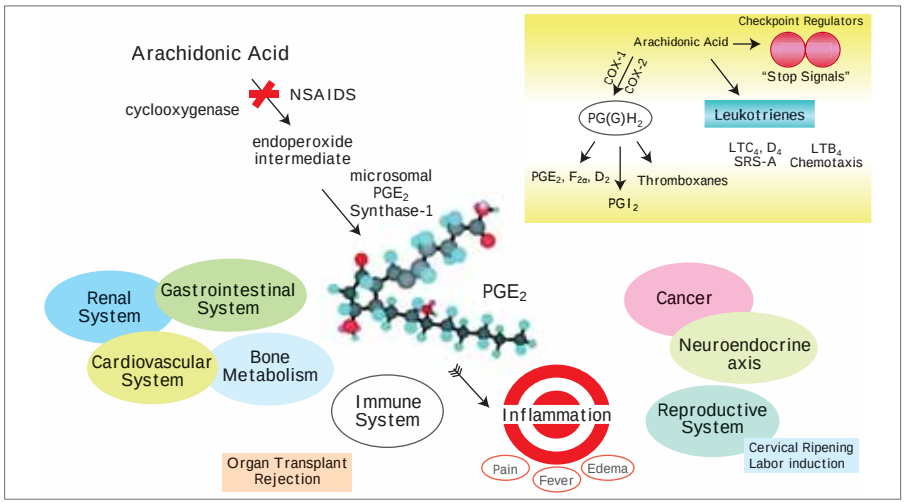

Figure 2. *Diverse actions of PGE2 and selective targeted biosynthesis in inflammation and Fever. The Insert diagram illustrates some major enzymatic classes of eicosanoids cyclooxygenases and lipoxygenase that are involved in the pathway.*[22]

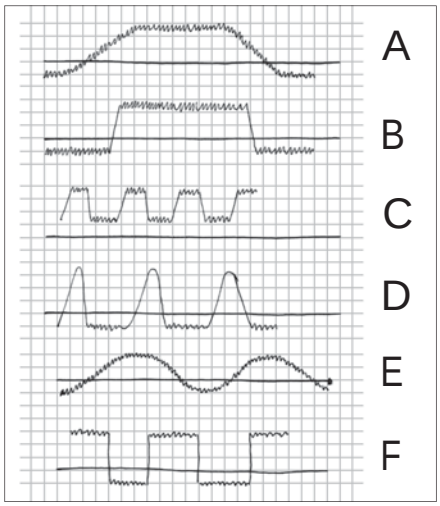

Figure 3. *Performance of the various types of fever.*[31] *A = Fever continues; B = Fever continues to abrupt onset and remission; C = Fever remittent; D = Intermittent fever; E = Undulant fever; F = Relapsing fever.*

1. **Hyperthermic fever** is characterized by high temperatures usually at or above 40.5ºC (105ºF). This differs from uncontrolled hyperthermia and can be described as an increase above the thermoregulatory set point due to insufficient thermoregulation and excessive heat production. Hyperthermia is not caused by illness but because the body overheats as we find in heat stroke. It is due to overexposure to high temperatures and less consumption and evaporation of water. The body may not be able to regulate its temperature and antipyretics cannot bring the temperature down.
2. **Continuous or Sustained fever** occurs when the body temperature day to day is above normal and does not fluctuate more than 1ºC during the day. This is exhibited among patients with typhoid fever, urinary tract infections, brucellosis, typhus, and lobar pneumonia.
3. **Remittent fever** does not return to normal, remains above normal and fluctuates more than 1ºC in 24 h as found in patients with infective endocarditis.
4. **Intermittent fever** is manifested when there is a daily decline to normal or below normal levels, then elevation again. Examples include quotidian fever with 24 h periodicity which is typical in malaria, tertian fever with 48 h periodicity is also typical in tertian malaria and quartan fever with 72 h periodicity which is typical of *Plasmodium malariae* infection (quartan malaria).
5. **Relapsing fever** is characterized by alternating febrile episodes with a day or days of normal body temperature between episodes. This is manifested in tick borne infections.
6. **Hectic or septic fever** has frequent chills and sweats with daily temperature fluctuations to a high level. Fever associated with septic shock is an example.
7. **Pel-Ebstein Fever** is associated with Hodgkin's lymphoma and is characterized by continuous alternation of prolonged elevated body temperature for a week and prolonged low temperature for the following week.
8. **Neutropenic fever or febrile neutropenia** requires serious and immediate medical attention. It is fever during the absence of the normal immune function. This is common among patients receiving immune suppressing chemotherapy.
9. **Febricula or low grade fever** is fever of unknown cause, absence of other symptoms, and the patient fully recovers within a week. This can be manifested in Candidiasis, Norovirus infections, urinary tract infection (UTI), or in adverse reactions to immunization.
10. **Hyperpyrexia** is a severe elevation of body temperature greater than or equal to 41.5ºC (106.7ºF). It may indicate a serious medical condition. This is manifested in enteroviral infections, roseola, measles, intracranial hemorrhaging, sepsis, drug effects, serotonin syndrome, thyroid syndrome, Kawasaki syndrome, and neuroleptic malignant syndrome.

DOES FEVER CAUSE BRAIN DAMAGE?

Some people believe that high fever can cause brain damage. Unless the fever is over 42ºC (107.6ºF), brain damage from a fever generally will not occur. Fever caused by infectious agents will seldom go over 40.5ºC (105ºF) unless the patient is trapped in a hot place and is overdressed.[32]

WHAT TO DO FOR A FEVER?

The first important way of determining fever is to check the body temperature with accurate thermometer. After evaluation of fever symptoms, one should decide whether there is a need to take action to bring it down or not. Among children, one should consider how the child acts during the course of the fever. Lethargic and weak children should be given more attention. A call to the pediatrician is required when the temperature is over 37.8ºC (100ºF). Once there is a need to treat fever, one should consider options for medication. Antipyretics like ibuprofen, acetaminophen, and aspirin are most common medications to treat fever. Aspirin should not be given to a child with symptoms of flu because of its association with Reye's syndrome. The different types of antipyretics have different rates of effectiveness. To make a decision to administer it again depends on how the body reacts to it. However, there are few options if one prefers to try to reduce fever without any medication. The most common method is taking a bath in lukewarm water and placing cool packs or cool rags on the forehead, under the arms, and in the groin area and avoid wrapping the person with warm clothes

or a blanket because this will slow down the dropping of the body temperature. It is better to dress the patient with comfortable clothes and provide a comfortable environmental temperature. It is not advisable to expose the patient to ice bath or rub alcohol on the skin. These are not effective ways of bringing down a fever and both of these can be dangerous. If fever persists, consult the doctor.[33]

OTC MEDICATIONS AND HOME CARE [34]

There are important differences in the pharmacology, efficacy, and side-effect profiles of antipyretics and analgesics although these agents seem to share a common mechanism of prostaglandin inhibition. The risk-benefit ratio of this class of drugs has been extremely favorable considering their often-unsupervised use. However, even these drugs pose significant risks to certain patient populations when used inappropriately.[35,36] Schug (2006) found that paracetamol plus tramadol combination is also free of organ toxicity associated with selective and non-selective non-steroidal anti-inflammatory drugs.[37] Hence, this combination offers an effective and well-tolerated alternative to anti-inflammatory drugs or other paracetamol plus weak opioid combinations.[37] Schnitzer (2003) found that a tramadol/acetaminophen combination is effective in acute or chronic moderate-to-moderately severe pain due to the rapid onset of acetaminophen and the sustained effect of tramadol.[38] Non-prescription antipyretics available in Hong Kong are presented in Table 1. The only NSAIDs, ibuprofen, which can be sold without a prescription under the law of Hong Kong, is used as an antipyretics, especially for children in paediatric practice.

On the other hand, cooling gels although they are non-pharmaceutical products, they play a similar function to dispatch heat by applying them to the skin or head. As they can be purchased without any prescriptions, they are also listed in Table 1 as a non-prescription antipyretic product.

USE OF TCM FOR FEVER[39-51]

Traditional Chinese Medicine (TCM) has gained its uniqueness due usefulness for curing illness for more than 3000 years. Its approach is basically different from that of Western medicine. It is based on a

Table 1. Non-prescription Antipyretics Available in Hong Kong

Class	Brand	Main Ingredient	Dosage Forms & Package	Manufacturer	Forensic Classification
Salicylates	ASPIRIN*	Acetylsalicylate	Tablet 100 mg x 600s	Beacons	Non-poisons
	CORTAL FOR ADULTS	Acetylsalicylate	Tablet 500 mg x 20 or 200s	GlaxoSmithKline	Non-poisons
	DISPRIN-SOLUBLE ASPIRIN	Acetylsalicylate	Tablet 300 mg x 96s	Reckitt Benckiser	Non-poisons
Acetaminophen (Paracetamol)	ARFEN PLUS	Acetaminophen	Tablet 500 mg x 20 or 100s	Medochemie	Non-poisons
	BEN-U-RON SUPP	Acetaminophen	Supp 125 mg x 10 or 250 mg x10s	Bene-Chemie	Non-poisons
	BIOGESIC SUSPENSION	Acetaminophen	Tablet 500 mg x 20 or 500s	Biomedis	Non-poisons
	CHRISTAMOL	Acetaminophen	Tablet 500 mg x 20 or 1000s, 300 mg x 1000s; Suspension 125 mg/5 ml x 3.6 L, 250 mg/5 ml x 3.6 L	Christo	Non-poisons
	CORTAL FOR CHILDREN	Acetaminophen	Tablet 80 mg x 24s	GLaxoSmithKline	Non-poisons
	DHAMOL	Acetaminophen	Tablet 500 mg x1000s, 10 x 10 x 10s; Suspension 250 mg/5 ml x 3.8 L, 500 mg/5 ml x 3.8 L	DHA	Non-poisons
	EUROPAIN	Acetaminophen	Tablet 250 mg x 1000a, 300 mg x 1000s, 500 mg x 1000s; Syrup 125 mg/5 ml x 30, 60, 120, 180, 240, 480 ml or 3.6 L	Europharm Laboratories	Non-poisons
	PANADOL	Acetaminophen	Capsule 500 mg x 12s; Tablet 500 mg x 20, 150 or 1000s; Chewable Tablet 120 mg x 24s	GLaxoSmithKline	Non-poisons
	PANADOL ACTIFAST	Acetaminophen	Tablet 500 mg x 8 or 10s	GLaxoSmithKline	Non-poisons
	PANADOL CHILDREN'S SUPSENDION	Acetaminophen	Suspension 120 mg/5 ml x 60 ml or 1 L	GLaxoSmithKline	Non-poisons
	PANADOL EXTEND	Acetaminophen	Caplet 665 mg x 18 or 180s	GLaxoSmithKline	Non-poisons
	PANADOL EXTRA	Acetaminophen	Tablet 500 mg x 10s; Compack 500 mg x 12, 20 or 30s (compack)	GLaxoSmithKline	Non-poisons
	PANADOL LONG LASTING	Acetaminophen	Caplet 665 mg x 12s	GLaxoSmithKline	Non-poisons
	PANADOL MENSTRUAL	Acetaminophen	Caplet 500 mg x 12s	GLaxoSmithKline	Non-poisons
	PICAPAN	Acetaminophen	Tablet 500 mg x 10 x 10s	DHA	Non-poisons
	PORMUS	Acetaminophen	Tablet 500/35 mg x 50 x 10s	Unison	Non-poisons
	PROGESIC	Acetaminophen	Tablet 500 mg x 20s; Suspension 250 mg/5 ml x 3.6 L	Xepa-Soul Pattinson	Non-poisons
	SERIMOL	Acetaminophen	Tablet 650 mg x 1000s	Raza	Non-poisons
	UNI-FEBRIN	Acetaminophen	Syrup 120 mg/5 ml x 450 ml or 3.6 L; Elixir 250 mg/5 ml x 450 ml or 3.6 L	Universal Pharm	Non-poisons
Cooling patch	Cooling gel sheet 小林退熱貼, (冷卻膠片)	Cooling gel**	6 patches per box, 2 pachtes/ aluminum pack,	小林制藥	Non-pharmaceutical products
	Tiger Balm cooling patch	Cooling gel	6 patches per box, 2 pachtes/ aluminum pack, 105mm*45mm per sheet, lasts for few hours	Haw Par Corp Ltd	Non-pharmaceutical products
	Hauugen Ice-Non Cooling gel sheet日本無比退熱貼,	Cooling gel	6 貼裝, 每盒3包, 每包2片，8小時降溫。	Made in Japan, sole agent, Poon's Pharm.	Non-pharmaceutical products
	樂適退熱貼,	Cooling gel	6 貼裝, (每盒3包, 每包2片)，持續10時間 (降溫)。	Supplier:Forward Medicine Ltd	Non-pharmaceutical products

* Acetylsalicylate tablet at the dose of 100 mg is used as an antiplatelet. When the dose is raised to 300 mg or more, it can be used as antipyretics.
** Cooling gel is water soluble polymer composed of methyl p-Hydroxybenzoate, propyl p-Hydroxybenzoate, L-menthol, tartaric acid, colourant blue-1, concentrated glycerin, polyhydric alcohol, deionized water

holistic view of the human body based on the concept of Daoism in understanding the universe. The treatment is based on the differentiation of syndromes and on the diagnosis. The evaluation of a syndrome includes the confrontation between the pathogenic factor, body resistance, cause, mechanism, location, and nature of the disease. There are different treatments even for those with identical diseases. In fact, similar syndromes of different diseases can be treated in a similar manner. It is basically based on the yin-yang and five elements theories. These theories combine the phenomena and laws of nature regarding the physiologic and pathologic interrelationships of the human body. One of the typical TCM therapies includes herbal medicines besides acupuncture and qigong exercises. These therapies involve internal effects to internal organs, stimulation of certain parts of the external body, and restoration of the orderly information flow inside the whole being of an individual, respectively.

Herbs are a major component of Chinese medicine. There are more than 6000 different medicinal compounds listed in the Chinese pharmacopoeia. Today, there are more than 600 different herbs that are in common use to cure disease. Herbs are classified according to different dimensions like temperature and taste. Some herbs are used to warm, cool, tonify, and even neutralize the system. They can also be mixed to have an overall balance of effects on the body. For instance, herbs with a sour taste can be used against constriction, perspiration due to deficiency, cough, diarrhea, seminal and urinary problems, and under performance of metabolism. For instance, bitter taste herbs can act for clearing heat as in fever, appetite enhancement, and even enhancement of bowel movement. Herbs with a sweet taste have tonic functions to the body systems. Sweet herbs are also pain relievers. Spicy herbs enhance circulation of the blood, perspiration and metabolism. On the other hand, salty herbs have the softening function, removal of inflammatory masses, and abnormal tissue proliferation.

Chinese herbal medicine is prepared in different formulations. They can be delivered singly or combined with herbs having the same effect. There are many herbs that are given singly to alleviate signs and symptoms of disease. Besides the commonly known tea (*Camellia sinesis*), Figure 4 shows some herbal plants known to have antipyretic and analgesic effects.[40-51]

Figure 4. *Some Herbal Plants known to have antipyretic and analgesic effects.*[40-51] ***Uppermost*** *(L to R): Euphorbia hirta L., Panax ginseng, Morinda officinalis;* ***Middle:*** *Abrus mollis, Plantago asiatica, Valeriana officinalis;* ***Bottom:*** *Aeschylus hippochastanum, Andrographis paniculata, Lycium chinense*

Usually, a formula containing at least 4-20 herbs are combined to treat a certain ailment. These herbal formulae can be delivered in different preparations. Decoction serves as a tea and can be consumed several times during the day after boiling. Pre-made formulae are easily taken by the patient because they are already prepared as a tablet, pill, capsule, powder, or even water extracts. However, they are less potent compared with decoction because the concentration of the herbs may be low and the contents or dosages not adjusted. Another type of herbal formulation is granulated herbs. These are powdered extracts that are highly concentrated. They are mixtures of different powder residues from different dehydrated decoctions. The powder of these granulated herbs is dissolved in hot water to convert it back to decoction before consumption. The original potency of the decoction is retained while the necessity to prepare the herbs at home is skipped.[39]

Herbal formulae in Chinese medicine can also be classified according to their specific effects on different ailments. For instance, the Cold and Flu Formula (Yin Qiao San; Table 2) is appropriate for Wind-Heat Pattern. Fever, runny nose with yellowish-colored mucus, sweating, productive coughing with thick yellowish phlegm, headache, sore throat, dry mouth, rapid pulse rate, thirst, and yellowish tongue are some of the symptoms of the Wind-Heat pattern. The Wind-Cold Formula (Jiu Wei Qiang Huo Tang; Table 2) is used to treat symptoms of Wind-Cold pattern such as mild fever, aversion to cold, absence of sweat, sneezing, chest congestion, running nose with clear mucus, cough with clear mucus, itching throat, a tight pulse, and a thin, white tongue coating. When cold or flu symptoms are relieved, Immunenergy (Shi Quan Da Bu Wan; Table 2) is a well-known tonic to strengthen the immune system and prevent the relapse of the disease.[39]

FEVER IN CHILDREN

One of the most common challenges among parents is when their children have fever. Fever is common among children because they are at high risk of infection due to weak immune responses. Fever in children may be caused by bacterial infections, viral infections, medications, illicit drugs, and illnesses related to exposure to heat. Infants may develop irritability, lethargy, become warm, show increased breathing, seizure, headache, difficulty of sleeping, crying, feeling uncomfortable, and loss of appetite. Sometimes fever can be adverse response to immunization but the chance of this happening is very slim. If the body temperature of the child is above normal and continuously coupled with convulsions, the parent should seek prompt medical advice from the doctor.[52-55]

Table 2. Commonly known Chinese medicinal formulas for effective alleviation of fever[39]

Cold & Flu Formula (Yin Qiao San)	Wind-Cold Formula (Jiu Wei Qiang Huo Tang)	Immunenergy Formula (Shi Quan Da Bu Tang)
Forsythia (Lian Qiao)	Notopterygium (Qiang Huo)	Angelica (Dang Gui)
Honeysuckle (Jin Yin Hua)	Ledebouriella (Fang Feng)	Cnidium (Chuan Qiong)
Platycodon (Jie Geng)	Cang Zhu (Atractylodes)	Peony (Bai Shao)
Mint (Bo He)	Asari (Xi Xin)	Rehmannia (Shu Di Huang)
Bamboo Leaf (Dan Zhu Ye)	Cnidium (Chuan Qiong)	Ginseng (Ren Shen)
Licorice (Gan Cao)	Dahurian Angelica (Bai Zhi)	Atractylodes (Bai Zhu)
Schizonepeta (Jing Jie)	Rehmania (Shen Di Huang)	Poria (Fu Ling)
Soy Bean (Dan Dou Gu)	Skullcap (Huang Qin)	Licorice (Gan Cao)
Arctium (Niu Bang Zi)	Licorice (Gan Cao)	Astragalus (Huang Qi)
		Cinnamon (Rou Gui)

ANTIPYRETIC USE IN CHILDREN

The usual practice of most parents when their child has a fever is to administer antipyretics.[56-57] It has to be noted that fever is not a disease rather a natural response of the body to fight the infection.[57] It is more important to improve the child's overall well-being rather than making the body temperature normal. Safe storage of antipyretics, encouraging fluid intake, and keen observation of other signs and symptoms of the disease should be taken into consideration by parents and caregivers of the febrile child.[56] For instance, there is no significant difference in the safety and effectiveness of ibuprofen and acetaminophen in a febrile child which is generally healthy.[56] Parents should be aware that the use of antipyretics and analgesics may not prevent febrile seizures.[62-63] Based on evidences, combining these two products is more effective in normalizing body temperature than using it singly; however, complications that may arise because of this combined treatment have to be considered.[56]

OTHER CAUSES OF FEVER[64]

Infectious diseases whether bacterial, viral, fungal, and parasitic infections are the most common cause of fever. It is a common manifestation during upper respiratory tract infections, ear infections, diarrhea, dysentery, pneumonia, and even danger signs like sepsis, meningitis, and septicemia. Malaria is a protozoan infection which is also associated with fever and chills. The recurrence of fever and chills can be used to distinguish one type of malaria from the other based on the clinical signs and symptoms. Relapsing fever, on the other hand, is caused by *Borrelia sp*. of bacteria transmitted by lice and deer ticks. After the first 1 or 2 h of penicillin or tetracycline dosing, a condition known as Jarisch-Herxheimer Reaction is associated with relapsing fever. It is due to the release of Tumor Necrosis Factor (TNF) by lysis of the spirochete.[65-66] Streptococcal pharyngitis should be treated to prevent subsequent development of rheumatic fever associated with rheumatic heart disease.[67] Scarlet fever is caused by Group A streptococci.[67] It is manifested by fever of 39-40ºC, sore throat, vomiting, headache, tonsillitis, inflammation of mouth mucosa, strawberry tongue, small scarlet red blotches on the folds of the groin, armpits, trunk and face sparing the skin around the mouth. The redness disappears and the skin exfoliates within a week.[67] Dengue fever is caused by a Flavivirus transmitted by the mosquitoes *Aedes aegypti* and *A. albopictus*. It commonly occurs as an epidemic in Southeast Asia especially Philippines, Thailand, Vietnam, Indonesia, and other countries in the world. It is now endemic in Africa, the Americas, Eastern Mediterranean, and the Western Pacific.[69] Dengue fever is characterized with a sudden high fever, often as high as 40-40.5ºC (104–105ºF). Two to five days after the fever starts, a flat, red rash may appear over most of the body. A measle-like rash appears later in the disease. Increased skin sensitivity may be experienced by infected people and it may be very uncomfortable.[70] Its deadly complication is Dengue Hemorrhagic fever (DHF) which is characterized by high fever, circulatory failure, and hepatomegaly. The fever continues up to seven days and can be as high as 41ºC with convulsions and other complications. The patient may rapidly enter in a critical state of shock and die within 12-24 h.[69,70] There is no specific treatment, specific medication and no available vaccine for dengue.[69] Supportive therapy like maintenance of the circulating fluid volume of the patient is the utmost care.[69] The only method of prevention and control is to combat the vector mosquitoes.[69] Dengue is listed as one of the emerging and re-emerging infections of the National Institute of Allergy and Infectious Diseases (NIAID) under category A, B, and C Priority Pathogens.[71,72] Fever can also be caused by other arthropod borne viruses including yellow fever virus, West Nile virus, Japanese encephalitis virus, St. Louis encephalitis virus, tick-borne encephalitis virus, Omsk hemorrhagic fever virus, Kyasanur forest disease virus, and many others.[73] Fever can also have non-infectious etiology.[64] For instance, malignancies and rheumatologic disorders can cause fever but may be non-infectious. These conditions require thorough assessment.[64]

FEVER OF UNKNOWN ORIGIN (FUO)

Fever of unknown origin is characterized by elevation in the body temperature with no explanation for the fever by the physician. The fever is more than 38.3ºC (101ºF) on several occasions without diagnosis for 3 or more weeks.[74] Petersdorf and Beeson (1961) categorize it into five conditions namely, neoplasms (e.g. lymphomas, leukaemias), infections (e.g. abscesses, endocarditis, tuberculosis, and complicated urinary tract infections), miscellaneous disorders (e.g. alcoholic hepatitis, granulomatous conditions), connective tissue diseases (e.g. temporal arteritis and polymyalgia rheumatica, Still's disease, systemic lupus erythematosus, and rheumatoid arthritis), and undiagnosed conditions.[75]

CONCLUSION

Fever is the most common health problem of many people whether it is due to stress in work or immune responses after infection. As many people believe that high body temperature may damage the brain, it is the main reason why most parents panic to see the doctor whenever their children are having fever. This is also the reason why antipyretics are one of the most frequently purchased medicines as they can block the generation of excess body heat. Although many NSAIDs type of analgesics are also effective antipyretics, they require a prescription from the doctor before they can be purchased. The currently available antipyretics that could be purchased without a prescription belong to either salicylates or acetaminophen. Besides, some commonly known traditional Chinese medicines for dispelling fever are also described as they are available over-the-counter. However, the real actions, long term safety and scientific evidence of many Chinese medicines are still lacking. This poses a challenge to scientists and the health authorities to put more efforts and resources to studying their uses.

Author's background

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Quantification of Active Pharmaceutical Ingredients in Different Preparations of Paracetamol

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ABSTRACT

This study was aimed at evaluating the dosage strength of active pharmaceutical ingredients (API) in different preparations of paracetamol from Hong Kong and other parts of China and comparing them with their counterparts from the United States (US). Twenty-one paracetamol-containing products obtained in retail pharmacies and hospitals from Hong Kong, China and Taiwan, as well as two preparations from the US were studied using high performance liquid chromatography (HPLC) following the US Pharmacopoeia (USP) method for paracetamol. The identity of the API was also confirmed using liquid chromatography mass spectrometry (LC/MS). The USP method was sensitive and specific for measuring paracetamol despite the presence of other commonly used ingredients. All preparations showed low inter-tablet/capsule variability, indicating good and consistent dosage strength. Paracetamol dispensed at three Hong Kong public hospitals came from the same supplier and were shown to have low inter-tablet variability and to contain dosage strength that was highly consistent with the product label, as compared to those purchased from six different retail pharmacies in Hong Kong and the two from the US. In addition, all preparations, including those from China and Taiwan, showed the amount of API to be within 10% variations of the specified label and met the USP requirement for qualification of paracetamol drug products. These results showed that the paracetamol preparations collected from selected areas in Hong Kong and greater China are of high quality in terms of tablet/capsule consistency in dosage strength and also the amount of API is consistent with the specified label.

Keywords: *paracetamol, API, quantity, HPLC, LC/MS*

INTRODUCTION

As advanced technology and trained personnel become more available, pharmaceutical companies that focused on the manufacturing of generic medicine are on the rise in the Fareast. China has been producing its own APIs and finished products for many off-patent drugs for general consumption. Although the Pharmaceutical Service of the Department of Health in Hong Kong and the State Food and Drug Administration of China are advancing their standards rapidly in the recent decade, there is still a widely-held perception that the quality of finished pharmaceutical products made in Asia and available in Hong Kong may be below international standards. There are also questions on whether hospital dispensed medicines are as effective as those from high-end retail pharmacy in Hong Kong. To address whether these perceptions have any validity, we elected to independently evaluate the dosage strength of one of the most commonly used medications in the greater China market (i.e. Hong Kong, China and Taiwan) - paracetamol.

Paracetamol is the international nonproprietary name for acetaminophen, the United States (US) adopted name of the same substance. It is the most commonly used over-the-counter (OTC) analgesic and antipyretic for the relief of headaches, fever, minor aches and pains. It is also a major ingredient in most OTC cold and flu remedies. Paracetamol belongs to the class of drugs known as “aniline analgesics.” It is the active metabolite of phenacetin. Paracetamol consists of a benzene ring core, substituted by a hydroxyl group and the nitrogen atom of an amide group in the *para* (1 and 4) positions, respectively (Figure 1). In the laboratory, paracetamol is usually prepared by adding sodium nitrate to phenol and the desired *p*-nitrophenol isolated from the *ortho*- by product. The nitro group of the intermediate is then reduced with sodium borohydride to *p*-aminophenol, and then acetylated with acetic anhydride, resulting in the formation of paracetamol. Industrial manufacturing of paracetamol usually begins with nitrobenzene. Paracetamol is available in various formulations, including tablet, capsule, liquid suspension, suppository, intravenous and intramuscular.

The aim of the present study was to quantify the amount of API in different oral tablet/capsule preparations of paracetamol collected in selected areas in Hong Kong, China and Taiwan and to compare with the corresponding brand and generic products obtained from

the US using high performance liquid chromatography (HPLC). In addition, the identity of the API in these preparations was verified using liquid chromatography mass spectroscopy (LC/MS).

MATERIALS AND METHODS

A total of twenty-three different preparations of paracetamol were collected either from retail pharmacies or from hospitals. These include nine products from Hong Kong (six OTC products from retail pharmacies and three from different public hospitals), eight products from China (all OTC products obtained from retail pharmacies in Nanjing, Shenzhen, and Tianjin, China), and four from Taiwan (three OTC products from retail pharmacies and one from a private hospital). Two products were also collected from a major chain retail pharmacy from the US, including one brand and one generic product. In addition, two preparations of aminopyrine/phenacetin combination products (from Shantou, China) were also obtained and used as specificity controls for the assays. All products were collected between October 1st and November 30th, 2010 and all products were well before their expiry dates when this study was performed (Table 1).

Paracetamol (acetaminophen) reference standard was purchased from Sigma-Aldrich Company (St Louis, MO). NanoPure® water (Barnstead water purification system, Thermo Fisher Scientific, Waltham, MA, USA) and HPLC-grade methanol (EM Science/ EMD Chemicals, Gibbstown, NJ, USA) were used.

Apparatus

Quantification of paracetamol was performed with a Waters Alliance 2695 chromatographic system, a Waters model 996 photodiode-array detector, and a Waters Empower chromatography data system (Waters Corporation, Milford, MA, USA). Mass spectrometry identification of paracetamol was performed with a LC/MS system consisting of Shimadzu HPLC system and 4000 QTrap LC/MS/ MS (Applied Biosystems, Foster City, CA, USA) with the data system Analyst 1.4.1. HPLC separation was carried out using an Inertsil® ODS-2, 5 µm 4.6 x 150 mm column (Agilent Technologies, Santa Clara, CA, USA).

Sample Preparation

Three tablets or capsules from each product were analyzed for inter-tablet/ capsule variability. The three paracetamol tablets obtained from the Hong Kong public hospitals were from the same supplier and therefore, the variability of

Table 1. List of Paracetamol Preparations with Dosage Strength, Place of Acquisition, Retention Times and Average Areas in HPLC, Detected Amount versus Label (wt/wt %) and Inter-tablet/capsule Variability within Each Preparation

Item #	Strength	Mono/Combo Rx	Tablet/ Capsule	Place of Acquisition	Manufacturer	RT (min)	Average Area in HPLC	% of Label	CV (%)
Preparations from the United States									
1	500 mg	Paracetamol (500 mg)	Tablet	USA (Retail Pharmacy)	Supplier A (Brand)	3.4	367971	93.2%	0.38%
2	500 mg	Paracetamol (500 mg)	Tablet	USA (Retail Pharmacy)	Supplier B (Generic)	3.4	374162	94.7%	1.05%
Preparations from Hong Kong									
3	500 mg	Paracetamol (500 mg), Caffeine (65 mg)	Tablet	Hong Kong (Retail Pharmacy)	Supplier C (Generic)	3.4	375530	95.1%	3.27%
4	500 mg	Paracetamol (500 mg)	Tablet	Hong Kong (Retail Pharmacy)	Supplier D (Generic)	3.4	372441	94.3%	4.64%
5	500 mg	Paracetamol (500 mg)	Capsule	Hong Kong (Retail Pharmacy)	Supplier E (Generic)	3.4	355220	96.1%	2.44%
6	500 mg	Paracetamol (500 mg)	Tablet	Hong Kong (Retail Pharmacy)	Supplier F (Generic)	3.4	353006	101.5%	1.61%
7	500 mg	Paracetamol (500 mg)	Tablet	Hong Kong (Retail Pharmacy)	Supplier F (Generic)	3.4	366614	92.8%	3.69%
8	500 mg	Paracetamol (500 mg), Caffeine (30 mg)	Tablet	Hong Kong (Retail Pharmacy)	Supplier G (Generic)	3.4	362386	91.8%	3.27%
9	500 mg	Paracetamol (500 mg)	Tablet	Hong Kong (Public Hospital A)	Supplier H (Generic)	3.4	369013	93.4%	2.17%
10	500 mg	Paracetamol (500 mg)	Tablet	Hong Kong (Public Hospital B)	Supplier H (Generic)	3.4	366891	92.9%	1.10%
11	500 mg	Paracetamol (500 mg)	Tablet	Hong Kong (Public Hospital C)	Supplier H (Generic)	3.4	373614	94.6%	0.12%
Preparations from China									
12	500 mg	Paracetamol (500 mg)	Tablet	Guangzhou (Retail Pharmacy)	Supplier I (Generic)	3.4	384296	97.3%	4.24%
13	300 mg	Paracetamol (300 mg)	Tablet	Shenzhen (Retail Pharmacy)	Supplier J (Generic)	3.4	238246	100.5%	1.07%
14	650 mg	Paracetamol (650 mg)	Tablet	Tianjin (Retail Pharmacy)	Supplier A (Brand)	3.4	372610	94.3%	4.77%
15	500 mg	Paracetamol (500 mg)	Tablet	Nanjing (Retail Pharmacy)	Supplier K (Generic)	3.4	397054	100.5%	2.11%
16	250 mg	Paracetamol (250 mg), Propyphenazone (150 mg), Anhydrous Caffeine (50 mg)	Tablet	Nanjing (Retail Pharmacy)	Supplier L (Generic)	3.4	382203	96.6%	7.09%
17	300 mg	Paracetamol (300 mg)	Tablet	Nanjing (Retail Pharmacy)	Supplier M (Generic)	3.4	391504	99.1%	0.21%
18	650 mg	Paracetamol (650 mg)	Tablet	Nanjing (Retail Pharmacy)	Supplier N (Generic)	3.4	367508	93.1%	1.44%
19	500 mg	Paracetamol (500 mg)	Tablet	Nanjing (Retail Pharmacy)	Supplier O (Generic)	3.4	384950	98.7%	2.86%
Preparations from Taiwan									
20	500 mg	Paracetamol (500 mg)	Tablet	Taipei (Private Hospital)	Supplier P (Brand)	3.4	383975	97.2%	2.06%
21	500 mg	Paracetamol (500 mg), Caffeine (30 mg)	Tablet	Taipei (Retail Pharmacy)	Supplier Q (Generic)	3.4	385281	97.6%	3.06%
22	500 mg	Paracetamol (500 mg)	Tablet	Taipei (Retail Pharmacy)	Supplier P (Brand)	3.4	371781	94.1%	0.99%
23	500 mg	Paracetamol (500 mg), Caffeine (65 mg)	Tablet	Taipei (Retail Pharmacy)	Supplier Q (Generic)	3.4	376265	95.3%	3.65%

the paracetamol tablets from different dispensing sites of the same supplier was also tested in this setting.

Individual tablet or content of capsule was weighed and dissolved in 100 mL of HPLC mobile phase solution (75% water, 25% methanol, EMD Chemicals) facilitated by sonication for 15 minutes at room temperature. Twenty-five milliliters of each solution was transferred into a 50 ml centrifuge tube and centrifuged at 4000 rpm for 10 minutes at room temperature to remove any insoluble excipients. Appropriate volume of the supernatant was diluted to 50 mL with HPLC mobile phase solution to give the sample solutions a projected final concentration of 0.01 mg/mL of paracetamol. The paracetamol reference standard was weighed and dissolved in HPLC mobile phase with serial dilution to obtain a final concentration of approximately 0.01 mg/mL.

Assay Methods - HPLC

Tablets or capsules of paracetamol were analyzed using a reverse-phase HPLC procedure - a modified United States Pharmacopeia (USP) method.[1-3] HPLC analysis was performed by isocratic elution with a flow rate of 1.0 mL/min. The mobile phase composition was water/methanol (75:25 v/v). The column temperature was at 30°C. Injection volumes of samples were set at 10 µL and HPLC was run for 5 minutes per injection. Retention was detected using photodiode array detector set at 243 nm. Peak area was integrated and quantification was performed with external standardization using the measured peak area. Injections of reference standard were performed before and after all sample injections in order to ensure consistent results.

Samples of paracetamol preparations that contain caffeine were also run with the aforementioned isocratic HPLC conditions without interference with paracetamol. Samples containing propyphenazone, aminopyrine, phenobarbital and phenacetin required gradient elution, 75/25 (water/methanol) to 25/75 (water/methanol) in 15 minutes, in order to have these components eluted at retention times within a run time of 15 minutes.

Assay Methods – LC/MS

To confirm the identity of the API in each preparation, LC/MS was conducted for one tablet/capsule for each preparation. LC/MS analysis was performed in two parts: first, Q1 MS full scan using a positive ion mode with Turbo Ion Spray® (Electrospray) interface or (+) ESI identified the major molecular ion or parent ion; second, MS2 or product ion scan at selected m/z was used to obtain the product ion spectral data of the parent ion. The following settings were used: Ion Spray 5.0 kV, temperature set at 450°C, gas 1 using N_2 set at 50 psi, gas 2 using N_2 at 40 psi, curtain gas of N_2 at 10 psi, collision gas of N_2 at 5-10 psi, entrance potential of 10 V, declustering potential of 60 V, collision energy of 30-35 eV, and collision cell exit potential of 10 V. The scan range was set at 75 to 250 amu for both Q1 MS scan and enhanced product ion scan or MS2 at m/z 152 for paracetamol and at m/z 195 for caffeine. The HPLC condition was modified with gradient wash between each injection, (72/28 (A/B) hold for 9 min, 0.2 min to 02/98 (A/B) hold for 3 min, 0.3 min to initial, where A is 0.1% formic acid in water and B is 100% methanol. Undiluted samples, the supernatant after centrifuge, were used for this analysis to optimize spectral data output.

RESULTS

All paracetamol preparations have the API detected with the retention time of exactly 3.4 minutes using the USP method. This retention time corresponded to that in the chromatogram of the reference standard for paracetamol. Caffeine was found to have a retention time of around 6.8 minutes by isocratic HPLC and did not interfere with paracetamol (Fig. 1). When the aminopyrine/phenacetin combination tablets (specificity control) were tested, there was no detection under 5 minutes. Samples containing propyphenazone, aminopyrine, phenobarbital and phenacetin analyzed by gradient elution within a run time of 15 minutes were found to have retention times of 9.3 and 9.8 minutes for aminopyrine and phenacetin, respectively, 9.3 minutes for phenobarbital and aminopyrine, and 12.9 minutes for propyphenazone (Figure 2).

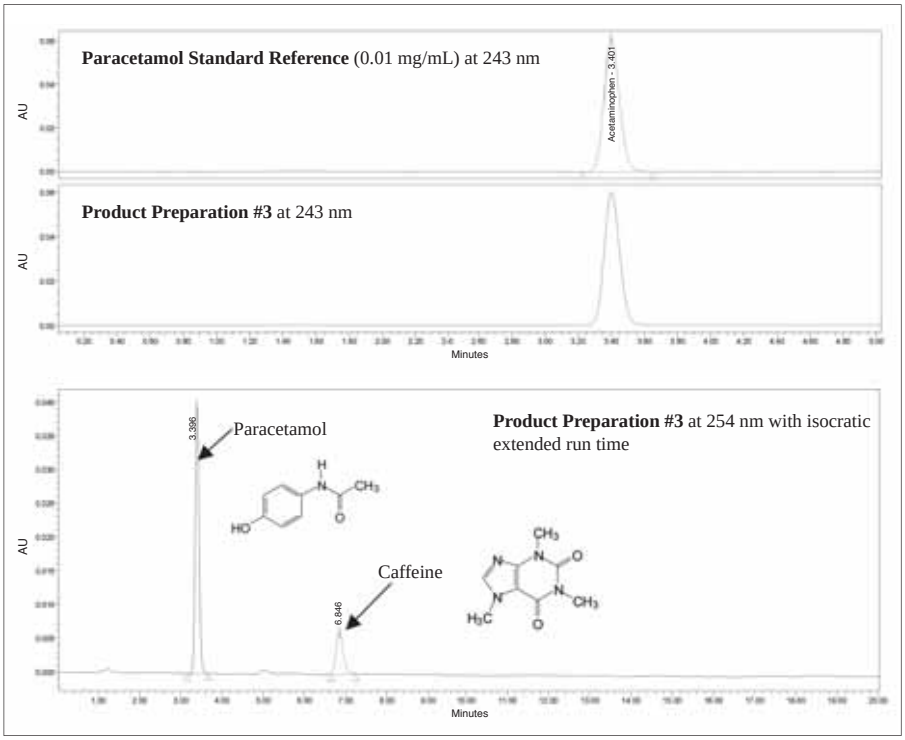

Figure 1. *Isocratic HPLC profiles of paracetamol in the standard reference and product preparation #3 (paracetamol and caffeine) at 243 nm and at 254 nm. The retention time of paracetamol in the standard and product preparation #3 was consistently 3.4 min and the retention time of caffeine was 6.8 min indicating no interference in the detection of both components in the preparations.*

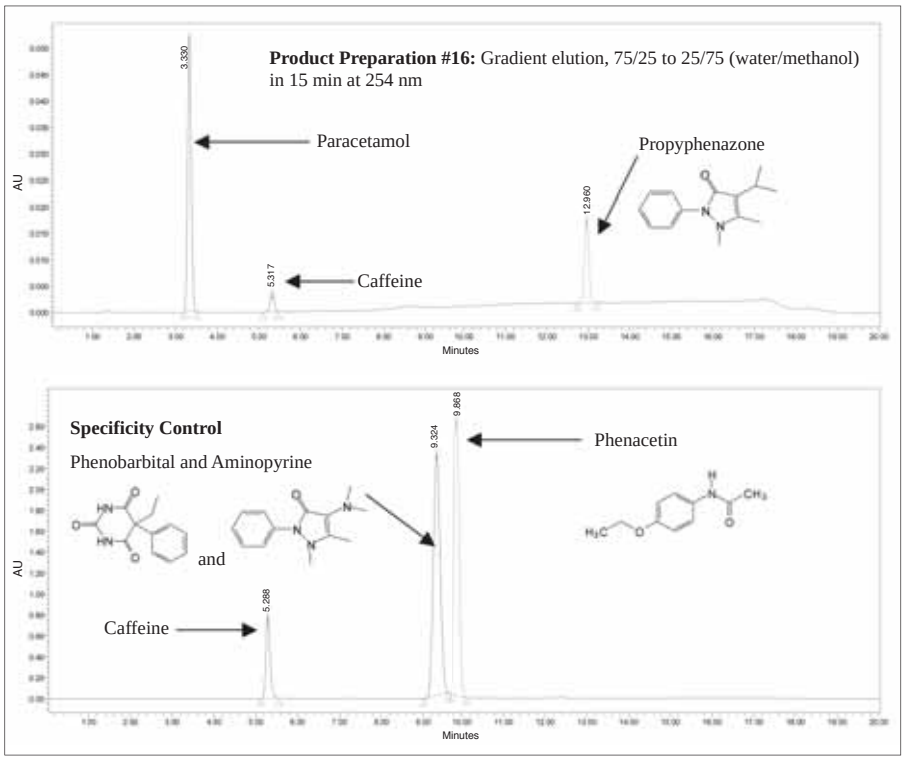

Figure 2. *Gradient HPLC profiles of product preparation #16 (paracetamol, caffeine, propyphenazone) and the specificity control (a control preparation without paracetamol but contains caffeine, phenobarbital, aminopyrine, and phenacetin). The retention times were discrete, at 3.4 min for paracetamol, 5.3 min for caffeine, 12.9 min for propyphenazone, 9.3 min for phenobarbital and aminopyrine and 9.8 min for phenacetin, showing no interference in the detection of all components in the preparations.*

These experiments showed that with the USP method, the peak with a retention time at 3.4 minutes was essentially paracetamol and other ingredients like caffeine, aminopyrine, phenobarbital, phenacetin, and propyphenazone could be differentiated by HPLC easily.

To further confirm the identity of the paracetamol, one tablet/capsule of each of the 23 preparations of paracetamol was subjected to LC/MS analysis. Figure 3 shows the LC/(+)ESI MS of the API with retention time of 3.4 min gave a protonated molecular ion at *m/z* 152, consistent with a molecular weight of paracetamol 151 Da. The product ion spectral data of the API that peaked at *m/z* 152 gave characteristic fragment ions at *m/z* 110, 93, and 92. This is consistent with the reference standard and structure of paracetamol, thus confirming the identity of paracetamol in these preparations. Likewise, the identity of caffeine was confirmed by the appropriate m/z of 195 and characteristic fragment ion of 138 of the API with retention time of 5.3 min by gradient HPLC.

Table 1 summarizes the results of this study. First, the variability of the three tablets/capsules within each preparation was small. The coefficient of variation (CV) for all preparations ranged from 0.12% to 7.09%, with an average of 2.49% and standard deviation of 1.71%. For the three preparations dispensed from Hong Kong public hospitals that came from the same supplier, the CV was particularly narrow ranging from 0.12% to 2.17%. In comparison, the CV ranged from 1.61% to 4.64% for the six preparations obtained from retail pharmacies in Hong Kong. The US brand paracetamol (acetaminophen) had a CV between tablets of 0.38% and the US generic drug had a CV of 1.05%.

Second, the amount of API in each preparation averaging three tablets/capsules was within 91.76% to 101.5% of the specified dosage of paracetamol in these preparations (250 mg, 300 mg, 500 mg, 650 mg). The average amount of API was 95.87% with a standard deviation of 2.77% of the specified dosage. The Hong Kong products from public hospitals ranged from 92.9% to 94.6% as opposed to those from retail pharmacies that had the wider range of 91.8% to 101.5%. The US brand paracetamol (acetaminophen) had an amount of 93.18% and US generic had 94.74% of the specified amount in the label.

DISCUSSION

This pilot study showed three important points. First, the USP assay method for paracetamol is adequate in detecting paracetamol reliably and other commonly used ingredients will not affect the detection and quantification. Second, the variability of the amount of API in the preparations was low. Third, the tablets/capsules do contain close to the specified dosage strength of API on their label and meet industry standard in this regard.

For reliable quantification of API, the assay method has to be consistent and unaffected by other ingredients commonly used in these preparations. Our study showed that with a HPLC run time of less than 5 minutes following the specified USP conditions, paracetamol can be consistently detected at a retention time of 3.4 minutes. Importantly, the other commonly used ingredients like caffeine, aminopyrine, phenobarbital, phenacetin, and propyphenazone all had retention times that exceed 5 minutes. To confirm the identity of paracetamol, LC/MS was performed in all 23 preparations and the molecular weight was confirmed. The characteristic fragmentations were also detected, providing further evidence that this assay method is reliable and accurately detects paracetamol.

With this reliable detection method, we showed that the variability of the amount of API in the tablets/capsules within the same preparation was low. All samples had inter-tablet/capsule variability of less than 10%. Apart from one preparation at 7.09%, all other preparations had variability of less than 5%. The product with the second highest variability of 4.77% was manufactured by a major multinational company. The particularly low variability of the three preparations from Hong Kong public hospitals (ranged from 0.12% to 2.17%)

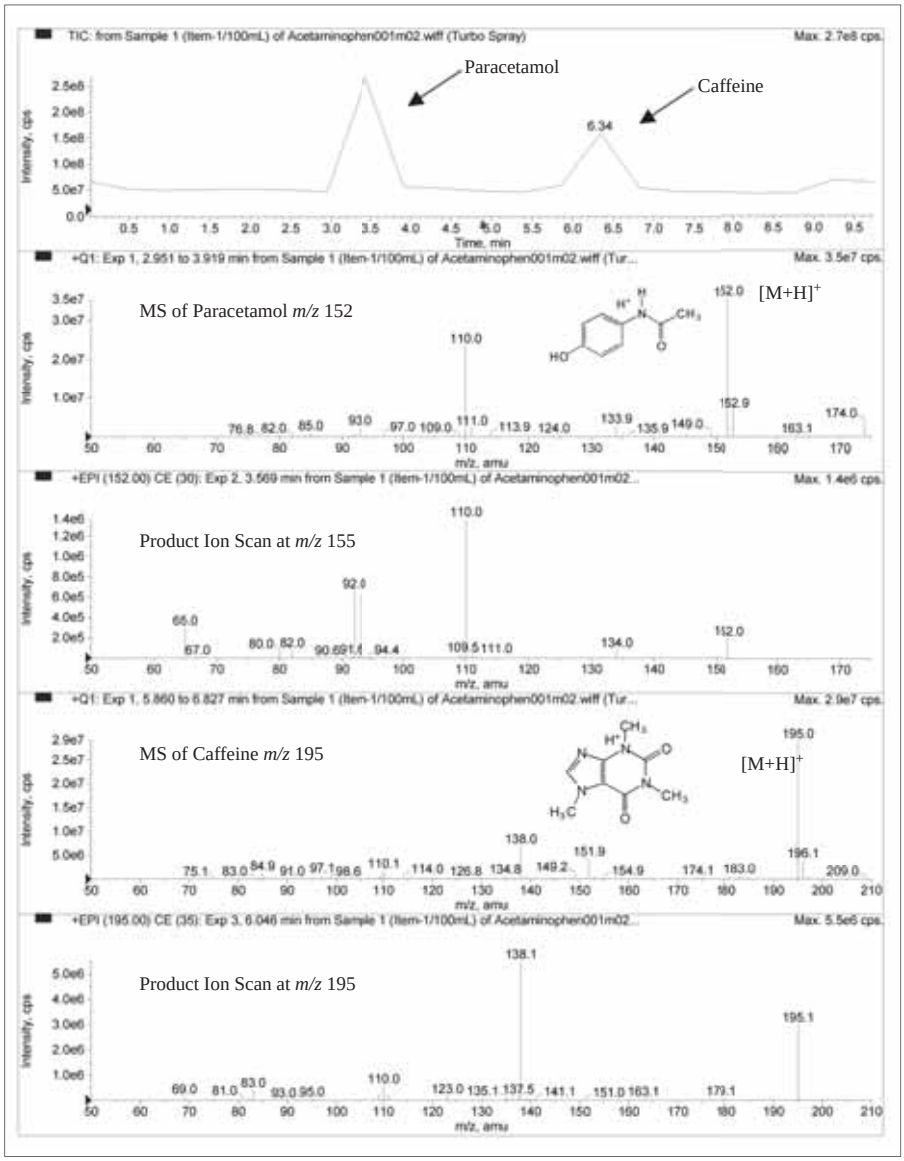

Figure 3. *LC/(+)ESI MS and MS2 Spectral Data of Paracetamol and Caffeine from product preparation #3. LC/(+)ESI MS of the API with retention time of 3.4 min gave a protonated molecular ion at m/z 152, consistent with a molecular weight of paracetamol 151 Da. The product ion spectral data of the API that peaked at m/z 152 gave characteristic fragment ions at m/z 110, 93, and 92. This is consistent with the reference standard and structure of paracetamol, thus confirming the identity of paracetamol in these preparations. Likewise, the identity of caffeine was confirmed by its characteristic m/z of 195 and fragment ion m/z of 138.*

that originated from the same supplier provides additional assurance of the quality of product that benefits the Hong Kong community.

Finally, all preparations contained an amount of API close to the specified dosage strength on the label. For a regular potency test, 20 tablets/capsules are "pooled" together and the amount determined. In this study, the amount of paracetamol contained in all the tested samples was at or more than 250 mg and was within the range to be accurately quantified on a per tablet/capsule basis. Three tablets/capsules per preparation were measured for assessing the inter-tablet/capsule variability. Our data showed that all preparations from both US and greater China (from bigger cities) met the industry standard of within 10% of the specified amount according to USP specifications. This study, which was conducted independently, provided unbiased confirmation to debunk the misconception that paracetamol available in Hong Kong and greater China is inferior to that in the US.

It should be noted that this is a pilot study designed to address quantity of dosage strength of paracetamol preparations available in selected places in greater China. These positive findings lay the foundation for further evaluation of the dissolution profiles, purity of API, identity and amount of excipients to adequately confirm the quality of paracetamol. Moreover, systematic collection of samples from representative areas/regions including rural, less developed areas as well as major retail pharmacies will generate comprehensive information to ascertain the quality of the product. Similarly, the quality of other medications can be evaluated. Independent studies such as this are important to ensure that the health interests of consumers are well protected by both the State Food and Drug Administration and local regulatory agencies.

Acknowledgements

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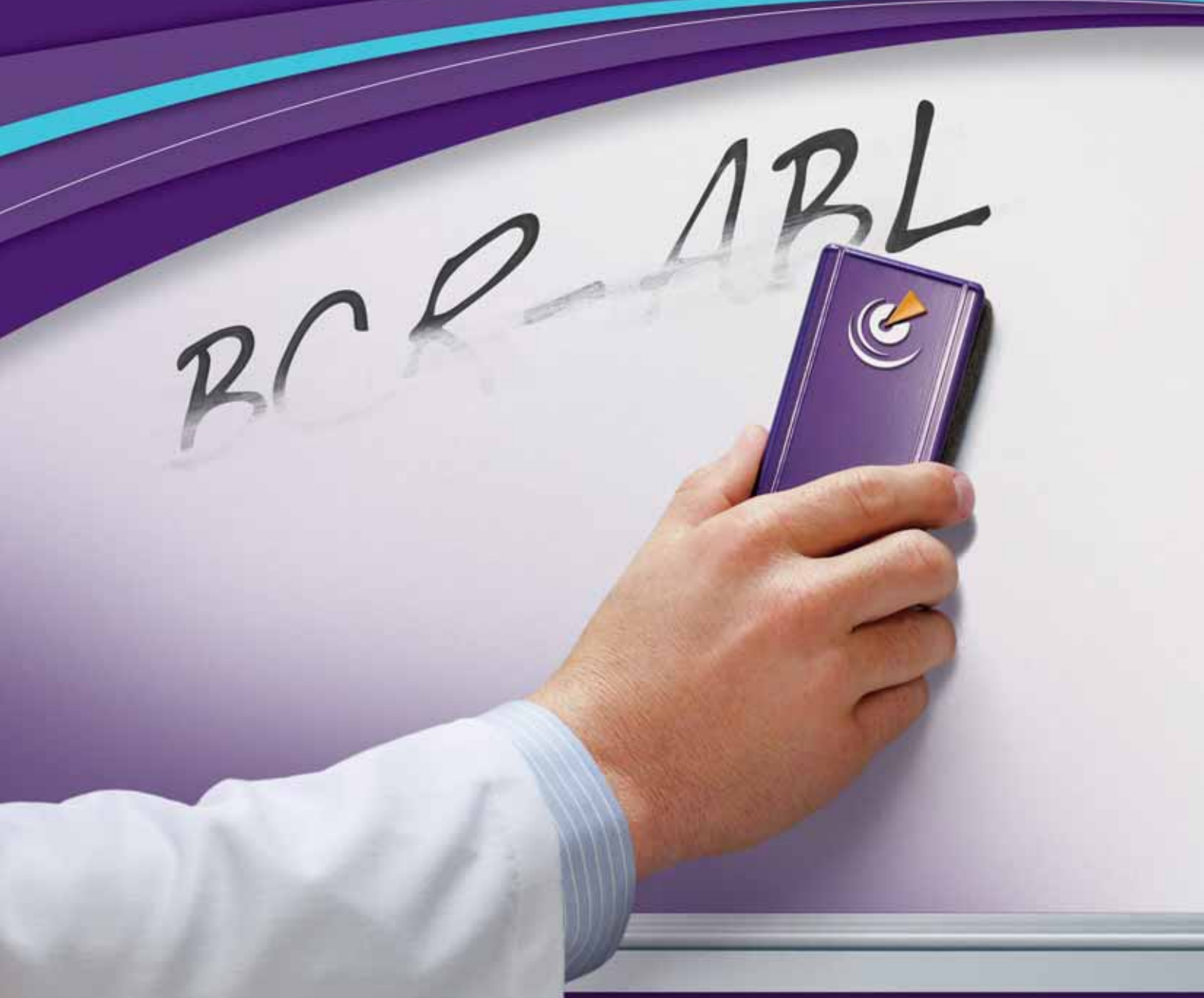

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Mini-Review

Bioactive Compounds in *Lonicera japonica* Thunb.(忍冬) and Its Biological Effects

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Botanical Name: *Lonicera japonica* Thunb.

Family: Caprifoliaceae

Latin: *Lonicera japonica* Thunb.

Common names/other names: Japanese honeysuckle, *Lonicera japonica*, *Lonicera*, *Caulis lonicera japonica*, *Flos lonicerae*, Chevrefeuille, Honeysuckle flower, Jinyinhua, Gold silver flower, Erhua, Shuanghua, Suikazura, Madreselva, Rendong, Woodbine

Chinese Name: 忍冬(Rendong)

Part Usually Used: Stem, leaf and flower

Common Uses: Clean toxic heat, dispel wind-heat, antiphlogosis, antivirus, promote urination, and relieve itching

ABSTRACT

***Lonicera japonica* Thunb. is an evergreen twining vine that is widely planted in Asian countries. The flower buds, named Jinyinhua (金銀花) in Chinese, contain abundant bioactive compounds including flavonoids, saponins, iridoid glucosides and volatile oils. Chlorogenic acid and luteoloside are the main flavonoids in the flower buds. With numerous natural bioactive constituents, Jinyinhua has been reported as a potent antipyretic having pharmacological properties such as anti-inflammation, antioxidant, anticancer, antivirus etc. However, it might cause poisoning, gastrointestinal upset, blood clotting and contact dermatitis or rash in humans. Thus, it is strongly recommended to avoid usage in pregnant or breastfeeding women and people who have hypersensitivity to honeysuckle flower. Different aspects of its natural compounds and their beneficial effects are reviewed in this article.**

Keywords: *Lonicera japonica, chlorogenic acid, anti-inflammation, antioxidant, toxic heat*

INTRODUCTION

Lonicera japonica Thunb. is a traditional Chinese medicine that belongs to the Caprifoliaceae family. It is a very commonly used herb that grows widely in China, Japan, Korea, and countries in southeast Asia.[1] The plant prefers sandy, loamy and clay soils; and its habitats are mainly woodland garden, dappled shade, shady edge and ground cover.[2] The flowers of this plant are hermaphrodite with both male and female organs. It generally opens at dusk, and the strongest aroma of the flower is emitted around midnight.[3] Thus, the flowers can be pollinated by bees and hawkmoths.[4] Scientific evidence indicates that the flower buds, namely Lonicera Flos, are the most important medicinal part, that are rich in bioactive constituents such as flavonoids, saponins, iridoid glucosides and volatile oils.[3,5-7] According to clinical trials, the flower buds are recognized as a potent herb for the therapy of toxic heat, wind-heat, inflammation, itching, fever and swelling etc..[8,9] In this article, the natural bioactive compounds, pharmacological effects on human health and other aspects of *L. japanase* are generally reviewed.

DESCRIPTION AND IDENTIFICATION

Macroscopic appearance

The vine of *L. japonica* Thunb. can climb up to 10 m. The flowers open white and fade to yellow from June to July. As

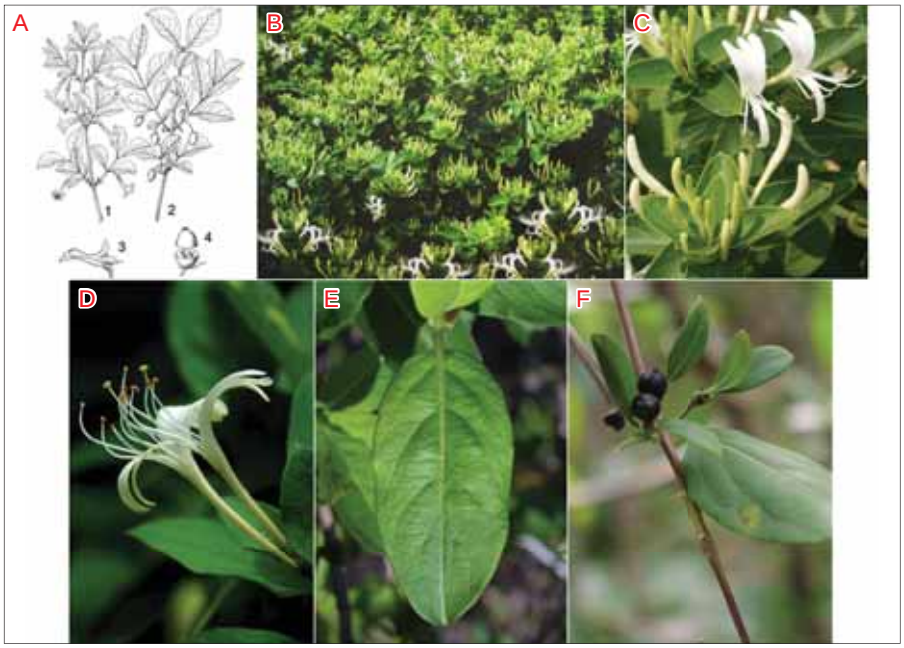

Figure 1. *Pictures of Lonicera japonica Thunb.. (A) Sketch; (B) Lonicera Japonica in its habitat; (C) Flowing branching; (D) Flower; (E) Leaf; (F) Fruit. (Photos taken form http://baike.baidu.com/view/16387.htm by Yang ZR et al.)*

shown in Figure 1, the flower buds are club-shaped and slightly curved, and the whole length is around 2 to 3 cm. The upper part of the buds is dilated and thicker and are 3 mm in diameter while the lower part is smaller being 1.5 mm in diameter. The color of the buds is light yellow or yellowish-brown, and the surface of the buds is densely covered with strigose, long glandular hairs. The calyx tube is globose-shaped with five triangular lobes or teeth at the apex. Each lobe is hairy and about 1 mm long. The corolla is tubular shaped and double-tongued, having five stamens adnated to the tube wall or one pistil with one long style. The flower is sweetly vanilla scented but slightly bitter tasting. The leaves are commonly oval shaped at around 3 ~ 8 cm long and 2 ~ 3 cm wide. The fruit is a globose-shape deep blue berry, with a diameter in the range of 5 ~ 8 mm, that contains numerous seeds. (Fig. 1).[10,11]

Actually, there are four other flower buds from other *Lonicera* species that are also called "Jinyinhua" in China because of the similar morphology. The four species are *L. macranthoides* Hand.-Mazz., *L. hypoglauca* Miq., *L. confusa* DC. and *L. fulvotomentosa* Hsu et S. C. Cheng. Macroscopic appearances of these five flowers have been compared by Chu *et al.* (2011) (shown in Table 1 and Fig. 2).[10]

Microscopic description

The surface view of the Lonicera Flos buds reveals that there are two kinds of glandular hairs. For the first kind, the glandular hairs are turbinate and the head is 48 ~ 108μm in diameter, which contains 10 ~ 33 cells arranged to 2 ~ 4 layers in the lateral view. The stalk is 70 ~ 700 μm long and contains 1 ~ 5 cells. For the second kind, the subrounded or slightly oblate glandular hairs containing 4 ~ 20 cells are 20 ~ 64 μm in diameter. The stalk is shorter being 24 ~ 80μm in length and contains 2 ~ 4 cells. The non-glandular hair is unicellular with tiny verrucae on the surface, some of which possess are orneous spiral shaped. It is around 45 ~ 900 μm in length, 14 ~ 37 μm in diameter, and 5 ~ 10 μm in thickness. The diameter of the calcium oxalate clusters is 6 ~ 45 μm. Pollen grains are globose or round triangle shaped with three aperture channels (Fig. 3).[10,12] The transverse section of cuticle, wall of non-glandular hairs and vascular bundles of the flower buds are also shown in Figure 3.

Table 1. Morphologic characteristics of five *Lonicera* flower buds

Species	Bud diameter (mm)	Bud length (cm)	External color	Hairs
L. japonica Thunb.	1.5–3	2–3	Yellowish-white or greenish-white	Externally covered with yellowish-white pubescence densely
L. macranthoides	1–2	3–4.5	Yellowish-white or greyish-green	Externally covered with greyish-white pubescence densely
L. confusa	0.5–2	1.6–3.5	Reddish-brown or grayish-brown	Externally covered with greyish-white or pale yellow pubescence densely
L. hypoglauca	0.8–2	2.5–4.5	Pale yellowish-brown or yellowish-white	Externally covered with pubescence sparsely and short-stemmed glandular hairs or glabrous
L. fulvotomentosa	1.5–2	1–3.4	Pale yellowish-brown or grayish-brown	Externally covered with yellowish-brown hairs, short and thick

(Cited from Chu et al. 2011)[10]

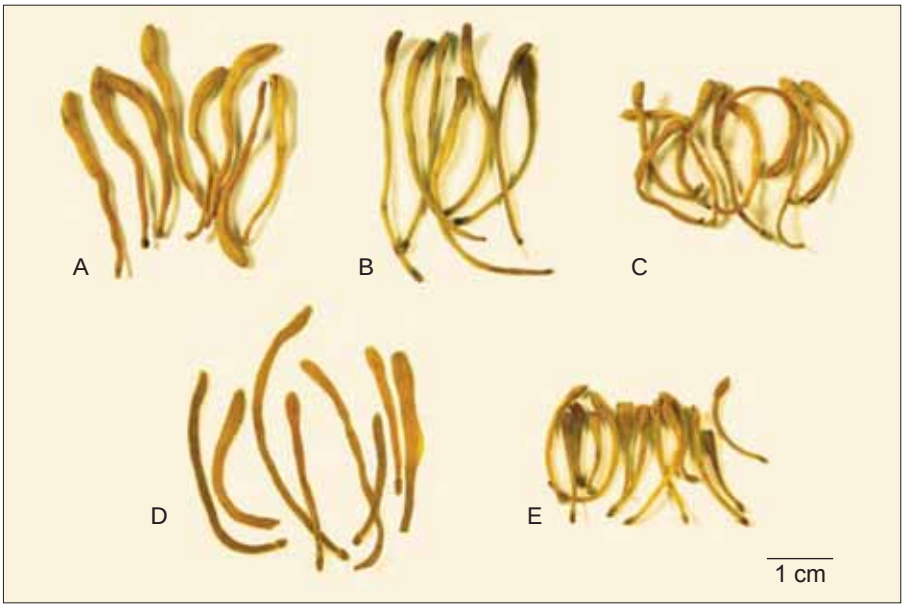

Figure 2. *Photos of five species of Lonicera flower buds.* ***(A)*** *L. japonica;* ***(B)*** *L. macranthoides;* ***(C)*** *L. confuse;* ***(D)*** *L. hypoglauca;* ***(E)*** *L. fulvotomentosa. Cited from Chu et al. (2011)*[10]

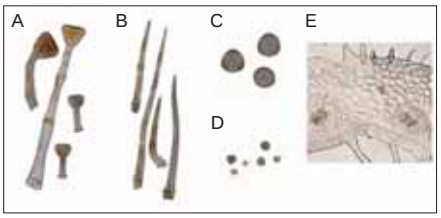

Figure 3. *Microscopic characters of Flos lonicera. (A) Glandular hairs; (B) Non-glandualr hairs; (C) Pollen grains; (D) Calcium oxalate clusters; (E) Transerse section of the flower. (Cited from Chu et al.)*[10]

Genetic and proteomic methods

According to the report of Wang *et al.* (2007) and Peng *et al*. (2010), five closely related species of *Lonicera* could be further identified by two accurate and rapid genetic methods.[13,14] By using the restriction endonuclease EcoN I, the mutation site in the nuclear ribosomal DNA (nrDNA) internal transcribed spacer (ITS) region of *L. japonica* could be identified. Moreover, a pair of allele-specific primers has also been designed for diagnostic PCR on the nrDNA ITS2 region.

BIOACTIVE CONSTITUENTS

Phenolic acids

Chlorogenic acid, namely 5-*O*-caffeoyl-quinic acid (CQA), is one of the most important bioactive phenolic components in the flower and caulis of *L. japonica* (Fig. 4A).[5] It is an ester form of *trans*-caffeic acid with quinic acid (1L-1 (OH),3,4/5-tetrahydroxycyclohexane carboxylic acid).[15] Caffeic acid is also found in flower buds of honeysuckle.[16]

Flavonoids

Luteoloside, luteolin, quercetin, chrysoeirol-8-O-neohesperidoside,

tricin-7-O-neophesperidoside, lonicerin, luteolin-7-O-galactoside, rutin, hyperoside, quercetin, avicularin are the main flavonoids in the flower and caulis of *L. japonica*.[16,17] Two bioflavonoids, 3'-O-methyl loniflavone [5,5'',7,7''-tetrahydroxy 3'-methoxy 4',4'''-biflavonyl ether] and loniflavone [5,5'',7,7'',3'-pentahydroxy 4',4'''-biflavonyl ether], along with chrysin, have been identified from the leaf of *L. japonica* by Kumar *et al*.[18] Chemical structures of major flavonoids are illustrated in Figure 4.

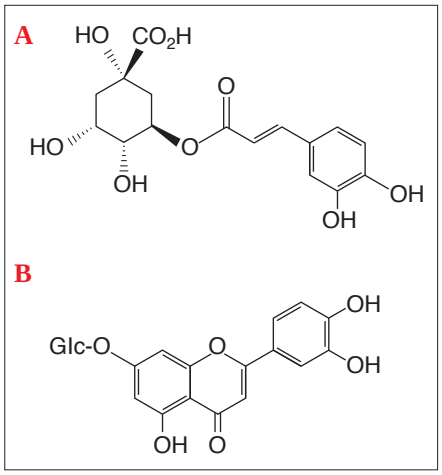

Figure 4. *Chemical structures of major phenolic acids and flavonoids. (A) Chlorogenic acid; (B) Luteoloside.*

Saponins

According to the report, there are two major kinds of saponins in Lonicera Flos, one of which contains hederagenin aglycone while another contains oleanolic acid.[19] The following saponins have been found in the flower buds, including macranthoidin A, macranthoidin B, macranthoside A, macranthoside B, dipsacoside B, hederagenin-28-O-β-d-glucopyranosyl(6-->1)-O-β-d-glucopyranosyl ester, and hederagenin-3-O-α-l-arabinopyranosyl(2-->1)-O-α-l-rhamnopyranoside.[20] A new triterpenoid glycoside oleanolic acid 28-O-α-L-rhamnopyranosyl-(1→2)-[β-D-xylopyranosyl(1→6)]-β-D-glucopyranosyl ester has also been isolated from the ethyl acetate fraction of *Flos lonicera*.[7,21]

Iridoid glucosides

Several iridoid glucosides have been identified from the honeysuckle flower, which includes 7-epi-loganin, sweroside, loganin, 7-epi-vogeloside, secoxyloganin, L-phenylalaninosecologanin, 6′-O-(7α-hydroxyswerosyloxy) loganin, 7-O-(4-β-D-glucopyranosyloxy-3-methoxybenzoyl) secologanolic acid, (Z)-aldosecologanin, and (E)-aldosecologanin, have also been isolated.[6,22]

Volatile oils

Schlotzhauer *et al*. (1996) have suggested that germacrene D is the major volatile compounds in freshly opened flowers and in flowers even after 12 or 24 h of storage.[23] The content and verities of volatile oils in flower and caulis are similar, in which the majority compounds are palmatic acid and linoleic acid.[24]

IDENTIFICATION, ISOLATION, AND PURIFICATION OF BIOACTIVE COMPONENTS

The crude extract of honeysuckle is conventionally extracted by solid-liquid or solvent extraction, which is further accompanied with gel and polyamide chromatography analysis.[25] A microwave-assisted extraction (MAE) technique has been reported for the improvement of chlorogenic acid extraction from the flower buds of *L. japonica*. Compared with the conventional heat-reflux extraction method, the extraction efficiency of the MAE method could be achieved by 6.14% within 5 min with 50% ethanol extraction solvent at 60°C.[18] Researchers also indicated that, after macroporous HPD-850 resin treatment, the extracted concentration of chlorogenic acid increased 4.46 times compared to eight other macroporous resins.[25] Extraction of volatile oils in Lonicera Flos has been optimized for the supercritical CO_2 extracting method. Effects of pressure, temperature, flow of CO_2 and extracting time on the extraction yield have been studied by orthogonal design. With the optimum flowing rate at 4.0 kg/h and pressure at 12 MPa, the extraction rate was 4.32 times higher than the control steam distillation method within 1.5 h at 35°C.[26]

The separation and purification of the bioactive chlorogenic acid has been widely studied. High-speed counter-current chromatography and molecular imprint have been introduced for the separation and identification of CQA from the crude extract of the flower.[2,5] A pH-gradient counter-current chromatography method has been developed by Wang *et al.* (2008) to isolate the chlorogenic acid from the flowers and buds.[27] High performance liquid chromatography (HPLC) has been recognized as one of the most advanced and high efficient analytical techniques for the quality and quantity analysis of bioactive compounds.[28,29] There have been some studies on the HPLC analysis of chlorogenic acid and other flavonoids in Lonicera Flos.[30,31] RP-HPLC was also introduced for the analysis of chlorogenic acid, caffeic acid, sweroside and loganin in the *caulis* of *L. japonica*.[32]

The capillary electrophoresis (CE) technique is a powerful analytical instrument and is widely used in separating and analyzing bioactive components in traditional herbal medicine.[33,34] It possesses a lot of advantages such as high efficiency, high selectivity, high flexibility, high resolving power, small sample volume and easy method development over other separation techniques.[35,36] Capillary zone electrophoresis (CZE) coupled with solid-phase extraction (SPE) has been developed for the detection of flavoniods in Lonicera Flos.[16] Moreover, a sensitive and rapid ion liquid modified glassy carbon electrode method for the detection of total flavonoids in the flower of *L. japonica* has also been reported.[37] Two bioflavonoids, 3'-O-methyl loniflavone and loniflavone along with luteolin and chrysin, have been isolated and established by ESI-QTOF-MS spectroscopic methods.[18]

Seven major saponins including macranthoidin A, macranthoidin B, dipsacoside B, macranthoside A, macranthoside B, hederagenin-28-O-β-d-glucopyranosyl(6-->1)-O-β-d-glucopyranosyl ester, and hederagenin-3-O-α-l-arabinopyranosyl(2-->1)-O-α-l-rhamnopyranoside have been separated by HPLC using evaporative light scattering detection (ELSD).[20] Five major iridoid glucosides were separated from *Flos lonicera* by a new HPLC method using evaporative light scattering detection.[22] Four new iridoid glucosides including L-phenylalaninosecologanin, 7-O-(4-β-D-glucopyranosyloxy-3-methoxybenzoyl) secologanolic acid,

6′-O-(7α-hydroxyswerosyloxy) loganin and (Z)-aldosecologanin, together with (E)-aldosecologanin, have also been isolated.[6] Phenolic acids, iridoids and flavonoids like chlorogenic acid, caffeic acid, loganin, sweroside, secoxyloganin, rutin and luteolin 7-O-glucoside could be simultaneous analyzed by HPLC from the caulis part as well.[17] In addition, one hundred and fifty volatile compounds, which include hydrocarbons, alcohols, aldehydes, ketones, esters and miscellaneous, have been isolated from the flowers and analyzed by GC and GC-MS.[3]

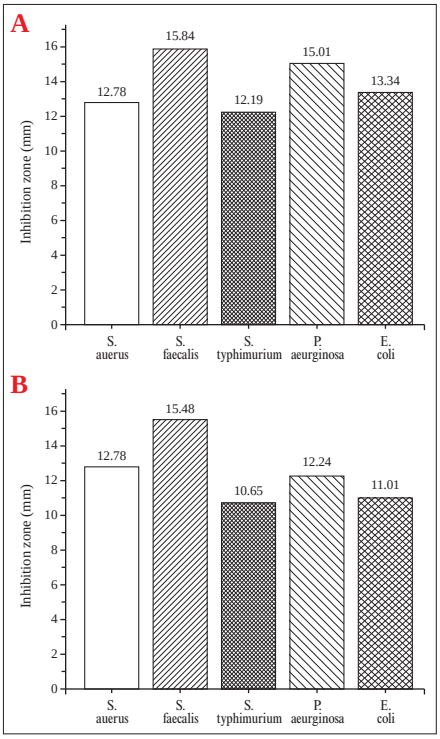

Figure 5. *Bactericidal effect of different L. japonica extracts. (A) Decoction; (B) Ethanol extract.*

PHARMACOLOGICAL EFFECTS

Anti-inflammatory activity

According to the report of Lee *et al.* (1995), the *n*-butanol fraction, which mainly consisted of loniceroside A, lonicerin and loganin, exhibited potent anti-inflammatory activity in mice and rats models compared to aspirin.[38] Su *et al.*(2006) also have reported that the volatile oil extracts exert anti-inflammatory effects on the ear swelling model in mice.[26] This activity could be also obtained in two in vivo models such as the vascular permeability and air pouch models.[8] Our previous research studied on the bactericidal effect of different extracts of honeysuckle by the agar diffusion method indicated that, decoction and ethanol extract could efficiently inhibit bacteria such as *Staphylococcus aureus, Streptococcus faecalis, Pseudomonas aeurginosa, Escherichia coli* and *Salmonella typhimurium* (data not published). The order of inhibition effects is shown in Figure 5. It was demonstrated that, the inflammatory inhibitory effects mainly involved the production of the pro-inflammatory mediators and the inhibition of nitric oxide (NO) production and tumor necrosis factor-alpha (TNF-α) secretion.[39]

Antioxidant activity

A rapid method for the selecting of natural antioxidants by DPPH-HPLC-DD-TOF/MS has been developed by Tang *et al.* (2008). The antioxidant activity of some active antioxidants like chlorogenic acid, 1-*O*-caffeoylquinic acid (1-*O*-CQA), caffeic acid, 4-*O*-CQA, rutin, isoquercitrin, luteolin-7-*O*-glucoside, lonicerin, luteolin, 1,4-*O*-diCQA, 3,5-*O*-diCQA, 1,3-*O*-diCQA, 3,4-*O*-diCQA and 4,5-*O*-dicaffeoylquinic acid (4,5-*O*-diCQA) have been assayed and identified.[40] The antioxidant effects of different extract fractions have been studied by Choi *et al.* (2007) as well.[7] As shown in Table 2, the antioxidant capacities were evaluated by the total reactive oxygen species (ROS), 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical, peroxynitrite (ONOO-) and hydroxyl radical (·OH) assays. Other research also indicated that chlorogenic acid in Lonicera Flos contributed most to the potent antioxidant activity in the water, methanolic and 70% ethanolic extracts.[9,41] Moreover, in the rat model, the oxidative stress could be efficiently reduced by chlorogenic acid.[42]

Anti-tumor activity /Anti-carcinogenic activity

Jiang *et al.* (2001) have reported the cytotoxicity effects of chlorogenic acid in human salivary gland tumor (HSG) and oral squamous cell carcinoma (HSC-2) model. Moreover, the addition of $CoCl_2$ exerted apoptotic-inducing effects by reducing the cytotoxic activity and

Table 2. Antioxidant activities of different extracts from *Flos lonicerae.*

	IC_{50}(μg/mL)			
	DPPH	**Total ROS**	**$ONOO^-$**	**·OH**
MeOH extract	83.15	NS	11.63±2.33	42.55±2.10
CH_2Cl_2 fraction	182.35	NS	22.77±7.23	40.34±2.26
EtOAc fraction	4.37	27.58±0.71	0.47±0.05	12.13±0.79
n-BuOH fraction	80.12	NS	14.29±2.98	12.13±0.79
H_2O fraction	320.35	NS	16.66±4.22	NS
L-Ascorbic acid	1.37			
Trolox		25.04±0.64		5.73±0.21
DL-Penicillamine			0.70±0.06	

NS = no inhibitory effect at a final concentration. (Cited from Choi et al. 2007)[7]

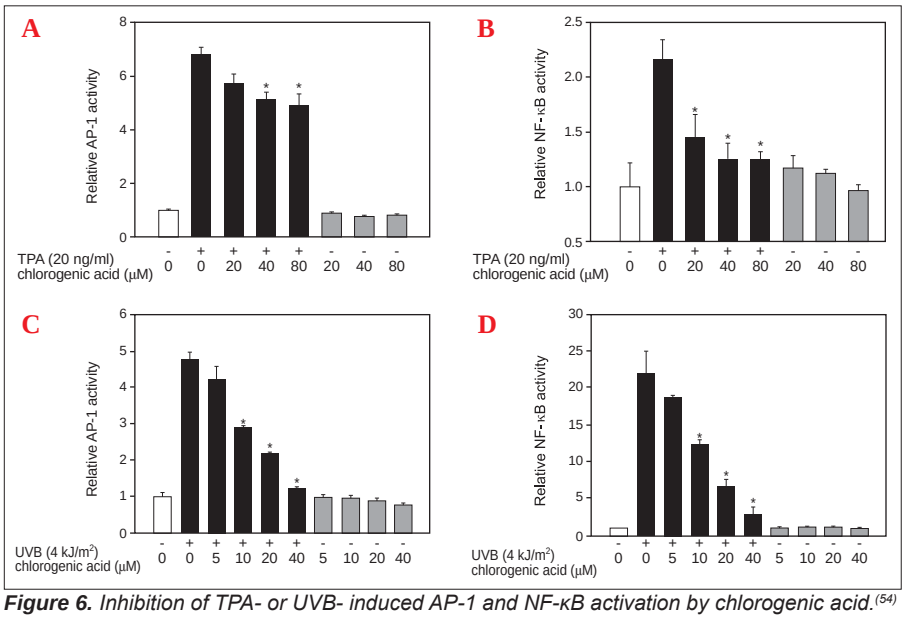

Figure 6. *Inhibition of TPA- or UVB- induced AP-1 and NF-κB activation by chlorogenic acid.*[54]

oxidation potential, which involved the conformation change of the chlorogenic acid molecule.[43]

Chlorogenic acid could strongly inhibit the matrix metalloproteinase-9 activity in a human hepatocellular carcinoma cell line (Hep3B) with a dose-dependent manner, and the IC_{50} was recorded as 30~50 nM.[43] The angiogenic enzymes (MMP-9) is thought to be directly involved in cancer cell invasion and metastasis,[44,45] which are fundamental characteristics of malignant tumor cells.[46,47] Moreover, the anticancer effects were also observed in the large intestine, liver and tongue of hamsters or rats.[48-51]

In human colon cancer cell (DLD-1), stomach cancer cell (KATO III), and promyelocytic leukemia cell (HL-60) lines models, chlorogenic acid and its derivatives exhibit potent apoptosis-inducing abilities, which involved the increase of caspase-3 activity, expression of c-Jun and DNA fragmentation etc..[52] Chlorogenic acid also suppresses the activities of Bar-Abl tyrosine and c-Abl kinases, and induces apoptosis in chronic myelogenous leukemic cells. The apoptosis inducing effect is p38 mitogen-activated protein kinase-dependent.[53,54] Moreover, by suppressing the activities of activator protein (AP)-1 and mitogen-activated protein kinase (MAPKs), phosphorylation of c-Jun NH_2-terminal kinases, and activation of nuclear factor (NF) -κB, chlorogenic acid could strongly inhibit cell proliferation of UVB or 12-*O*-tetradecanoylphorbol-13-acetate induced cancer epithelial cell line JB6 (Fig. 6).[54] Reports presented by previous researchers also indicated that, the AP - 1 and NF-κB play an important role in the neoplastic transformation in the mouse epidermal cell line JB6.[55-58]

Anti-mutagenic activity

The anti-mutagenic activities of chlorogenic acid and its derivatives have been investigated as well.[59,60] Nakamura *et al.* (1997) have reported the inhibiting effect of aqueous crude extract of Tochu (*Eucommia ulmoides*) leaf, which is rich in chlorogenic acid, on the trigger of chromosome aberrations in CHO cells and mice models. Results indicated that, the frequency of chromosome aberrations as well as the ratio of micronuclei were significantly decreased *in vivo* and *in vitro*.[59] The antimutagenicity capacity of the derivatives of caffeylquinic acid like mono-, di- and tricaffeoylquinic acid have been studied by Yoshimoto *et al*. (2002) as well.[60] The antimutagenicity activity of these compounds was mainly due to the quantity of caffeoyl groups that bound to quinic acid.

Anti-HBV activity

Inhibition effects of chlorogenic acid on HBV replication have been demonstrated by Wang *et al.* (2009). By inhibiting HBV-DNA replication and HBsAg production, chlorogenic acid possesses potent anti-HBV activity towards HepG2 cells. Moreover, the research also indicates there is a reduced level of serum DHBV in the DHBV-infected duck model after chlorogenic acid treatment.[61]

Anti-angiogenic activity

According to the report of Yoo *et al.* (2008), chick chorioallantoic membrane angiogenesis could be efficiently inhibited by the ethanol extract of *L. japonica* in a dose dependent manner.[8]

Antinociceptive/ antianalgesic activity

In the mice acetic acid-induced constriction model, the anti-nociceptive activities of the *Flos lonicera* have been demonstrated.[8] Dos *et al.* (2006) reported the antipyretic effects of chlorogenic acid caused by formalin-induced pain test. Results showed that, the number of flinches in the late phase of the pain test was remarkably reduced by chlorogenic acid at the concentration of 50 and 100 mg/kg.[62]

Antidiabetic activity

The antidiabetic effects of chlorogenic acid and its derivatives have been studied as well. These natural chemical compounds present potent inhibition effects on the hepatic glucose 6-phosphatase (G6Pase), which is a remarkable factor in the non-insulin-dependent type 2 diabetic state. The IC_{50} of chlorogenic acid is 230 μM. For the derivatives, change in the ester residue in the 3-position of chlorogenic acids exhibits only poor effects on suppressing capacity. However, 100-fold more strong inhibitory effects were obtained after introduction of 4-chlorophenylpropyl side chain in the 1-position (IC_{50}=2.5 μM).[63] Further research work indicated that, the 4-caffeoylquinic acid (CQA) and 5-CQA contribute 40% and 25% for the G6Pase inhibition, respectively.[64]

Other biological effects

According to the research of Dos *et al.* (2006), dosage of 50 and 100 mg/kg chlorogenic acid could inhibit carrageenin-induced paw edema after the second hour of treatment compared to the control.[62] It is also reported that, water extract of Japanese honeysuckle could significantly inhibit the activity of PAR2 agonists-induced myeloperoxidase (MPO) and the expression of tumor necrosis factor (TNF)-α in paw tissue.[65] The polyphenolic compounds isolated from *L. japonica* Thunb. could also exert potent inhibitory effects on platelet activation, platelet thromboxane biosynthesis and hydrogen peroxide-induced endothelial cell injury.[66]

SIDE EFFECTS/ADVERSE EFFECTS/ TOXICITY

Poisoning

As indicated previously, several kinds of saponins have been identified and purified from the caulis and leaves of *L. japonica*. Saponin is a toxin with a bitter taste that is commonly found in various natural plants. Numerous studies have indicated plant poisoning symptoms in young children who have ingested lots of honeysuckle.[67,68] However, since saponins cannot be absorbed by the human body, and their content in foods could be mostly removed by cooking and changing the cooking water, this kind of bioactive compounds would not be harmful for humans.[69]

Gastrointestinal upset and stomach cramp

Plant poisoning of *L. japonica* can cause symptoms of gastrointestinal upset and stomach cramp as well.[70] It is recommended that, those who are having gastrointestinal upset or spleen problems should not take Jinyinhua, because the symptoms might be worse after taking this kind of herb.[71]

Blood clotting

L. japonica has been reported to slow blood clotting, which might increase the chances of bruising and bleeding. Considering it might increase the risk of extra bleeding during and after surgery,

it is strongly recommended that usage of honeysuckle 14 days prior to a planned surgery be discontinued.[70,71]

Contact dermatitis

Allergic reactions to *L. japonica* are commonly recognized. Skin problems like urticaria or rash might be caused by usage of honeysuckle. Moreover, contact dermatitis might also be triggered after being contact with this herb.[72]

DOSAGE AND METHODS OF ADMINISTRATION

In order to exert the beneficial effects, it is suggested that 6 ~ 15 g or 3 ~7 g dry weight of *Flos lonicera* in aqueous extract should be taken each time.[11,73]

SAFETY EVALUATIONS/ CONTRAINDICATIONS

Actually, there is little scientific evidence about the safety evaluations on *L. japonica*. It has been reported that an intravenous preparation consisting of honeysuckle and two other herbs was safely used in children for up to one week.[70] Acute and subacute toxicity tests also indicated that, oral dosage of 5 g/kg of the ethanol extract from the leaves of *L. japonica* Thunb. would not induce mortality and gross appearance of the rat model, and oral dose of 1 g/kg per day for two weeks also won't affect the body and organ weights in rat models. Furthermore, neither gross abnormalities nor histopathological changes were obtained in the tested rats.[74] Nonetheless, for safety considerations, pregnant or breastfeeding women and people who have allergy or hypersensitivity to honeysuckle should avoid usage of this herb.[75]

DRUG INTERACTIONS

Ingested honeysuckle with anticoagulant and antiplatelet drugs could induce blood thinning, even bruising and bleeding.[76] Anticoagulant and antiplatelet drugs generally include aspirin, clopidogrel, diclofenac, ibuprofen, naproxen, dalteparin, enoxaparin, heparin and warfarin and others.[77] It was recorded that, symptoms of bronchiolitis in children with respiratory syncytial virus (RSV) infection could be efficiently relieved by intravenous injection of *L. japonica, Baikal skullcap* and forsythia.[78]

In addition, *Flos lonicera* accompanied with peach kernel, red peony root, *Forsythia suspensa,* curcuma, and common bur reed rhizome have potent beneficial effects on health like blood circulation invigoration, bruise dispersion, pain relieving, pathogenic heat removing, consciousness recovering and gynecological diseases therapy.[79] A medicinal formula contains several herbs including Lonicera Flos, Scutellariae Radix Sophorae Fructus, Sanguisorbae Radix, Rhei Radix et Rhizoma, *Curcumae* Radix, Rutidosperma and Siegesbeckiaeherba Cleome has been developed and claimed to be capable of stopping bleeding, clearing toxic heat, relieving pain, removing dampness and expelling wind. The formula is highly effective with 100% effective rate and 98% cure rate.[73] Another formula consisting of dried flower buds of *L. japonica* and dried roots of *Anemarrhena asphodeloides* Bunge is also efficient for the treatment of osteoarthritis *in vivo*.[80]

FUTURE DIRECTIONS

With abundant bioactive compounds, *Flos lonicera* could exert potent beneficial pharmacological effects on human health. The most important anti-inflammatory effects of the flower buds have been widely reported. However, the molecular mechanism of the anti-inflammation effects of Lonicera Flos is still undiscovered. Moreover, little scientific evidence about the contraindications and adverse effects of *L. japonica* have been reported. To further develop the efficiency of clinical therapy and dose usage of this herb, more attention should be focused on the molecular mechanisms of the biological effects and the safety evaluations.

Author's background

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Hong Kong Pharmacy Conference 2012

It is my great pleasure to announce that our pharmacy conference this year will be held on Feb 4-5, 2012 at the Hong Kong Convention and Exhibition Center. This year, our theme is Pharmacist: Your health care partners! 藥劑師 – 健康之侶! With no exception from the previous years, we will have a well-structured program addressing the current, popular and interesting issues in our profession. Practical issues on the community pharmacy, hospital pharmacy, manufacturing and even new application of information technology will be discussed in the conference. Frontiers and experts would gather in this special occasion to exchange their ideas and perspectives on these current issues.

Renowned speakers will also be invited to give us stimulating speeches on the day one plenary session. They will share their views on how pharmacists can contribute as a partner of the health care team and how pharmacists can do for their patients. Pharmacist now is one of the members of the health care team but our roles should definitely evolve further to contribute more to the team and provide better pharmaceutical care to patients.

On day two program, we will discuss on the practical issue to put this direction into practice. Updates on the therapeutic options, myths about the Chinese medicine and the amazing new technology which can free our hands from dispensing are all included in the program. It is a rare chance to mingle with pioneers and authorities from the diverse areas of practice.

If you don't want to miss the great opportunity to be enlightened by this inspiring conference, register now. You can register online through our website http://www.pharmacyconference.org/ or you can download the registration form and send it back to us by post.

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Ritchie Kwok
Vice-chairperson of Hong Kong
Pharmacy Conference 2012

Pharmacist: your Healthcare Partner
藥劑師 – 健康之侶

Hong Kong Pharmacy Conference 2012
4th – 5th February, 2012
Hong Kong Convention and Exhibition Center

Day 1 (4th February, 2012)

Time	Topics
1:30pm	Registration
2:30pm - 2:40pm	Opening ceremony
2:40pm - 2:50pm	Welcome speech by the Chairman of the Conference
2:50pm - 3:00pm	Opening Remarks
3:00pm - 3:40pm	Theme 1: Planting the Seed – Training Healthcare Partners By Prof. Ian WONG, Professor of Pharmacology & Pharmacy, The University of Hong Kong
3:40pm - 4:10pm	Break, poster and exhibition
4:10pm - 4:50pm	Theme 2: Environmental Toxins – What Pharmacists Should Know By Dr. Sze Hong NG, Associate Consultant, Hong Kong Poison Information Centre
4:50pm - 5:30pm	Theme 3: Public health topic to be confirmed
6:00pm - 6:45pm	Pre-Conference Dinner Symposium
7:00pm - 10:00pm	Conference Dinner

Day 2 (5th February, 2012)

Concurrent Session	I	II	III
Topics	**Information Technology**	**Community Practice**	**Hospital Practice**
8:30am - 9:10am	In-patient Medication Order Entry – What's in it for me? By Mr. Frank CHUNG & Ms. Bonnie LAM, Pharmacists, Chief Pharmacist's Office, Hospital Authority, Hong Kong	Communication in the Community – the Art, the Science and the Balance Speakers to be confirmed	Imaging Technology in Diagnosis of Lung & Cardiovascular Diseases By Dr. William WONG, Associate Consultant, Tung Wah Hospital, Hospital Authority, Hong Kong
9:10am - 9:50am	The Journey in Achieving Track and Trace of Pharmaceutical Products in Public Hospitals By Ms. S C CHIANG, Senior Pharmacist, Chief Pharmacist's Office, Hospital Authority, Hong Kong		The art of ECG interpretation – how it saves lives By Dr. Chi Yeung CHEUNG, Pamela Youde Nethersole Eastern Hospital, Hospital Authority, Hong Kong
9:50am – 10:30am	e-Health Records : Informatics – Pharmacist's Ambition By Mr. Johnny WONG, Pharmacist, Chief Pharmacist's Office, Hospital Authority, Hong Kong		Therapeutic Hypothermia By Dr. Kevin BOX, Critical Care Pharmacist, University of California San Diego
10:30am – 11:00am	Coffee Break - Poster & Exhibition		
11:00am - 11:40am	Drug related Problems: Hidden in the Elderly Population By Prof. Vivian LEE Associate Professor, School of Pharmacy, Faculty of Medicine, The Chinese University of Hong Kong	EBM of Complementary and Alternative Medicines By Prof. Clara LAU	Treating Chronic Kidney Disease – Mineral and Bone Disorder – para, plar… are they reaching the par? By Prof. Cheuk-Chun SZETO, Professor, Department of Medicine and Therapeutics, Faculty of Medicine, The Chinese University of Hong Kong
11:40am – 12:20pm	Community Pharmacists: providing a Peace of Mind to Medication Management in Old Age Homes. By Mr. Peter SUEN Pharmacist and CEO, ActiveCarePharmacy	Community topic to be confirmed	Update on the treatment for cardiac arrhythmia in year 2011 By Dr. Kai Hang YIU, Clinical Assistant Professor, Cardiology Division, Department of Medicine, The University of Hong Kong
12:20pm – 1:00pm	Partnering with the Old Age Homes: Lost and Found by the Visiting Pharmacists By Ms. Stella HO, Mr. Alessandro LEUNG & Ms. Grace TANG, Visiting Pharmacist, The Hong Kong Pharmaceutical Care Foundation Dr. Chui Ping LEE Senior Instructor, School of Pharmacy, Faculty of Medicine, The Chinese University of Hong Kong	Community topic to be confirmed	Managing dementia & agitation in nursing home: drugs or no drugs By Prof. Timothy KWOK, Professor, Department of Medicine and Therapeutics, Faculty of Medicine, The Chinese University of Hong Kong
1:00pm – 1:40pm	Lunch Symposium		
1:40pm - 2:30pm	Lunch Poster & Exhibition		
2:30pm – 4:00pm	Plenary session		
4:00pm – 4:15pm	Closing by Vice Chair		

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† Only for *LOCAL* registrants who are undergraduates majoring in Pharmacy, Medicine, Nursing or Chinese Medicine; students of Higher Diploma in Pharmaceutical Technology (IVE); pharmacy interns; members of the Pharmaceutical Staff Association (PSA); members of the Hong Kong Pharmacy Technicians Association (HKPTA) or members of the Hong Kong Society of Pharmaceutical Technology and Health Care Professionals (PTHeP). **Relevant affiliations must be stated above to be eligible to apply for the special offer.**

In case of any disputes, the decision of the Conference Organizing Committee shall be final.

Pharmacy Outreach Service

CHAN, Peter Ka Hing[a,b]; KWOK, Fanny Luk Man[a,b]; KONG, Kathy Wing Yan[a,b]; PANG, Panny Tin Yi[a,b]; LAW, Yuen To[a,c]; SO, Jenny Man Pui[a,d]

[a] *Students of the School of Pharmacy, The Chinese University of Hong Kong, Shatin, NT, Hong Kong at the time of conducting the study.*

[b] *Resident pharmacists at Princess Margaret Hospital, Kowloon Hospital, Tuen Mun Hospital and Kwong Wah Hospital respectively, of the Hospital Authority, Hong Kong,*

[c] *Pharmacy intern at Hong Kong Sanatorium and Hospital, Hong Kong.*

[d] *Pharmacy intern at Queen Mary Hospital, Hospital Authority, Hong Kong.*

BACKGROUND

Pharmacy Outreach Service (POS) was initiated in the summer of 2007 by the School of Pharmacy, The Chinese University of Hong Kong (CUHK). It is a medication review and counselling service which targets at our senior citizens. Pharmacists and pharmacy students visit elderly centres at regular times, meeting the elders and providing medication review for them and detailed counselling on their diseases and medications.

The goal of POS is to improve chronic disease management for the elders. Hong Kong has been facing the problem of aging population, and the patient load and cost brought to our healthcare system by the old age group is no doubt our major concern now and in the foreseeable future. Overseas studies have already demonstrated that pharmacist participation in disease management and patient care can improve clinical outcomes.[1,2,3]

Following our pioneers who had done the preliminary study in 2007-2008, it was known that similar pharmacist intervention conducted locally also had a significant impact on the blood pressure control and disease knowledge improvement.[4] POS was then developed to a continuous project. Through POS, we hope that pharmacists can actively share responsibilities in the disease management of the elders and help to reduce overall medical cost by achieving a better control of chronic diseases in these patients.

INTERVENTIONS & DEVELOPMENT

Every year, POS is organized in cooperation with various elderly centres located mainly in Tseung Kwan O and Wong Tai Sin districts. The year-long project starts by inviting the elderly to a summer event at the elderly centre, in which pharmacists and pharmacy students volunteer to provide health measurements such as blood pressure (BP) and random capillary blood glucose (RCBG), educational talks on drug use, and an individual pharmacist consultation. By evaluating their disease control, appropriateness of the existing drug regimen, compliance, and knowledge on disease and medications, drug-related problems are identified and some elderly are selected to be reviewed periodically throughout the year.

During follow-up visits, similar measurements and counselling are carried out to reassess their conditions. Referral letters are written when appropriate to facilitate effective communication between the elderly and their physicians on drug-related matters. With the help of social workers, the caretakers of the elderly could be contacted for further information or discussion. After one year of follow-up, evaluation of the overall impact of the programme is made by comparing data collected at the summer event and the last follow-up visit.

Since the start of POS in 2007, BP and RCBG levels, drug compliance and disease knowledge have been the main criteria of assessment. The preliminary study had the shortest follow-up period of three months, while compliance and educational tools such as disease knowledge leaflets and drug diary were developed to aid pharmacist counselling. In POS 2008-09, follow-up period was extended to six months, each at four to six weeks' intervals. To find out the sustainability of the clinical impacts, cases from POS 2008-09 were carried forward to the following two years, along with newly recruited subjects for comparison. The follow-up interval was also lengthened to twelve weeks in order to align with the elders' out-patient clinic appointments mainly every eight to sixteen weeks. Home visits were occasionally done upon request by the social workers. In 2010, total cholesterol (TC) measurement was introduced as an additional monitoring parameter. The scale of POS has also expanded from 37 cases to more than 100 cases a year.

CLINICAL IMPACTS

After regular pharmacist intervention for an average of six months in the first year, the elderly subjects demonstrated a statistically significant improvement in BP control, in which the systolic BP reduced from 165.92 ± 18.64mmHg to 143.78 ± 20.91mmHg (p<0.001) while the diastolic BP reduced from 79.93 ± 11.01mmHg to 67.98 ± 8.93mmHg (p<0.001). In addition, there was an increase in percentage of subjects achieving the RCBG goals at the latest intervention compared with the baseline. Meanwhile, knowledge on hypertension and diabetes mellitus management also improved after pharmacist interventions. A "Chinese New Year effect" was observed such that the goal attainment rate of RCBG was lower during Chinese New Year, which is believed to be the effect of the poor diet control during the festival.

The largest impact on BP was seen during the first half of the first-year follow-up, but it is worth noting that BP levels fluctuated during the gap between the end of a year of POS and the start of the next, and were stable again after the follow-up visits resumed. This highly suggested that continuous visits are necessary for good disease control. Meanwhile, the blood glucose level showed an overall downward trend throughout the first two years, but it may need a longer time to show a significant improvement. In fact, overseas studies also showed that RCBG goal is more difficult to achieve when compared to BP goals. Our results were consistent with other studies worldwide.

For the third year of follow-up, we did not see a significant decrease in the average BP. This was probably due to the fact that the average baseline BP was lowered to an extent that room for further improvement was small, which implied POS had made a remarkable and its maximal impact on the average blood pressure of the elderly during the first year and the effect had sustained through to the third year.

In addition, during the third year of follow-up, we discovered that the average TC level rose especially after Chinese New Year, echoing the results from the first year such that the diet affected not only RCBG but also TC. This probably hinted that pharmacists should expand their role in intervening the elders' diet through POS.

DRUG-RELATED PROBLEMS IDENTIFIED

During the interventions, a number of drug related problems (DRPs) were identified. The majority was pertaining to non-compliance to the therapy. The reasons for non-compliance varied among the elderly, which included complicated regimen, misunderstood indications and fallacious concept about adverse drug reactions (ADRs).

Non-compliance could be as simple as missing doses. It could be solely due to forgetfulness, especially when the elderly was going out. Cognitive impairment due to advanced age or morbidities, and complicated regimens which involve multiple daily dosing frequencies of different drugs also contributed to the problem. Compliance aids such as pill boxes or drug diaries were offered to help the elders.

On the other hand, the indications of the drugs could be misunderstood, although many of the drugs issued by public hospitals or clinics do have their indications printed on the labels. Illiteracy was thought to be the major contributing factor to this DRP, since as many as 25% of our elderly subjects were illiterate, and the short consultation time at hospitals or clinics might not warrant in-depth explanation to the patients. By periodically revisiting the elderly, more thorough and detailed counselling was provided and the DRPs were continuously assessed.

Pill split was another common DRP arising from the need of administering fine dosages as minute as one-fourth of a tablet. With no suitable aids, the elderly used bare hands, knives or even their teeth to split the pills, not to mention that some elders even take the whole pill, which gave rise to another DRP—overdosage—to avoid the pill-cutting act. While providing pill cutters was one of the solutions, prescribers are encouraged to take into account their patients' ability to split pills when designing a regimen.

Other common DRPs included the need of additional medication or dose adjustment, suspected ADRs, as well as duplicated or potentially inappropriate medications (PIMs).

Although stated in the Beers Criteria for geriatrics,[5] we found many elders prescribed with PIMs. At the time of starting POS, propoxyphene-containing products were still available on the market and the top prescribed PIM was actually dologesic (a combination product of paracetamol and dextropropoxyphene), which had more ADRs than paracetamol alone but only a mere advantage as an analgesic over the latter. Methyldopa, an antihypertensive not preferred by current guidelines, and antihistamines, were also commonly prescribed.

LIMITATIONS & POSSIBLE IMPROVEMENTS

There were some major limitations in our study. Firstly, the past medical history and the medication profile were all self-reported by patients and thus might not be complete, making us unable to identify all DRPs. Direct communicating methods with the prescribers were also not established, while referral notes or the elderly were relied on to present the DRPs to the prescribers.

Case sharing on Drug Related Problems

Fanny Kwok:
"An elderly subject brought some azathioprine tablets and told the pharmacist that he bought them without prescription in a community pharmacy. It was found that he was once prescribed azathioprine for severe eczema. The doctor has decided to discontinue the azathioprine therapy since the condition was already under control. The elderly, however, thought that this medication 'really works' and thus continue to take it for 'prophylaxis' without telling the doctor. Azathioprine is an immunosuppressant which requires regular monitoring for signs of myelosuppression and other side effects. Also, it interacts with drugs like allopurinol, a commonly prescribed drug for gout prophylaxis in geriatrics. The interaction can lead to azathioprine toxicity if not appropriately managed. The risk of taking azathioprine without medical supervision was explained to the elderly, and he was advised to seek medical consultation to assess the need of continuing azathioprine therapy and the current health condition after taking long term azathioprine without monitoring."

On the other hand, RCBG might not give a good estimation on the blood glucose control. However we have been using RCBG instead of fasting or two-hour postprandial blood glucose because it was difficult to ask the elderly to fast or have their meals according to the appointment time. Glycosylated haemoglobin (Hb_{A1c}) measuring devices were also not commercially available. Similarly, TC was not as informative as individual cholesterol components, i.e. low density lipoprotein (LDL), high density lipoprotein (HDL) and triglycerides (TG), which could lead us to a more comprehensive assessment of the lipid profile of the elderly.

The ideal solution to all of the above limitations would be collaborating with hospitals or clinics to contact the prescribers directly or access the medical records, for example, medication history and laboratory data.

Besides, with insufficient manpower, the number of elderly that we could follow, and the number of visits that we could

provide, were limited. Along with the loss of elderly subjects recruited at the beginning of the study over time, and the absence of a control group due to ethical reasons that pharmacist interventions have established benefits on disease control, it was clear that the statistical power of our study was constrained.

Moreover, as aforementioned, our findings suggested that the diet control also played an important role on the disease control of the elderly. We hope to provide thorough diet recommendation to every elderly if time and manpower allow so. With the cooperation of the elderly centres, it is also desirable to discuss and provide suggestions on the specially designed diet provided by them.

How do you think about participating in this program as a pharmacy student?

Kathy Kong:
"When I was a student, POS offered me an opportunity to experience direct patient contact and conduct patient counselling by myself, which were not possible in our daily lectures. Meanwhile, because of POS, I gained more knowledge on disease management in geriatric patients, such as diet and lifestyle recommendations, drugs of choice and the appropriate dosages. POS is a really good preparatory course for a students' real practice after graduation."

Panny Pang:
"As a student, I was always thankful to have chances to talk to the elderly face-to-face. Not only was it an opportunity to study the cases, but also to develop a real interest in people. Through organizing the events, I also better understood the needs of the community elderly centres and gained some insights of how we could cooperate with other professionals to provide more different services to benefit our community."

PROSPECTS & CONCLUSION

More and more elderly centres have been approaching us, asking for our specialized services for their centres. Through POS, not only did we improve the health and disease management among elderly, but also gained trust from the elderly, their caretakers and the social workers as well. The image of pharmacists is promoted and our role is more well-known to the public. With more available resources, the service could be expanded and improved. We believe it would be a win-win situation to both the society and us, as geriatric care has become an indispensable part in our healthcare system due to the increasing number of elderly.

In the future, we hope to have an even closer relationship with social workers, who are more approachable to the elderly. With their support, better disease management could routinely be promoted, the family members of the elderly could be reached and educated for better caretaking, and home visits could be arranged for the convenience of the elderly and spotting more DRPs.

To conclude, continuous POS has contributed to the sustained enhancement in chronic disease management, disease knowledge and compliance of the elderly. For the wellbeing of the elderly, there is no doubt that POS should keep on running and fine-tuning its services and interventions in order to maximize its benefits. We hope more pharmacists could get involved in this meaningful programme and contribute to the society in this very special way.

How did the experience impact on your current post as a pharmacist or pharmacy intern?

Jenny So:
"From the study, we learned that problems like the misunderstanding of indication and the fear of adverse drug reactions would lead to non-compliance. The experience of POS constantly reminds me to make sure my patients understand what their medicine is for, what adverse effects to expect, etc. They should also be encouraged to ask when they have any queries, as both the enhancement in disease knowledge and improvement in compliance will ultimately favour the clinical outcomes."

Peter Chan:
"Now I am working as a resident pharmacist in a public hospital. It is challenging facing numerous patients and counselling them in short conversions Experience in POS gives me confidence to handle different patients and deliver information effectively even though I am a new member in a large institution. Information like time of drug administration (e.g. gemfibrozil taken before meals) was found to be easily forgotten by the elders in POS. This experience could alert me what should be emphasised on during counselling."

Summer Outreach Service 2010

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Use in patients with hepatic or renal insufficiency
Renal impairment
No dose adjustment is necessary.
Hepatic impairment
The clinical data with Daxas in patients with mild hepatic impairment classified as Child-Pugh A are insufficient to recommend a dose adjustment and therefore Daxas should be used with caution in these patients.
Patients with moderate or severe hepatic impairment classified as Child-Pugh B or C should not take Daxas

Contraindications:
Hypersensitivity to roflumilast or to any of the excipients.
Moderate or severe hepatic impairment (Child-Pugh B or C).

Precautions:
Rescue medicinal products
Roflumilast is an anti-inflammatory substance indicated for maintenance treatment of severe COPD associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add on to bronchodilator treatment. It is not indicated as rescue medicinal product for the relief of acute bronchospasms.

Weight decrease
In 1-year studies (M2-124, M2-125), a decrease of body weight occurred more frequently in patients treated with Daxas compared to placebo-treated patients. After discontinuation of Daxas, the majority of patients had regained body weight after 3 months.
Body weight of underweight patients should be checked at each visit. Patients should be advised to check their body weight on a regular basis. In the event of an unexplained and clinically concerning weight decrease, the intake of Daxas should be stopped and body weight should be further followed-up.

Special clinical conditions
Due to lack of relevant experience, treatment with Daxas should not be initiated or existing treatment with Daxas should be stopped in patients with severe immunological diseases (e.g. HIV infection, multiple sclerosis, lupus erythematosus, progressive multifocal leukoencephalopathy), severe acute infectious diseases, cancers (except basal cell carcinoma), or patients being treated with immunosuppressive medicinal products (i.e.: methotrexate, azathioprine, infliximab, etanercept, or oral corticosteroids to be taken long-term; except short-term systemic corticosteroids). Experience in patients with latent infections such as tuberculosis, viral hepatitis, herpes viral infection and herpes zoster is limited.
Patients with congestive heart failure (NYHA grades 3 and 4) have not been studied and therefore treatment of these patients is not recommended.

Psychiatric disorders
Daxas is associated with an increased risk of psychiatric disorders such as insomnia, anxiety, nervousness and depression. Rare instances of suicidal ideation and behavior, including completed suicide, have been observed in clinical trials. Therefore, the risks and benefits of starting or continuing treatment with Daxas should be carefully assessed if patients report previous or existing psychiatric symptoms or if concomitant treatment with other medicinal products likely to cause psychiatric events is intended. Patients should be instructed to notify their prescriber of any changes in behavior or mood and of any suicidal ideation. Moreover, Daxas is not recommended in patients with a history of depression associated with suicidal ideation or behaviour.

Persistent intolerability
While adverse reactions like diarrhoea, nausea, abdominal pain and headache mainly occur within the first weeks of therapy and mostly resolve on continued treatment, Daxas treatment should be reassessed in case of persistent intolerability. This might be the case in special populations that may have higher exposure, such as in black, non-smoking females or in patients concomitantly treated with the CYP1A2 inhibitor fluvoxamine or the dual CYP3A4/1A2 inhibitors enoxacin and cimetidine.

Theophylline
There are no clinical data to support the concomitant treatment with theophylline for maintenance therapy. Therefore, the concomitant treatment with theophylline is not recommended.

Lactose
Daxas tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Drug Interactions:
Interaction studies have only been performed in adults.
A major step in roflumilast metabolism is the N-oxidation of roflumilast to roflumilast N-oxide by CYP3A4 and CYP1A2. Both roflumilast and roflumilast N-oxide have intrinsic phosphodiesterase 4 (PDE4) inhibitory activity. Therefore, following administration of roflumilast, the total PDE4 inhibition is considered to be the combined effect of both roflumilast and roflumilast N-oxide. Clinical interaction studies with CYP 3A4 inhibitors erythromycin and ketoconazole showed increases of 9% of the total PDE4 inhibitory activity (i.e. total exposure to roflumilast and roflumilast N-oxide). Interaction studies with CYP1A2 inhibitor fluvoxamine, and the dual CYP3A4/1A2 inhibitors enoxacin and cimetidine resulted in increases of the total PDE4 inhibitory activity of 59%, 25% and 47%, respectively. A combination of Daxas with these active substances might lead to an increase of exposure and persistent intolerability. In this case, Daxas treatment should be reassessed.
Administration of the cytochrome P450 enzyme inducer rifampicin resulted in a reduction in total PDE4 inhibitory activity by about 60%. Therefore, the use of strong cytochrome P450 inducers (e.g. phenobarbital, carbamazepine, phenytoin) may reduce the therapeutic efficacy of roflumilast.
Co-administration with theophylline resulted in an increase of 8% of the total PDE4 inhibitory activity.

In an interaction study with an oral contraceptive containing gestodene and ethinyl oestradiol, the total PDE4 inhibitory activity was increased by 17%.
No interactions were observed with inhaled salbutamol, formoterol, budesonide and oral montelukast, digoxin, warfarin, sildenafil and midazolam.
Co-administration with an antacid (combination of aluminium hydroxide and magnesium hydroxide) did not alter the absorption or pharmacokinetics of roflumilast or its N-oxide.

Side Effects:
In clinical COPD studies, approximately 16% of patients experienced adverse reactions with roflumilast (compared to 5% in placebo). The most commonly reported adverse reactions were diarrhoea (5.9%), weight decreased (3.4%), nausea (2.9%), abdominal pain (1.9%) and headache (1.7%). The majority of these adverse reactions were mild or moderate. These adverse reactions mainly occurred within the first weeks of therapy and mostly resolved on continued treatment.

Forensic Classification:
P1S1S3

ONBREZ BREEZHALER®
(Novartis)

Active Ingredient:
Indacaterol maleate

Presentations:
Onbrez Breezhaler 150 and 300 microgram inhalation powder, hard capsules. Each capsule contains indacaterol maleate equivalent to 150 and 300 microgram indacaterol respectively and the delivered dose leaving the mouthpiece is equivalent to 120 and 240 microgram indacaterol.

Pharmacological Properties:
The pharmacological effects of beta$_2$-adrenoceptor agonists are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyses the conversion of ATP to cyclic AMP. Increased cyclic AMP levels cause relaxation of bronchial smooth muscle. When inhaled, indacaterol acts locally in the lung as a bronchodilator. Indacaterol is a partial agonist at the human beta$_2$-adrenergic receptor with nanomolar potency. In isolated human bronchus, indacaterol has a rapid onset of action and a long duration of action.

Indications:
Onbrez Breezhaler is indicated for maintenance bronchodilator treatment of airflow obstruction in adult patients with chronic obstructive pulmonary disease (COPD).

Dosage and Administration:
The recommended dose is the inhalation of the content of one 150 microgram capsule once a day, using the Onbrez Breezhaler inhaler. The dose should only be increased on medical advice. The inhalation of the content of one 300 microgram capsule once a day, using the Onbrez Breezhaler inhaler has been shown to provide additional clinical benefit with regard to breathlessness, particularly for patients with severe COPD. The maximum dose is 300 microgram once daily. Onbrez Breezhaler capsules must not be swallowed.

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

Precautions:
Onbrez Breezhaler should not be used in asthma due to the absence of long-term outcome data in asthmatics.

As with other inhalation therapy, administration of Onbrez Breezhaler may result in paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs treatment should be discontinued immediately and alternative therapy substituted.

Onbrez Breezhaler is not indicated for the treatment of acute episodes of bronchospasm, i.e. as rescue therapy. In the event of deterioration of COPD during treatment with Onbrez Breezhaler, a re-evaluation of the patient and of the COPD treatment regimen should be undertaken. An increase in the daily dose beyond the maximum dose of 300 microgram is not appropriate.

Indacaterol should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, hypertension), in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to beta$_2$-adrenergic agonists.

Indacaterol may produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, blood pressure, and/or symptoms. In case such effects occur, treatment may need to be discontinued. In addition, beta-adrenergic agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave and ST segment depression, although the clinical significance of these observations is unknown. Clinically relevant effects on prolongation of the QT_C-interval have not been observed in clinical studies of Onbrez Breezhaler at recommended therapeutic doses. Beta$_2$-adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce adverse cardiovascular effects.

Inhalation of high doses of beta$_2$-adrenergic agonists may produce increases in plasma glucose. Upon initiation of treatment with Onbrez Breezhaler plasma glucose should be monitored more closely in diabetic patients.

Interactions:
Sympathomimetic agents may potentiate the undesirable effects of Onbrez Breezhaler. Onbrez Breezhaler should not be used in conjunction with other long-acting beta$_2$-adrenergic agonists or medicinal products containing long-acting beta$_2$-adrenergic agonists.
Concomitant hypokalaemic treatment with methylxanthine derivatives, steroids, or non-potassium-sparing diuretics may potentiate the possible hypokalaemic effect of beta$_2$-adrenergic agonists, therefore use with caution.
Beta-adrenergic blockers may weaken or antagonise the effect of beta$_2$-adrenergic agonists. Therefore indacaterol should not be given together with beta-adrenergic blockers (including eye drops) unless there are compelling reasons for their use. Where required, cardioselective beta-adrenergic blockers should be preferred, although they should be administered with caution.
Inhibition of the key contributors of indacaterol clearance, CYP3A4 and P-glycoprotein (P-gp) raises the systemic exposure of indacaterol by up to two-fold. The magnitude of exposure increases due to interactions does not raise any safety concerns given the safety experience of treatment with Onbrez Breezhaler in clinical studies of up to one year at doses up to twice the maximum recommended therapeutic dose.

Pregnancy and Lactation:
Indacaterol may inhibit labour due to a relaxant effect on uterine smooth muscle. Onbrez Breezhaler should only be used during pregnancy if the expected benefits outweigh the potential risks. It is not known whether indacaterol/metabolites are excreted in human milk. Available pharmacokinetic/toxicological data in animals have shown excretion of indacaterol/metabolites in milk. A risk to the breast-fed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Onbrez Breezhaler therapy.

Side Effects:
Nasopharyngitis, cough, upper respiratory tract infection and headache, diabetes mellitus and hyperglycaemia, ischaemic heart disease, muscle spasm and peripheral odema

Forensic Classification:
PIS1S3

TELFAST ORAL SUSPENSION PEDIATRIC 6 mg/ml
(Sanofi Aventis)

Active Ingredient:
Fexofenadine (as hydrochloride).

Presentation:
White uniform aqueous suspension with a raspberry cream flavour. Each mL contains fexofenadine HCl 6mg (30mg/5mL) equivalent to 5.6 mg fexofenadine. Available in bottle presentation of 150 mL.

Pharmacological Properties:
Fexofenadine is the carboxylic acid metabolite of terfenadine. It is an orally-active non-sedating histamine H_1-receptor antagonist that is administered as the hydrochloride salt in Telfast. Oral administration of fexofenadine to guinea pigs, indicated that fexofenadine antagonized histamine-induced skin wheals in a dose-dependent manner. Fexofenadine is not associated with significant ECG abnormalities. Doses of fexofenadine ten times greater than the dose of terfenadine that produces prolongation of QTc intervals do not prolong QTc intervals in anaesthetized rabbits and conscious dogs.

Indications:
Relief of symptoms associated with seasonal allergic rhinitis in children aged 6 to 11 years.
Relief of symptoms associated with allergic rhinitis or urticaria in adults and children aged 12 years or older.

Dosage and Administration:
Children aged 6 to 11 years: Seasonal Allergic Rhinitis: 5 mL (30mg) twice daily, when required.
Children aged 12 years or older and Adults: Allergic Rhinitis:10 mL (60mg) twice daily, when required; Seasonal Allergic Rhinitis: 20 mL (120mg) or 30 mL (180mg) once daily, when required; Urticaria: 30 mL (180mg) once daily, when required.

Contraindications:
Telfast is contraindicated in patients with a known hypersensitivity to fexofenadine, terfenadine or any of its excipients.

Precautions:
Effects on Fertility
In rat fertility studies, dose-related reductions in implants and increases in post implantation losses were observed at oral doses equal to or greater than 150 mg/kg of terfenadine respectively; these doses produced plasma AUC values of fexofenadine that were equal to or greater than three times the human therapeutic value respectively (based on a 60 mg twice daily fexofenadine HCl dose).

Use in Pregnancy
Category B2. Reproductive toxicity of fexofenadine in animals was assessed through terfenadine exposure. No evidence of teratogenicity was observed in animal reproduction studies (rat and rabbit) when terfenadine was given at oral doses of up to 300 mg/kg/day throughout organogenesis, which corresponds to levels of systemic fexofenadine exposure 4- and 32-fold higher, respectively, than those anticipated in clinical use. Decreased pup weight and survival occurred in rats when terfenadine was given at oral doses of 150 mg/kg/day and above throughout pregnancy and lactation.

Use in Lactation
Telfast is not recommended for nursing women unless, in the physician's judgment, the potential benefit to the patient outweighs the potential risk to the infant.

Carcinogenicity
The carcinogenic potential and reproductive toxicity of fexofenadine HCl were assessed using terfenadine studies. No evidence of carcinogenicity was observed when mice and rats were given daily oral doses of 50 and 150 mg/kg of terfenadine for 18 and 24 months, respectively; these doses resulted in plasma AUC values of fexofenadine that were two to four times the human therapeutic value (based on a 60 mg twice daily fexofenadine HCl dose).
Fexofenadine showed no genotoxic activity in a series of assays for gene mutations and chromosomal damage.

Drug Interactions:
Co-administration of fexofenadine with erythromycin or ketoconazole has been found to result in a 2 - 3 times increase in the level of fexofenadine in plasma. The changes were not accompanied by any effects on the QT interval and were not associated with any increase in adverse events compared to the drugs given singly. Fexofenadine had no effect on the pharmacokinetics of erythromycin or ketoconazole.
No interaction between fexofenadine and omeprazole has been observed. However, the administration of an antacid containing aluminium and magnesium hydroxide gel 15 minutes prior to fexofenadine HCl causes a reduction in bioavailability, most likely due to binding in the gastrointestinal tract. It is advisable to leave 2 hours between administration of fexofenadine HCl and aluminium and magnesium hydroxide containing antacids.

Side Effects:
Headache, fatigue, dizziness or drowsiness, nausea, nervousness, insomnia, sleep disorders and paroniria. In rare cases, rash, urticaria, pruritus and hypersensitivity reactions with manifestations such as angioedema, chest tightness dyspnoea, flushing and systemic anaphylaxis have been reported.

Forensic Classification:
PIS1S3

NEW INDICATIONS

GARDASIL® 加衛苗®
(MSD)

New Indications:
Boys and Men
GARDASIL is indicated in males from the age of 9 through 26 years for the prevention of genital warts (condyloma acuminata) caused by HPV types 6 and 11.

Dosage:
GARDASIL should be administered intramuscularly as 3 separate 0.5-mL doses according to the following schedule:

First dose: at elected date
Second dose: 2 months after the first dose
Third dose: 6 months after the first dose (See Immunogenicity, Schedule Flexibility)

Paediatric population: There is no experience with the use of Gardasil in children below 9 years of age.

Method of Administration:
GARDASIL should be administered intramuscularly in the deltoid region of the upper arm or in the higher anterolateral area of the thigh.

GARDASIL must not be injected intravascularly. Neither subcutaneous nor intradermal administration has been studied. These methods of administration are not recommended.

The prefilled syringe is for single use only and should not be used for more than one individual. For single-use vials a separate sterile syringe and needle must be used for each individual.

The vaccine should be used as supplied; no dilution or reconstitution is necessary. The full recommended dose of the vaccine should be used.

It is recommended that individuals who receive a first dose of Gardasil complete the 3-dose vaccination course with Gardasil.

Forensic Classification:
P1S1S3

LIPITOR®

atorvastatin calcium – crystalline form

Power to do more

More Evidence across More Patient Types

Moderate Risk

Hypertension

36% RRR

of nonfatal MI + fatal CHD in patients with hypertension ($p=0.0005$)[1]

Diabetes

37% RRR

time to first occurrence of major CV events in patients with diabetes ($p=0.0005$)[2]

High Risk

CHD

59% RRR

of nonfatal MI in patients with CHD ($p=0.0001$)[3]

CHD

22% additional RRR

of major CV events in patients with CHD ($p<0.001$)[4]

Highest Risk

ACS

16% RRR

of major CV events in patients with ACS ($p=0.005$)[5]

References: 1. Sever PS, Dahlöf B, Poulter nR, et al; for the ASCOT investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-lipid lowering Arm (ASCOT-lA): a multicentre randomised controlled trial. Lancet. 2003;361(9364):1149-1158. **2.** Colhoun hm, Betteridge DJ, Durrington Pn, et al; on behalf of the CARDS investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet. 2004;364(9435):685-696. **3.** Athyros VG, Papageorgiou AA, mercouris BR, et al. Treatment with atorvastatin to the national Cholesterol education Program goal versus 'usual' care in secondary coronary heart disease prevention: the GReek Atorvastatin and Coronary-heart-disease evaluation (GREACe) study. Curr Med Res Opin. 2002;18(4):220-228. **4.** laRosa JC, Grundy Sm, waters DD, et al; for the Treating to new Targets (TnT) investigators intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med. 2005;352(14):1425-1435. **5.** Cannon CP, Braunwald e, mcCabe Ch, et al; for the Pravastatin or Atorvastatin evaluation and infection Therapy-Thrombolysis in myocardial infarction 22 investigators intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med. 2004;350(15):1495-1504. **Detailed information is available upon request.**

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