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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

Looking Back on 2010: A Year Strived for A Higher Standard

A Busy but Fruitful Year

Twenty ten has been another busy yet fruitful year for the editorial board of the Hong Kong Pharmaceutical Journal. In order to regularly publish four issues per year on time on voluntary bases is really not a simple work. But we have made it. All together, we have published nearly thirty articles. Hence, I would like to thank all contributors and all active members of the editorial board. Thanks are, in particular, due to Ms Mary Catherine Cheng for her help when I was unable to carry out the compilation task for the News and Communication section. My special gratitude are also given to her wholehearted devotion to editing the summer issue when I had to organize and chair two International meetings on top of my tight research schedule and teaching load in the University, and subsequently to participate in other two conferences at about the same time.[1-5]

Notable amongst the year's achievements have been the launch of a completely new style of design for the cover page and a wider coverage relevant to pharmacist's trainings or professional practices in each section. We have also witnessed a few jointed efforts involving authors outside the Hong Kong territories (p.156). All these collaborative works are good for the journal and we hope that further developments and expansions could be realized in the near future. Certainly, we sincerely hope that academic staffs and students from both local pharmacy schools could make some contributions and share some of the responsibilities so that the rooting and growth of this journal are feasible.

Goal of Pharmacy Practice

On the other hand, if we look back we would not be surprised to find out what dominating last year's news on medication were those related to the sale or administration of drugs and medicinal products causing adverse outcomes in patients due to their poor quality. Although these incidences might also be found in other countries, safe and efficient distribution of medication to patients is the most important objective of a pharmacist.[6] This editor has been asked by people in several occasions about the criteria of selecting news for inclusion in the journal. My simple reply is that as long as it could raise or alert the standard of pharmacy practices, it is worthwhile to be reported. Of course, news could be good or bad. But unfortunately, it turned out bad in most of the cases. In this issue, the same ratio is also found.

High Quality Drug via Continuous Research and Regular Review

The administration of high quality and effective drug cannot happen unless the whole society has the determination to strive for a better understanding how drug works and made. This requires continuous exploration and research. Even so, no one can guarantee the best drug could be identified or made right away. Hence, regular review and assessment of drugs currently in use are necessary. The rationale for these exercises may be for the sake of improving their efficacy, safety or simply eliminating the overuse of resources. An in-depth study performed by Lee and Cheung on the complexation of indomethacin, which is a well known poorly soluble drug, through molecular inclusion to a cavity molecule (p.149) is a typical example for the former; while a report written by Chung et al on the acarbose utilization pattern and impact of pharmacist intervention (p.144) taken place couple years ago in a local teaching hospital is an example for the later. The results of these two studies are interesting and deserve our attention. An exploratory study on the effectiveness to prevent contraception by means of oral contraceptive (p.134) showed that it is equally reliable in comparison to that by surgical sterilization. This kind of regular study or survey is necessary if we want to eliminate any fault.

Pharmacist's Emotional Quotient and Patient Care

During the recovery process of a patient, the quality of drugs is not the only determination factor. Emotional quotient (EQ) of a pharmacist, in many occasions, also plays an important role.[7] Being more empathic and sensitive in patient interactions would help sense the underlying fears and concerns of patients. The benefit of high EQ for a pharmacist as addressed in an article written by Chong & Sheung (p.129), suggests that it is an essential ingredient for routine patient counseling and communication. However, this criterion for a pharmacy student has frequently been ignored in these days' training. Consequently, many of them are blamed for lacking empathy and commitment to their professionalism.

Legislative Regulation: the Last Choice

The introduction of legislative regulation, perhaps, is the last but always unavoidable option to safe guard the supply of good healthcare materials or products for Sale. Although implements of law in the aspect of healthcare haven't been addressed much in this journal, it is a very effective step to prevent irresponsible or greedy practices. Nevertheless, whenever there is any new regulation, it wouldn't be missed.

As you read through each article in this issue, most likely during the Chinese New Year holidays, we hope you enjoy all the information and new knowledge present.

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INSTRUCTIONS FOR AUTHORS

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- Herbal Medicines & Nutraceuticals
- Society Activities
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Comments on any aspects of the profession are also welcome as Letter to the Editor.

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

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

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

Tea Oil Contains Carcinogenic Substance

Date: September 1, 2010

The Hunan province Quality Inspection Bureau discovered in March that a portion of the tea oil produced by China manufacturers failed to meet safety standards. The oil contained the carcinogenic substance, Benzopyrene, which exceeded six times the allowable limit. The authority did not order a recall of the tea oil and prohibited the media to report the incident and explained it was to prevent turmoil in society. The public found out that the 5 litres tea oil were put on sale twice with a 15% discount. As the tea oil contained low content of saturated fats and higher Vitamin E content, it was widely accepted as a green food by the public. Experts suspected that the excess in benzopyrene is due to wrong procedures in processing the oil.

Source: Apple Daily News

Abbott Withdraws Sibutramine From Market

Date: October 8, 2010

The US Food and Drug Administration (FDA) announced that Abbott Laboratories has withdrawn the obesity drug sibutramine (Meridia) from the market in light of clinical trial data pointing to an increased risk for stroke and myocardial infarction. FDA asked Abbott Laboratories to pull the drug from the market after it evaluated data from a postmarketing study of the drug's cardiovascular safety. The study, called the Sibutramine Cardiovascular Outcomes Trial (SCOUT), demonstrated a 16% increase in the risk for serious cardiovascular events such as nonfatal heart attack, non fatal stroke, the need for resuscitation after the heart stopped, and death in a cohort of patients given sibutramine compared with another given a placebo. FDA advised physicians to stop prescribing sibutramine and for patients to stop taking it and talk to their healthcare provider about alternative weight-loss regimens.

Source: http://www.fda.gov/medwatch

Pi Chong (蜱蟲) Attacks Shenzhen

Date: October 15, 2010

It was reported that Pi Chong, which have spread to more than ten provinces in China, have invaded Shenzhen. Citizens in Yim Tin reported that Pi Chong were found in their homes. The tiny insect has size of a grain of rice, with 8 legs. After bitten by the insect, a person would develop red spots all over the body which required treatment in the hospital. The health authority initially confirmed that the red spots on the patients were caused by Pi Chong, but there have not been sufficient cases reported to the Centre for Disease Prevention. The doctors reinstated that Pi Chong bites were not 100% infectious. However patients with high fever above 38 degree Centigrade, nausea, vomiting and fatigue should seek treatment in the hospital. There were reported cases of death caused by Pi Chong's bites in more than ten provinces in China.

Source: Apple Daily News

NeoChem Found To Manufacture Drugs During Suspension Period

Date: October 26, 2010

Neochem started to recall 37 of their products yesterday upon the request of DH. Citizens can return the drugs through their doctors or seven designated pharmacies in Hong Kong. According to a staff of one of the designated pharmacies in Yau Ma Tei, he said that there has not been any return goods so far. The drugs were mostly prescription medicines and were not purchased in the pharmacies. When asked by the reporter, Dr. York Chow, Secretary of Health Food Bureau, said that this was the first time that a drug manufacturer had been found by inspectors of DH to manufacture drugs during suspension period. The offence is very serious, DH would seek legal advice and the manufacturer may be prosecuted. As the case is still under investigation, he declined to give further comments.

Source: Sing Tao Daily

Cancellation of the Registration of Sibutramine Products

Date: November 3, 2010

Due to the serious side effects of sibutramine, the Department of Health announced the cancellation of the registration of all sibutramine products. In Hong Kong, there were 20 companies which held the registration of 45 sibutramine products. Sibutramine was very frequently prescribed for weight loss. The most frequent side effects include headache, palpitation, nausea, constipation, dry mouth and insomnia. In high dose, it can cause increase heart rate and blood pressure. Recent studies revealed that for patients on sibutramine in comparison to patients on diet and exercise, there is a definite increase in risk of cardiovascular events, heart attack and stroke. The Registration Committee considered that the risk of cardiovascular diseases out weigh the benefit of slight decrease in weight for patients, and decided to cancel the registration of sibutramine products in Hong Kong.

Source: Apple Daily News

Study Finds Herbal Remedy Helps Fatty Liver

Date: November 6, 2010

The herb Phyllanthus (真珠草), common in tropical and subtropical regions and sold in Hong Kong as a proprietary Chinese medicine, has a reputation of protecting the liver because of anti-inflammatory and anti-oxidant properties. Professor Wong Wai-sun Vincent and researchers from the Chinese University of Hong Kong tested the herbal remedy Phyllanthus (真珠草) on cells in mice over the past two years and found that it helped in controlling inflammation and fatty liver. When mice with fatty liver were fed Korean Phyllanthus for 10 days, the inflammation and fat accumulation in their livers were reduced. Professor Henry Chan Lik-yuen said the herb was able to destroy the mechanism causing inflammation in human bodies, so more serious conditions caused by fatty lever such as cirrhosis could be avoided. He said the medicine had few side effects and would be safe for most patients. CUHK has started the clinical trial in human. They have recruited 60 patients with fatty liver. Half of the patients will be fed 6 capsules, each containing 200mg of Phyllanthus, every day for 48 weeks. Researchers will look at the efficacy of the herbs in human. The other half will be the control group. The clinical trial should be completed within 2011.

Source: South China Morning Post

Caution against Products Containing Undeclared Western Medicine

Date: November 8, 2010

The Department of Health (DH) urged members of the public not to buy or use a topical proprietary Chinese medicine (pCm) called “Loong Fung Trade Mark Singapore Chi Len Chun Fung Oil” (Registration number: HKP-01728), as it was found to contain a western medicine, aspirin. The product is indicated for relieving joint pain. The DH inspected the premises of the manufacturer, Chan Yat Hing Medicine FTY, a licensed pCm manufacturer, and demanded that all the batches of the product be recalled from the market. The appeal and recall order followed detection of trace amount of aspirin (a western drug ingredient) in the product by the Government Laboratory during the DH’s market surveillance. According to the manufacturer, about 10,200 bottles of the product were manufactured in 2009. About 2,500 bottles have been supplied to the local market, and 2,900 bottles have been exported to the United States (US). The remaining 4,800 bottles are still in the factory. So far, no report has been received about consumers feeling unwell after using the product.

The Department of Health (DH) also called on members of the public not to buy or use a product labelled as “An Chuang San Ri Qing (Xian Tao Lu)” as it was found to contain an undeclared western medicine, metronidazole, a drug used for treatment of anaerobic and protozoal infections. The appeal was made following DH’s market surveillance under its established vigilance system. According to Lee Sze Trading Company, a licensed proprietary Chinese medicine wholesaler, the product was imported from the Mainland for sale in Hong Kong. The wholesaler was instructed to immediately recall the product.

Source: Apple Daily News

WPRO Expert Meeting in Hong Kong on Regional Strategy for Traditional Medicine

Date: November 18, 2010

Experts of the World Health Organization (WHO) met in Hong Kong for two days (November 18 to 19) to discuss a draft strategy that is designed to steer traditional medicine in the Western Pacific Region (WPR) into the next decade. The meeting was attended by about 25 experts from the WHO and 11 countries in the region. The event, entitled "Experts' Consultation Meeting on Regional Strategy for Traditional Medicine in the Western Pacific Region, 2011-2020", was organised by the WPR Office with support from the Department of Health. The Director of Health, Dr P Y LAM, was elected as chairperson of the meeting.

Source: http://www.dh.gov.hk/english/press/2010/101118.html

Cancer Drug Shortages Are Placing Patients at Risk

Date: November 19, 2010

Across the United States, shortages of many critical drugs, including several cancer drugs, are placing patients at risk. The American Society of Clinical Oncology (ASCO) announced that the oncology community is facing severe and worsening shortages of many critical therapies, including but not limited to doxorubicin, leucovorin, etoposide, nitrogen mustard, vincristine, propofol, and morphine. Dr. Michael Link, MD, president-elect of ASCO said that shortages of critical cancer drugs are causing delay in treatment, which can impact survival. Additionally, administration of alternative therapies can lead to less optimal treatment and increased costs for patients and increases administrative burdens for oncology practices. The current drug shortages listed on the web site of FDA indicate that most are due to "manufacturing delays" and "increase demand".

Captain Valerie Jensen, RPh, associate director of CDER said that the factors contributing to these shortages, especially of older parental products, include limited production capacity at the firms making these products; fewer firms are making these products each year since they are often discontinued in favor of newer, more profitable products.

Source: http://www.medscape.com/viewarticle/732883 print

Propoxyphene Withdrawn From US and European Market

Date: November 19, 2010

FDA has asked that propoxyphene, sold under the brand names Darvon and Darvocet by Xanodyne Pharmaceuticals, be removed from the US market. The decision also applies to generic manufacturers and the makers of propoxyphene-containing products. New clinical data showed that the drug puts patients at risk for potentially serious or even fatal heart rhythm abnormalities. An estimated 10 million patients have used these products. The FDA is advising healthcare professionals to stop prescribing propoxyphene. Patients should contact their doctors to discuss switching to another pain management therapy. However, they have been asked not to stop the drug immediately. The effects of propoxyphene are not cumulative. Once patient stops taking the drug, the risk goes away. A phased withdrawal of propoxyphene is already underway in Europe. The European Medicines Agency made that decision in June 2009.

Source: http://www.medscape.com

US to Ban Five Chemicals That Mimic Marijuana

Date: November 26, 2010

The US government has moved to outlaw five chemicals used in herbal blends to make the synthetic marijuana sold in drug paraphernalia shops and on internet to a growing number of teens and young adults. The Drug Enforcement Administration (DEA) began the 30-day process to put the chemicals in the same drug category as heroin and cocaine. The agency acted after receiving increasing numbers of reports since 2009 about the products from poison centers, hospitals and law enforcement agencies. The five chemicals mimic THC, the active ingredient in Marijuana, and are not approved by FDA for human consumption. The DEA spokeswoman said makers of fake pot blends – including "Spice", "K2", "Blaze" and "Red X Dawn" – label the mixtures as incense to try to hide their intended purpose. Ultimately, the blends are smoked like real marijuana to produce a high and are making users across the country sick.

Source: South China Morning Post

Chinese Drug Found To Cure Tropical Disease

Date: November 26, 2010

Researchers reported that they have successfully tested a Chinese developed drug against opisthorchiasis, a neglected tropical disease caused by a parasitic worm that threatens about 67 million people in Southeast Asia. It was reported in Lancet that Tribendimidine is as safe and effective against the tiny worm that causes the disease as the frontline drug, praziquantel, marketed as Biltricide. Opisthorchiasis is caused by a fluke that passes from fresh water snails to river fish. It is then transferred to humans if the fish is eaten raw or undercooked. The fluke holds up in the liver and bile duct, where it reproduces, causing abdominal pain and diarrhoea. In the long term, it increases the risk of jaundice, gall stones and cancer. According to the World Health Organization, Opisthorchis caused by parasitic worms is endemic in southeast Asia, the Siberian lowlands and eastern Europe. An estimated 67 million people are at risk of the disease, and 9 million are infected in Cambodia, Laos, and northeastern parts of Thailand and Vietnam.

A team led by Jennifer Keiser from the Swiss Tropical and Public Health Institute randomly gave 125 infected school children in the Attepeu province of Laos either tribendimidine, praziquantel or the antimalaria drugs mefloquine, artesunate and mefloquine. Tribendimidine scored the highest cure rate, 70%, followed by praziquantel (56%). Just four percent of children taking combined mefloquine and artesunate were cured, and four percent of those on artesunate only. No child was cured with mefloquine. Both tribendimidine and praziquantel also scored best in clearing the patient of parasite eggs and were generally well tolerated, with mild or moderate side effects. The results are very encouraging for Tribendimidine but would now need to confirm these results in larger clinical trials.

Source: South China Morning Post

Recall of three Jean-Marie Pharmaceutical Products

Date: November 26, 2010

The Department of Health (DH) ordered Jean-Marie Pharmacal Co. Ltd. (JM) to recall from the market a product which DH found to have a lower than the registered amount of an active ingredient, propantheline bromide. The company also voluntarily recalled two others which shared the same formulation. The drug found defective is Delna-U Tablet (HK-07441). JM is also recalling Elisa U Tablet (HK-07463) and Triganet Tablet (HK-28072) as a precautionary move with DH endorsement. Samples of Delna-U Tablet collected during DH's market surveillance were found by the Government Laboratory to contain only 0.69mg of propantheline bromide per tablet, as against the registered content of 3mg per tablet. Deviations from the registered amount of active ingredients of a pharmaceutical product could affect treatment effectiveness. All three products involved are used for the treatment of stomach pain and gastric ulcers. They are pharmacy medicines and can only be sold under the supervision of a registered pharmacist in pharmacies.

Based on the information in hand, Delna-U Tablet was supplied to local pharmacies and some private doctors as well as to Macau, while Elisa U Tablet and Triganet Tablet were only for export to Macau.

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

Mandatory Registration of Proprietary Chinese Medicine to Take Effect from 3 December 2010

Date: December 2, 2010

The legislation under the Chinese Medicine Ordinance (Cap 549, the Ordinance) concerning the mandatory registration of proprietary Chinese medicines (pCm) came into force on December 3, 2010. It is stipulated in section 119 of the Ordinance that all pCm must be registered by the Chinese Medicines Board (CMB) of the Hong Kong Chinese Medicine Council (CMC) before they can be sold, imported or possessed. To be registered, any pCm must satisfy the CMB's requirements in terms of its safety, quality and efficacy. Upon the implementation of section 119, the sale, import or possession of unregistered pCm in Hong Kong will be an offence, liable on conviction to a maximum fine of $100,000 and two years' imprisonment. The CMB may provide exemptions for pCm required for education or scientific research, including clinical trial; or imported for re-export; or prepared for or compounded by a registered or listed Chinese Medicine practitioner for supply or administer to a patient under his direct care.

Information to be provided through labelling and package inserts will only become mandatory from December 1, 2011 onward, such a date has been arrived at after balancing the consumer's right to know and operational feasibility. In the interim, lists of pCm which meet the requirements of the CMB have already been posted on the CMB's website at www.cmchk.org.hk. Members of the public can also call 2319 5119 to enquire if in doubt.

Source: http://www.info.gov.hk/gia/general/201012/02/P201012020203.htm

American Diabetes Association Revises Diabetes Guidelines

Date: December 23, 2010

The American Diabetes Association published new clinical practice recommendations in December 2009, the news story quickly became one of the most read articles on Medscape. The guidelines promote the use of the hemoglobin A1c(A1c) as a faster, easier diagnostic test that could help reduce the number of undiagnosed patients and better identify patients with prediabetes. A1c measures average blood glucose levels for a period of up to 3 months. Previously it was used only to evaluate diabetes control with time, but because it doesn't require fasting, A1c testing will encourage more people to get tested, leading to treatments and lifestyle changes that could prevent the worst effects of the disease.

Source: http://www.medscape.com/features/slideshow/year-in-medicine?src=ptalk

Calcium Boosts Heart-Attack Risk

Date: December 23, 2010

A large study found that calcium supplements taken without vitamin D may increase the risk for heart attack by as much as 30%. Researchers reported the findings on line July 29 in the British Medical Journal, based on meta-analysis of 15 randomized trials with up to 11,921 participants. Most guidelines for osteoporosis currently recommend the supplements, despite relatively small benefits in bone health, but senior author Dr. Ian R. Reid, from the University of Auckland in New Zealand said that in most cases, "discontinuation of calcium would seem appropriate." The study raised many questions, such as why calcium could have such effect during a relatively short period of time. Pending further research, some experts advised eating foods high in calcium rather than taking supplements.

Source: http://www.medscape.com/features/slideshow/year-in-medicine?src=ptalk

Deregistration of Pharmaceutical Products Containing Propoxyphene

Date: December 29, 2010

On 29 December 2010, DH announced that the Registration Committee of the Pharmacy and Poisons Board has decided that pharmaceutical products containing propoxyphene should be deregistered for public health protection. This is to take effect from January 10, 2011, to allow for necessary recall follow-up. The Committee has taken into consideration all the information available, including the effects of propoxyphene on human cardiac electrophysiology at therapeutic dose range, the availability of alternative analgesic drugs in Hong Kong and regulatory actions taken by other lead regulatory agencies. Internationally, propoxyphene has either been suspended or withdrawn from use in countries in the European Union, Singapore, the United Kingdom and the United States. After due risk assessment, the Committee concluded that the increased risks of serious abnormal heart rhythms caused by propoxyphene at therapeutic doses outweighed its benefits for pain relief. Therefore, a decision to deregister pharmaceutical products containing propoxyphene was made. Currently, there are 21 pharmaceutical products registered to contain propoxyphene (in the form of dextropropoxyphene) and being supplied by 13 companies in Hong Kong.

The wholesalers concerned should immediately stop trading or distributing propoxyphene-containing products and instead recall them from shelves before or by January 10, 2011. Doctors and pharmacists should also stop prescribing or dispensing propoxyphene-containing products and return their stocks to the respective wholesalers. Patients who are taking propoxyphene-containing products should consult their doctors or pharmacists to discuss alternative measures for pain management. The Department of Health will closely monitor the recall of propoxyphene-containing products.

Source: www.psdh.gov.hk

Emotional Quotient at Work --- a Pharmacist's Perspective

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ABSTRACT

Emotional quotient (EQ) is increasingly regarded as an indispensable competency for personal success, organizational effectiveness and professional recognition in healthcare professionals, and pharmacists are no exceptions. This article explores this long-neglected professional attributes, and discusses its significance to pharmacy practice and patient outcomes.

Keywords: *emotional quotient, intelligence, pharmacy, work, competency.*

INTRODUCTION

Observations that some health care professionals consistently outperform others in delivering pharmaceutical care point to the importance of emotional competence of both individuals and organizations as a positive predictor of ability or success in conforming to pharmacy's professional standards.[1, 2] It has been suggested that emotional quotient (EQ), or stated otherwise emotional intelligence (EI), contributes to personal career development, effective team collaboration, as well as organizational effectiveness much more than the traditional markers of ability and success.[3]

WHAT IS EMOTIONAL QUOTIENT (EQ)?

At present, there seems to lack a unanimous definition for EQ. In fact, proposed definitions for EQ are even contradictory to each other. EQ had been viewed as a skill,[4] an aptitude,[5] and a combination of both in past research.[6] In its simplest sense, EQ could be referred to as the ability to recognize and regulate emotions in ourselves and others.[7]

Up till now, the definition provided by Mayer and Salovey was considered as the most appropriate one in academia:[5] "The ability to perceive emotion, integrate emotion to facilitate thought, understand emotions, and to regulate emotions to promote personal growth."

This definition fits better to the distinguishing criteria of an "intelligence",[8] in that it reflects real life behavior. It is also intrinsically goal-directed and purposive, and involves internalization of a higher-order process.

ELEMENTS OF EQ

The Emotional Intelligence Questionnaire (EIQ) developed by Dulewicz and Higgs,[9] and the Emotional Quotient Inventory (EQi) developed by Bar-On[10] are the two main instruments to measure EQ. While the former presents several EQ elements, as well as having satisfactory construct validity and content validity to measure psychometric aspects of subjects, it fails to take into account the inter- and intra-personal components of EQ as the latter does. Thus, a revised EQ model incorporating the strengths of these two previous models was suggested in the literature (Table 1):[11]

As you can see, the seven EQ elements are grouped into **(1)** driver, which helps to energize people and motivates them to achieve higher goals; **(2)** constrainer, which acts as a control to restrain the driver from being in excess, undirected or misdirected; and **(3)** enablers, which are general traits that help individuals striking targets and achieving success by facilitating their performance.

HOW DOES EQ DIFFER FROM AQ AND IQ?

In contrast, intelligence quotient (IQ) measures the cognitive aspects of intelligence. These include logical reasoning abilities, spatial orientation, analytical skills, and language skills, etc.[12]

On the other hand, adversity quotient (AQ) is a measure of one's resilience and ability to persevere in the face of constant change, stress and difficulty.[13] Simply speaking, it measures how capable a person could resolve and overcome ongoing challenges so as not to be badly affected in his/her life.

To sum up, IQ measures your ability to articulate things; EQ measures your emotional stability; and AQ measures your tolerance of adversity.

Table 1. EQ components, elements and their meanings

Model Components	EQ elements	Descriptions
Driver	**Motivation**	Having the drive and energy to attain challenging long-term goals or targets.
Constrainer	**Conscientiousness**	Being consistent in one's words and actions, and behaving according to prevailing ethical standards.
Intra-personal enablers	**Self-awareness**	Being aware of one's feelings and being able to manage them.
	Emotional resilience	Being able to maintain one's performance when under pressure.
	Intuitiveness	The ability to make decisions, using reason and intuition when appropriate.
Inter-personal enablers	**Interpersonal sensitivity**	Showing sensitivity and empathy towards others.
	Influence	The ability to influence and persuade others to accept your views or proposals.

THE INTERRELATIONSHIP AMONG IQ, EQ AND AQ

It has been suggested that although IQ and EQ both play a role for success, neither of them appears to be a determining factor.[13] It is not uncommon to have people being equally brilliant and well-adjusted of their emotions, but some persist while others fall short and still others quit. Different adversity quotients (AQ) among them may be the cause.

There has been a saying that success is determined by three concomitant criteria. While IQ and EQ may pave the road to success to a certain extent, the real crucial determinant is the AQ scores that one possesses. Estimates are that IQ contributes about 20% to the factors that determine a person's success in life, while EQ is responsible for 80% or more.[14]

It is also believed that a person who has high EQ but low IQ would still easy bump into a really helpful benefactor; while a person possessing the reverse may have his talent left to rust. A person having both low EQ and AQ is likely to fail, whereas another who have high EQ but low AQ would only enjoy limited success.[13] Therefore, whether one can achieve high depends largely on his AQ.

Take mountain climbing as an example, the higher the altitude you want to conquer, the greater the difficulties and challenges you would encounter. While IQ may equip you with sufficient mountain information and knowledge of climbing techniques, you won't put them into practice unless you also get the necessary equipments (EQ) to execute your knowledge. In pursuance of success, a majority of people would opt to quit in face of adversity after they have obtained the basic satisfaction. Further uphill, still a certain number of people would choose to be campers when they confront greater resistance ahead. Only those who perseveringly pursue and have enormous desire for success (having also high AQ) could overcome adversity and ascend the summit eventually. The following figure (Fig. 1) presents an analogy that is often used to depict the interrelationship among IQ, EQ and AQ:[13]

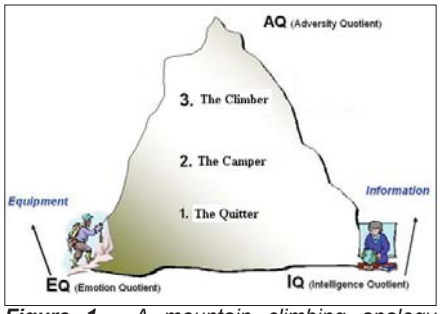

Figure 1. *A mountain climbing analogy illustrating the interrelationship among IQ, EQ and AQ.*

As a healthcare professional who possesses strong pharmaceutical knowledge, a pharmacist would not be so deficient in technical competence. Rather, it is usually how sufficiently we are equipped with personal and emotional skills (EQ) to do the job in a friendly and efficient manner.

Although IQ is genetic in nature and couldn't be affected much by life experience,[15] EQ and AQ could! Therefore, it would be meaningful to explore this emotional aspect of competence in order to find ourselves at least somewhere "uphill".

EQ AND PERSONAL SUCCESS

In his masterpiece "Emotional intelligence: Why it can matter more than IQ", Goleman also puts forward the significant impact EQ would affect human rationality, and thus individual behavior, when "the emotional faculty guides moment-to-moment decisions, enabling or disabling thought".[4] In fact, EQ not only encompasses "managing others", but also includes "managing self". A high EQ person would understand and recognize his own moods and emotional drives, and foresee his/her effects on others. Therefore, on many occasions, how we manage ourselves determines how we handle and maintain valuable interpersonal relationships, because having the ability to control and channelize disruptive impulse could calm down the person and let him/her think critically before execution.[16]

Apart from that, EQ also determines our potential for learning practical skills, because it affects how our brains process information.[15] Having compromised EQ would make a person more likely to resort to defensive and social withdrawal behaviors when they are unaware of the root causes of unrewarding interactions.[17] In addition, EQ also enlightens you with the passion to work for reasons that are beyond money and status, thereby enables you to pursue goals with energy and persistence.[18]

Ferdowsian postulated that EQ would drive an employee's performance.[19] In general, EQ correlates with performance ratings. Not only would EQ determines personal commitments, but it also governs how high the quality of your personal vision statement.[15]

In addition, EQ was also found to be positively related to life satisfaction and negatively associated with depression.[20] Several studies have delineated EQ's role in managing mood, moderating stress, subsequently leading a healthier, happier and more productive life.[21]

EQ AND LEADERSHIP / CONFLICT MANAGEMENT

While traditional ideal traits such as toughness, determination, vision, analytical and technical competencies are regarded as necessary skills for being a leader, they are just minimum requirements for success, and by no means are they sufficient for effective leadership.[22] It has also been argued that high EQ accounts for over 90% of the difference between ineffective and effective leadership. A best-trained leader with incisive minds and plentiful marvelous ideas would not be an authentic leader unless he is comprehensive and adaptive enough to his subordinates' emotions, since building working relationships, networks as well as rapport requires every party getting involved to seek for a common ground (Fig. 2).[23]

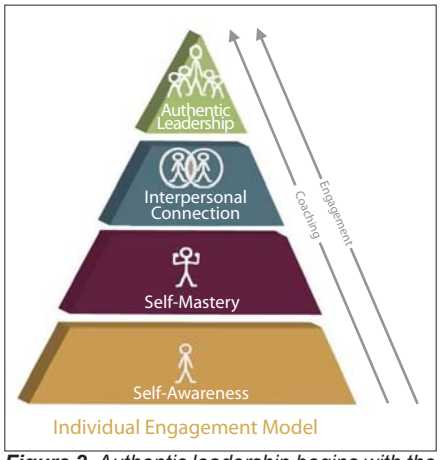

Figure 2. *Authentic leadership begins with the individual and extends to influencing others and building a leadership legacy.*

In human performance studies,[24] it was found that teams composed of individuals with high EQ will be more effective in resolving conflicts than teams of individuals with low EQ. Specifically, a team with higher collective EQ would have greater collective ability for its members to deal with their own emotions during problem solving. They are more likely to utilize integrative or collaborative tactics as the preferred conflict resolution style. An inclination to listen to alternative viewpoints and devise superior solutions without being afraid of threatening one's individual goals and self-esteem may be the possible explanations.[25]

It should be emphasized that such integrative or collaborative tactics in group work would not significantly discount effectiveness and timeliness of task completion. According to Cooper and Sawaf, EQ has a hallmark of "flexibility in response".[26] In times of extenuating conditions, such as time constraints, that requires prompt response and management, high EQ teams would incorporate a certain degree of dominating tactics to complete the team task on time, rather than going into endless dispute as in low EQ teams.

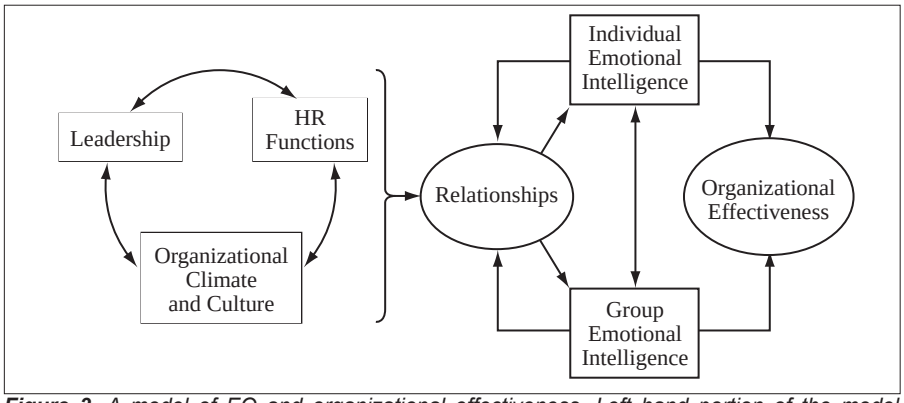

Figure 3. *A model of EQ and organizational effectiveness. Left hand portion of the model illustrates three organizational factors that are interrelated, each of these factors influences emotional intelligence through its impact on relationships.*

EQ IN THE WORKPLACE

In his book "Working with emotional intelligence",[27] Goleman stressed the utmost importance of EQ in the age of information and highly specialized work teams: "from the perspective of work, feelings matter to the extent that they facilitate or interfere with the shared goal". Without doubt, effective communication and collaboration are as critical as technical capabilities for task accomplishment.

Since organizations are comprised of groups of individuals, the interplay of emotional and practical intelligence could have significant impact on internal coherence, organizational flexibility, adaption to changes, and eventually success. Again, Goleman stated insightfully that "an emotionally intelligent organization needs to come to terms with any disparities between the values it proclaims and those it lives. Clarity about an organization's values, spirit, and mission leads to a decisive self-confidence in corporate decision making".[27] This implicates that EQ does matter in all aspects of corporate governance and organizational effectiveness, ranging from corporate communication, marketing, customer relationships, team interaction, staff morale, loyalty and job retention, as well as team unity and trustworthiness.[28] All in all, as an emotional soft skill, EQ would help organizations strive to achieve more with less (Fig. 3).

For example, in the pharmaceutical settings where a pharmacist may take up roles such as a sales representative, product specialist or marketing manager, EQ competency is important for building and maintaining strong business relationships. The job nature, as well as the competitive environment that such an industrial pharmacist has to face could sometimes be quite stressful. Given that customer satisfaction largely depends on his or her emotional experience during service encounter, having high EQ would allow the pharmacist to be emotionally adaptable and flexible enough to meet different clients' needs and expectations.[29] Similar work stress in hospital pharmacy settings also points to the importance of EQ training.[17]

EQ AND PHARMACEUTICAL CARE

It has long be blamed that current pharmacy students often lack empathy and a commitment to professionalism because they are highly focused on various technical aspects of competencies, rendering them more emotionally immature when compared to older generations of practitioners.[30, 31] It is now increasingly recognized that many intangible characteristics and traits may be more critical to successful pharmacy practice and the provision of healthcare.[32]

As pharmacy schools strive to graduate practitioners who cherish and uphold principles of pharmaceutical care practice, they are seeking to incorporate nontraditional factors such as interpersonal skills, social awareness, moral reasoning, empathy, motivation, self-awareness and self-control into admission criteria, apart from just baseline intellect and cognitive mastery.[32] This is in line with the belief that health professions are "an amalgam of clinical competence and a service-orientation towards caring".[33]

Pharmacists are in a favorable position to establish therapeutic relationships with patients, the quality of such relationships rest on the ability in responding to both technical aspects of the disease, as well as patients' associated emotional concerns.[1] The resulting covenantal pharmacist-patient relationship is believed to improve patient outcomes and treatment adherence.[1]

A pharmacist with high EQ is essential for routine patient counseling and communication. Being more empathic and sensitive in patient interactions would help sense the underlying fears and concerns of patients. The active listening and thorough understanding in the communication process would also permit successful removal of barriers towards patient-focused care and professional recognition.[34] High EQ also allows pharmacists to work cooperatively and effectively with other health care providers as a cross-functional team in pharmacy practice environments.[2]

WHY EQ IS OFTEN NEGLECTED AT WORK?

Despite its importance, the negligence of EQ by most has nothing to do with our educational curriculum. It is understood that we won't have a subject named emotional education in schools. Gibson, in his book, pinpointed the fact that: "emotions are…in every classroom---whatever is being 'taught'---feelings are inevitably in play and are affecting what is being learned. In every human encounter, feelings pervade and underpin experience and constitute the spur to action".[35]

Although emotional education indirectly "exists" all the time in schools, the role of emotions in schooling seems to be invisible, minor, irrelevant or occurring in a negative image or instrumental forms for social control.[36]

Invisible:

Traditionally, it is assumed that as a person grows up, he will "discover" and "develop" EQ on his own. However, the challenges in facilitating active learning show that this is not the case.

Minor or irrelevant:

Throughout students' school life, they are often rewarded by their achievements in cognitive and intellectual aspects of education, but are rarely valued of being able to comprehend, express and putting appropriate use of their emotions.

Occurring in a negative image:

To get things worse, emotions are often negatively-labeled and associated with pathological characters such as apathy, self-centeredness, emotional volatility, over-excitability, sentimentality, lack of self-control and self knowledge.

Occurring in instrumental forms for social control:

The over-emphasis of self-discipline in schooling indeed only helps build a stable, orderly classroom. On the downside, this overemphasis has caused students to internalize self-control of their emotional behaviors and hampered EQ development.[37]

COULD EQ BE DEVELOPED?

Within much of the literature relating to EQ, there exists strong concordance that it is a developable trait or competency.[38] Although the core EQ capabilities are developed within childhood, these are malleable and could be shaped, developed and changed through workplace experiences.

Further analyses into those EQ elements suggested that some EQ components are "developable", i.e. training would extend individual's range of skills and increase the overall capacities of these components. On the other hand, some EQ components are seen as merely "exploitable", i.e. they are deeply-rooted, formed earlier in life and training would help optimize the original capacities of these components, but not extending them.[38]

Not all the EQ elements are lying at the two extremities. Instead, some EQ components lies in between. The emotional elements are stated in Table 2.[38]

Although further research is needed to support this idea, it is almost certain that EQ as a whole is developable. Thus it would be reasonable for organizations to introduce training programmes and activities to boost up EQ of the staff.[39]

DEVELOPING EQ AT WORK

A group's EQ requires the same competencies as an individual's. The competencies mainly center on self and social awareness and relationship management. Since groups have their moods and needs and they act collectively, how the emotional competencies show up on a team level is a bit difficult. However, since emotions are contagious, raising the level of awareness of these core competencies through effective coaching seems promising.[40]

In their article, Druskat and Wolff stated the essence of group emotional intelligence in layman terms:[41] "Group emotional intelligence is about the small acts that make a big difference. It is not about a team member working all night to meet a deadline; it is about saying thank you for doing so. It is not about in-depth discussions of ideas; it is about asking a quiet member for his thoughts. It is not

Table 2. The "Develop-Exploit" continuum for Emotional Intelligence Questionnaire (EIQ) measuring EQ components.

EIQ elements	*Develop*	←------→	*Exploit*
Intra-personal enablers			
Self-awareness	✓		
Emotional resilience		✓	
Intuitiveness			✓
Interpersonal enablers			
Interpersonal sensitivity	✓		
Influence	✓		
Driver			
Motivation		✓	
Constrainer			
Conscientiousness			✓

Table 3. Building norms for three levels of emotional intelligence---individual, group and cross-boundary.

Individual	Group	Cross-Boundary
Norms That Create Awareness of Emotions		
Interpersonal Understanding 1. Take time away from group tasks to get to know one another. 2. Have a "check in" at the beginning of the meeting – that is, ask how everyone is doing. 3. Assume that undesirable behavior takes place for a reason. Find out what that reason is. Ask questions and listen. Avoid negative attributions. 4. Tell your teammates what you're thinking and how you're feeling. **Perspective Taking** 1. Ask whether everyone agrees with a decision. 2. Ask quiet members what they think. 3. Question decisions that come too quickly. 4. Appoint a devil's advocate.	**Team Self-Evaluation** 1. Schedule time to examine team effectiveness. 2. Create measurable task and process objectives and then measure them. 3. Acknowledge and discuss group moods. 4. Communicate your sense of what is transpiring in the team. 5. Allow members to call a "process check." (For instance, a team member might say, "Process check; is this the most effective use of our time right now?") **Seeking Feedback** 1. Ask your "customers" how you are doing. 2. Post your work and invite comments. 3. Benchmark your processes.	**Organizational Understanding** 1. Find out the concerns and needs of others in the organization. 2. Consider who can influence the teams' ability to accomplish its goals. 3. Discuss the culture and politics in the organization. 4. Ask whether proposed team actions are congruent with the organization's culture and politics.
Norms That Regulate Emotions		
Confronting 1. Set ground rules and use them to point out errant behavior. 2. Call members on errant behavior. 3. Create playful devices for pointing out such behavior. These often emerge from the group spontaneously. Reinforce them. **Caring** 1. Support members: volunteer to help them if they need it, be flexible, and provide emotional support. 2. Validate members' contributions. Let members know they are valued. 3. Protect members from attack. 4. Respect individuality and differences in perspectives. Listen. 5. Never be derogatory or demeaning.	**Creating Resources for Working with Emotion** 1. Make time to discuss difficult issues, and address the emotions that surround them. 2. Find creative, shorthand ways to acknowledge and express the emotion in the group. 3. Create fun ways to acknowledge and relieve stress and tension. 4. Express acceptance of members' emotions. **Creating an Affirmative Environment** 1. Reinforce that the team can meet a challenge. Be optimistic. For example, say things like, "We can get through this" or "Nothing will stop us." 2. Focus on what you can control. 3. Remind members of the group's important and positive mission. 4. Remind the group how it solved a similar problem before. 5. Focus on problem solving, not blaming. **Solving Problems Proactively** 1. Anticipate problems and address them before they happen. 2. Take the initiative to understand and get what you need to be effective. 3. Do it yourself if others aren't responding. Rely on yourself, not others.	**Building External Relationships** 1. Create opportunities for networking and interaction. 2. Ask about the needs of other teams. 3. Provide support for other teams. 4. Invite others to team meetings if they might have a stake in what you are doing.

about harmony, lack of tension, and all members liking each other; it is about acknowledging when harmony is false, tension unexpressed, and treating others with respect."

Druskat and Wolff further explained some examples of small changes that really make a difference in all organizations, through the collaboration of individuals. Norms to create and regulate emotions are divided into three levels: interpersonal skills, team management and external strategies. The corresponding tasks are shown in Table 3.[41] Building norms that build trust, group identity and group efficacy is the key for a talented team to optimize its potential and achieve victories regardless of substantial challenges.

CONCLUSION

The emergence of pharmaceutical care provision as a professional mandate has caused many practitioners to ponder deeply over another important aspect of intelligence, the emotional quotient (EQ), in delivering patient-centered care. The potential benefits that EQ training and development brings forward are likely to revolutionize every aspect of pharmacy practice. As the pharmaceutical care delivery becomes more complex and comprehensive over time, EQ is likely to play a differentiating role between star performers and typical performers. In essence, mastering EQ would assist you to better employ your exceptional analytical and intellectual skills, better maintain and develop interpersonal relationships, better create and sustain an atmosphere of interpersonal effectiveness in the workplace, and better counsel your patients.

While other quotients, such as moral quotient (MQ), daring quotient (DQ), financial quotient (FQ), mental quotient (MQ), will quotient (WQ), health quotient (HQ) and spiritual quotient (SQ) are constantly emerging and increasing realized as other important aspects of intelligence, further developing EQ may be the first, yet reasonable and feasible step along the journey to mastering all other quotients, as we gradually shift our focus from gross to subtle, finite to infinite and from tangible to intangible.

As pharmacists who are devoted to never-ending improvements, we should examine seriously the room for exploiting the benefits of EQ in our practice and personal growth.

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Overview on Currently Available Oral Contraceptives

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ABSTRACT

When oral contraceptives (OC) are being taken correctly, its efficacy approaches 99.7%. As most oral contraceptives are over-the-counter drugs in Hong Kong, it is important for pharmacists to understand the administration and safety issues pertaining to the use of OCs and convey thorough and appropriate safety messages to patients as well as to carry out essential screening procedures before the patients start their OC regimens. Pharmacists' counseling on the administration methods, miss-pill management and expected side-effects may enhance patients' compliance with the regimens. In this overview, the basic distinctions between combined oral contraceptive pills and progestin only pills, as well as the second generation and third generation OCs, are discussed. Further, the non-contraceptive benefits of OCs, adverse effects, carcinogenicity, drug-drug interactions and its effects in gestation and lactation periods are discussed. Finally, emphasis is put on different types of emergency contraception where the time of administration after unprotected sexual intercourse is an important determinant of effectiveness. The side effects and roles specific to emergency contraception are also described.

Keywords: *Oral contraceptives, combined oral contraceptive pills, progestin only pills, thromboembolism, The World Health Organization (WHO), emergency contraception*

INTRODUCTION

In Hong Kong, oral contraception, together with female sterilization, was the most popular methods of contraception in the past, but its usage had declined in these few decades. In 1982, the usage of oral contraceptive pills had a usage of nearly 27%, compared with around 8% in 2007.[1]

When oral contraceptives (OCs) are used correctly, their effectiveness approaches that of surgical sterilization.[2] With perfect use, their efficacy approaches 99.7%,[3] but typically the users of OCs may not be able to perform the perfect use of OCs according to the directions; therefore up to 8% of women may experience unintended pregnancy.[2] OCs can either be combined oral contraceptive pills (COCs), which contain a combination of estrogen and progestin, or progestin only pills (POPs).

COMBINED ORAL CONTRACEPTIVE PILLS

The two components in combined oral contraceptives (COCs) are estrogen and progestin. COCs first became available for general clinical use in the United States in 1960 and was then adopted rapidly in other countries.[4,5]

Estrogen suppresses follicular stimulating hormone (FSH) and luteinizing hormone (LH) release from the pituitary, which may contribute to preventing ovulation. However, the primary role of estrogen in COCs is to stabilize the endometrial lining to provide menstrual cycle control.[2]

Progestins in COCs provide most of the contraceptive effect primarily by thickening cervical mucus to prevent sperm penetration, slowing tubal motility to delay sperm transport, and inducing endometrial atrophy to prevent implantation even fertilized eggs have evolved.[2] In addition, progestin component in COCs is believed to be able to antagonize the effects of estrogen on the endometrium and thus reducing the associated risk of endometrial cancer; it is thought (but not proved) that estrogen, when being "unopposed" by progestins, may be responsible for the increased risk of endometrial and breast cancers.[5]

ESTROGENS IN COMBINED ORAL CONTRACEPTIVE PILLS

Estrogen content in combined oral contraceptives (COCs) is generally ethinylestradiol (EE). Most COCs contain estrogen at doses of 20-50 mcg in terms of EE.[2] The low-dose combination OCs currently available are modifications of the earlier pills, containing significantly less EE.[2,4] High-dose formulations are associated with more vascular and embolic events, cancers and significant side effects such as fluid retention, bloating, nausea and vomiting; reductions in EE doses have been associated with fewer side effects.[2]

The World Health Organization (WHO) has advised to use the lowest possible effective dose of OC preparations so as to minimize any potential risks.[5] 20 mcg EE is normally sufficient for contraception and cycle control; therefore they are usually the COCs of choice.[6]

Women weighing more than 90 Kg may have higher contraceptive failure rates with low-dose OCs and may benefit from pills containing 35–50 mcg of EE.[2,7] Women with regular heavy menses initially may also benefit from a higher dose of EE in COC because to suppress their high endometrial activity.[2]

PROGESTIN

Progestins vary in their progestational activity and differ with respect to inherent androgenic effects. Androgenic activity derived from progestins may cause increased appetite, acne and weight gain.[2] Women with oily skin, acne, and hirsutism should be given OCs with lower androgenicity.[2] Table 1 shows same of the COCs available in Hong Kong with their respective amount of EE and progestins in them.

PROGESTIN ONLY PILLS

Table 1. Examples of COCs in Hong Kong and the respective progestins contained						
Products	**Estrogen (mcg)**	**Progestins (mcg)**				
	Ethinylestradiol	Levonorgestrel	Desogestrel	Gestodene	Drospirenone	Cyproterone acetate
Loette®	20	100				
Harmonet®/ Meliane®	20			75		
Mercilon®/ Novynette®	20		150			
Yaz®	20				3000	
Microgynon 30® (ED)/ Nordette-21®/	30	150				
Marvelon®	30		150			
Gynera®	30			75		
Yasmin®	30				3000	
Diane-35®/ Daphne®/ Estelle-35 ED®	35					2000

Progestin only Pills (POPs) tend to be less effective than COCs and are associated with irregular and unpredictable menstrual bleeding.[2] POPs must be taken every day of the menstrual cycle at approximately the same time to maintain contraceptive efficacy. If it is taken more than 3 hours late, a backup method of contraception for 48 hours is needed.[2] POPs achieve contraceptive primarily by increasing thickness of cervical mucus, making sperm penetration difficult and reduce the hospitability of the endometrium for implantation. Since POPs may not block ovulation and nearly 40% of women continue to ovulate with POPs, the risk of ectopic pregnancy is higher with their use than with use of COCs. On the contrary, COCs can provide protection against pregnancy in general, including ectopic pregnancy.[8]

Despite the weaknesses, POPs are still indicated in some high risk women to eliminate the side effects of EE. For example, the WHO stated that women smoking >15 cigarettes per day or smokers <35 years old are contraindicated to COCs due to higher risk of thrombosis.[8] Also, estrogen intake is not recommended for lactating women[8,9] or women who have history of thromboembolic disease, heart disease, cerebrovascular disease or hypertriglyceridemia.[7,8] POPs should be considered for these groups of women.

DIFFERENT GENERATIONS OF PROGESTINS

The current OCs on the market are mainly second and third generation OCs. Second generation OCs almost always include levonorgestral as the progestogen component while third generation OCs contain either norgestimate, desogestrel, gestodene or drospirenone. It is suggested that third-generation OCs contains progestins with reduced androgenic activity. Therefore, third generation OCs are thought to have improved side-effect profiles, such as improving mild to moderate acne.[2] Moreover, same third generation OCs like gestodene are associated with less intermenstrual bleeding compared to the second generation OCs.[10] However, third generation progestogens are associated with a higher risk of thrombosis.[11]

NON-CONTRACEPTIVE BENEFITS OF OCS

Besides providing contraception, OCs also brings about other benefits, such as relieving women from menstruation related problems such as menstrual irregularity and dysmenorrhoea.[12] COCs may also alleviate the symptoms of endometriosis.[8] Lastly, as it may decrease menstrual blood loss and increasing hemoglobin concentrations, it can benefit patients who have iron-deficiency anemia.[8]

ADVERSE EFFECTS

Adverse effects may hinder compliance and therefore efficacy, so they should be discussed prior to initiating a hormonal contraceptive agent. Estrogen excess can cause nausea, bloating, headache and fluid retention; whereas low-dose estrogen COCs can cause early or midcycle breakthrough bleeding and spotting. COCs regimens should be continued for at least 3 months before adjustments are made based on adverse effects.[2]

OC USAGE AND ITS POSSIBLE LONG TERM RISKS

1. Cardiovascular diseases

In the document Medical *Eligibility Criteria for Contraceptive Use*, the WHO has outlined a list of contraindications for using COCs. Cardiovascular diseases which are considered as contraindications of OCs usage includes thrombophlebitis or thromboembolic disorder, cardial vascular diseases, valvular heart disease with thrombogenic complications (e.g., pulmonary hypertension, atrial fibrillation, history of endocarditis), diabetes with vascular involvement (e.g., nephropathy, retinopathy, neuropathy, other vascular disease or diabetes >20 years' duration), uncontrolled hypertension (160 mm Hg systolic or 90 mm Hg diastolic) and thrombogenic mutations (e.g., factor V Leiden, protein C or S deficiency, anti-thrombin III deficiency, prothrombin deficiency).[8]

In U.S. case-control studies, the risk of venous thromboembolism (VTE) in women currently using COCs was four times the risk in non-users.[7,13] Yet, VTE risks associated with OCs use is lower than that incurred during pregnancy. In addition, it is worth noting that superficial venous thrombosis such as varicose veins are not risk factors for deep vein thrombosis (DVT).[8]

COC users who smoke are at increased risk of cardiovascular diseases, especially myocardial infarction, compared with those who do not smoke. Studies also showed an increased risk of myocardial infarction with increasing number of cigarettes smoked per day.[14] Therefore, the WHO recommended that women smokers (>15 cigarettes per day) beyond the age of 35 should not use COCs.

It is desirable to have blood pressure measurements taken before initiation of COCs. Women who did not have a blood pressure check before COC use had an increased risk of acute myocardial infarction and stroke.[15] COC users with adequately controlled and monitored hypertension should be at reduced risk of acute myocardial infarction and stroke compared with untreated hypertensive COC users.[8]

The degree of risk of DVT or pulmonary embolism associated with major surgery varies depending on the length of time that a woman is immobilized. COCs are contraindicated in women who undergo prolonged immobilization with major surgery unless

they are currently taking anticoagulants.[8] An exception is that there is no need to stop OCs prior to female surgical sterilization.

2 Carcinoma

Breast cancer is a hormonally sensitive tumour, and the prognosis of women with current or recent breast cancer may worsen with COC use.[8] Among women with BRCA1 mutations, COC users may also have a small increased risk of breast cancer compared with non-users.[16] However, among COC users with a family history of breast cancer, there was no increased risk compared with non-COC users with a family history of breast cancer.[17]

Among women with persistent human papillomavirus infections, long-term COC use (> 5 years) may increase the risk of carcinoma in situ and invasive carcinoma.[18] Yet, cervical ectropion is not a risk factor for cervical cancer, and there is no need for restriction of combined hormonal contraceptive use.[8]

COCs are contraindicated to acute or chronic hepatocellular diseases with abnormal liver function, cirrhosis, hepatic adenomas, or hepatic carcinomas and the use may enhance the growth of liver tumours. In addition, COCs are metabolized by the liver and their use may adversely affect women whose liver function is compromised.

On the contrary of the above, the use of COCs reduces the risk of developing endometrial cancer and ovarian cancer.

DRUG-OCS INTERACTIONS

1. Anti-infective agents

Rifampin is identified to be able to impair the effects of OCs.[20] However, other anti-infective agents, with the exception of rifampin, have not significantly affected the pharmacokinetics of EE, levonorgestrel and norethindrone;[20] thus the contraceptive effectiveness of OCs was not affected.[19,20] Yet, it is important to note that there are individual patients who show large decreases in the plasma concentrations of EE when they take certain other anti-infective agents, notably tetracycline and penicillin derivatives. Because it is not possible to identify these women in advance, a cautious approach is advised.[20] It is still advisable that users take additional contraception during anti-infective treatments and for 7 days after completing the anti-infective course or having the last episode of vomiting and diarrhea.[20] A list of anti-infective agents with their effects on the plasma concentrations of steroid hormones in OCs is available in Table 2.

2. Anticonvulsants

In addition to some antibiotics, certain anticonvulsants may also interact with OCs and may reduce their effectiveness. This is because they can induce hepatic enzymes which can decrease serum concentrations of the estrogen or progestin component of OCs, or both. A list of anticonvulsants which can reduce serum levels of components in OCs and thus possibly impair the effectiveness of OCs is included in Table 3.

Therapeutic doses of vigabatrin do not induce hepatic enzymes. Nonetheless, a small randomized crossover clinical trial found EE level is lower during vigabatrin use than during placebo use.[7] Although these anti-convulsants can decrease plasma levels of the steroid hormone and some of them are associated with breakthrough bleeding, it is not observed that there is ovulation or accidental pregnancy during their use.[7]

There are other anticonvulsants that do not appear to decrease serum levels of contraceptive steroids in women using OCs and they are listed in Table 3. Although no formal pharmacokinetic data is available, the use of ethosuximide, which does not have enzyme-inducing properties, is not thought to have an impact on steroid levels in OC users.[7]

Some clinicians prescribe OCs containing 50 mcg of EE to women taking liver enzyme-inducing anticonvulsants and other medications that reduce plasma steroid levels; no published data support the enhanced contraceptive efficacy of this practice. Therefore, although the lower the dose of hormones in an OC, the greater the risk a drug interaction will compromise its efficacy; it is not recommended to manage the possible interaction only by increasing the dose of EE.[20] The use of condoms in conjunction with OCs or the use of an IUD may be considered for such women.

3. Anti-depressants

There is potential for drug interactions between certain antidepressant medications and OCs. For example, a clinical trial observed that use of St. John's Wort, a hepatic enzyme inducer, increases progestin and estrogen metabolism as well as breakthrough bleeding and the likelihood of failure of OC regimens.[7] In contrast, an aggregate analysis of randomized clinical trials of fluoxetine for the treatment of depression found that it does not increase pregnancy rates in OC users; efficacy of fluoxetine in treating depression was not affected by OC usage as well.[7] In addition, OC usage does not

Table 2. Anti-infective agents with their effects on the plasma concentrations of steroid hormones in OCs

Anti-infective agent that decreases steroid levels in women taking OCs [20]
Rifampin
Anti-infective agents that do not decrease steroid levels in women taking OCs [7]
Ampicillin
Doxycycline
Fluconazole
Metronidazole
Miconazole
Quinolone antibiotics
Tetracycline

Table 3. Interaction of anticonvulsants and OCs

Anticonvulsants that decrease steroid levels in women taking OCs [7]
Barbiturates (including phenobarbital and primidone)
Carbamazepine and oxcarbazepine
Felbamate
Phenytoin
Topiramate
Vigabatrin
Phenobarbital
Anticonvulsants that do not decrease steroid levels in women taking OCs [7]
Ethosuximide*
Gabapentin†
Lamotrigine†
Levetiracetam
Tiagabine†
Valproic acid
Zonisamide

*No pharmacokinetic data are available.
†Pharmacokinetic study used anticonvulsant dose lower than that used in clinical practice.

increase depressive symptoms in women with depression compared to baseline or to nonusers with depression.[22]

4. Anti-retroviral agents

Data from a number of small studies suggest that the steroid levels in OC users may be altered by the use of various antiretroviral (ARV) medications; ARVs have the potential to either decrease or increase the bioavailability of steroid hormones in OCs. However, as there is no clinical outcome studies, the clinical significance of these pharmacokinetic observations are unknown.[7] Still it is recommended that if a woman on ARV treatment decides to initiate or continue OC regimens, the use of condoms is of high importance for the prevention of HIV transmission and the compensation for any reduction in the effectiveness of the OCs.[8] Table 4 shows the effects on plasma levels of OC steroid and ARV brought by ARV-OC interactions.

It is worth noting that since serum progestin levels during use of POPs are lower than during COCs use, low-dose POPs are not appropriate choices for women using concomitant liver enzyme inducers which can further reduce serum level of the OC steroids.

HORMONE-FREE INTERVAL, WITHDRAWAL BLEEDING AND EXTENDED-CYCLE PILLS

OCs regimen available in Hong Kong usually provide hormones for 21 days, then 7 days of hormone-free interval during which withdrawal bleeding will take place. Another pack of pills should be started immediately after the 7-day hormone-free interval even if the menses is not completed.[2]

In overseas, there is a new trend in the OCs regimen—the extended-cycle pills. They may offer some benefits for patients who are affected by painful menstruation and excess menstrual blood loss. They increase the number of hormone-containing pills from 21 to 84 days, followed by a 7-day placebo phase, resulting in four menstrual cycles per year. One unique product in the U.S. even provides hormone-containing pills daily throughout the year.[23]

SUITABLE AGE GROUP FOR THE USE OF OCS

The WHO deems it safe to use OCs from menarche to the age of 40. Theoretical concerns about the use of OCs among young adolescents have not been substantiated. Beyond the age of 40, the risk of cardiovascular disease increases with age and may also increase with OC use. However, in the absence of other adverse clinical conditions, OCs can be used until menopause.

DISCONTINUING OCS AND THE RETURN OF FERTILITY

The average delay in ovulation after discontinuing OCs is 1-2 weeks, but delayed ovulation is more common in women with a history of irregular menses. Several large cohort and case-control studies show that infants conceived in the first month after discontinuation of an OC had no greater chance of miscarriage or being born with a birth defect than those born in the general population.

PREGNANCY AND BREAST FEEDING

The use of OCs is not required during pregnancy. On the other hand, there is no known harm to the woman, the course of her pregnancy, or the fetus if OCs are accidentally used during pregnancy.[8] However, OCs are contraindicated in breast-feeding women <6 weeks postpartum due to the theoretical concern that the neonate may be at risk due to exposure to steroid hormones during this period. Beyond the 6th week until the 6th month, the use of COCs during breastfeeding diminishes the quantity of breast milk, decreases the duration of lactation, and may thereby adversely affect the growth of the infant.[8]

In addition, before 3 weeks postpartum, there is some theoretical concern regarding the association between OC use and risk of thrombosis in the mother. This risk diminishes when blood coagulation and fibrinolysis are normalized by 3 weeks postpartum.[8]

Table 4. Pharmacokinetic interactions of antiretroviral drugs and COCs [8]

Antiretroviral	Contraceptive Steroid Levels	Antiretroviral Levels
Protease inhibitors		
Nelfinavir	↓	No data
Ritonavir	↓	No data
Lopinavir/ritonavir	↓	No data
Atazanavir	↑	No data
Amprenavir	↑	No data
Indinavir	↑	No data
Saquinavir	No data	No change
Nonnucleoside reverse transcriptase inhibitors		
Nevirapine	↓	No change
Efavirenz	↑	No change
Delavirdine	?↑	No data

ORAL EMERGENCY CONTRACEPTION

Oral emergency contraceptives (EC), also known as the morning-after pills, are used to prevent unwanted pregnancy after unprotected sexual intercourse (e.g., condom breakage, diaphragm dislodging, or sexual assault). It consists of higher doses of steroid hormones than the ordinary OCs.[2]

1. Optimal time in administering EC

EC may prevent fertilized egg from implanting into the endometrium or impair sperm transport and corpus luteum function. However, it will not disrupt the fertilized egg after implantation has occurred. To achieve optimal efficacy, the first dose of the EC regimen should be taken as soon as possible within 72 hours of unprotected intercourse.[24] It was found that the efficacy of EC is greatest when the contraceptive was given during the first 24 hours after unprotected intercourse; efficacy declined during the subsequent 24-hour periods.[25] EC efficacy diminishes as the time period between intercourse and initiation of contraception increases.[26] The effectiveness of EC administered after more than 120 hours has not been established.[26]

2. Different EC regimens

EC regimens can either be employing a combination of estrogen and progestin (the "Yuzpe" regimen) or can be consist of progestin alone when the regimens are initiated within 72 hours of unprotected intercourse.

The progestin-alone EC regimen normally employs levonorgestrel as the active agent, and there can be two administration methods of taking the levonorgestrel. The more traditional way of taking is to take levonorgestrel 0.75 mg stat then the other dose of levonorgestrel 0.75 mg in 12 hours (first dose within 72 hours of unprotective intercourse).[24]

The FDA has approved a newer way of administration, which is to take a single-dose of levonorgestrel 1.5 mg within 72 hours after unprotected intercourse. It

was found to be as effective in preventing pregnancy as levonorgestrel 0.75 mg every 12 hours for 2 doses.[24] Therefore it is a reasonable option, especially in women who may not be compliant with the two-dose regimen.[26]

If it is taken within the 72-hour time frame, the expected pregnancy (failure) rate of 8% (with no contraception) was reduced to approximately 1% with the progestin-only regimen (levonorgestrel 0.75 mg every 12 hours for 2 doses).[27]

3. Side effects

Nausea and vomiting is the most common side effect of EC.[25] Two comparative studies in which women receiving EC with either a "Yuzpe" regimen (levonorgestrel 0.5 mg and 100 mcg EE every 12 hours for 2 doses) or a progestin-only regimen (levonorgestrel 0.75 mg every 12 hours for 2 doses) indicate a lower incidence of nausea or vomiting with the progestin-only regimen.[25,27] In these 2 studies, nausea occurred in 23.1 versus 50.5% and in 16.1 versus 46.5% of women receiving the 2-dose levonorgestrel regimen versus the "Yuzpe" regimen, respectively, while vomiting occurred in 5.6 versus 18.8% and in 2.7 versus 22.4% of women with the levonorgestrel- or e"Yuzpe" regimen, respectively.[25,27] As the levonorgestrel regimen is better tolerated than the Yuzpe regimen, it is generally preferred when being readily available.[26]

If the Yuzpe method is prescribed, antiemetic given 1 hour before taking the EC dose may be warranted. It is needed to repeat the dose if users vomit within 3 hours after taking the dose of either the Yuzpe or levonorgestrel regimen. In addition to nausea and vomiting, many women will experience irregular bleeding regardless of which EC method is used, with the menstrual period usually occurring 1 week before or after the expected time.

4. EC as a contraceptive

Most experts state that there is currently no real contraindication to EC with the recommended regimens and that the benefits generally outweigh any theoretical or proven risk.[26] In addition, the levonorgestrel EC regimen may be used at any time during the menstrual cycle.[24] No current data regarding the safety of repeated use EC are available, but current consensus suggests the risks are low, and women can receive multiple regimens if warranted.[26]

However, even it is found that the levonorgestrel-only regimen would prevent 85% of pregnancies[25] while the Yuzpe regimen would prevent approximately 74% of pregnancies,[28] it is important to note that EC regimens are not as effective as most other forms of long-term contraception [26] Therefore, levonorgestrel for EC should not be used as a woman's routine form of contraception.[24]

In providing patient counseling regarding EC, pharmacists have a key role in providing counseling regarding timing of the dose, common adverse effects, and the use of a regular contraceptive method. It is also vital to counsel the patient that backup barrier methods should be used after EC usage for at least 7 days).[26]

CONCLUSION

Since all combined OCs are similarly effective in preventing pregnancy, the initial choice is based on the hormonal content and dose, preferred pattern of pill use, and coexisting medical conditions. It should be noted that OCs provide no physical barrier to the transmission of sexually transmitted diseases (STDs), including HIV. Male latex condoms are proven to protect against STD; therefore, using this as a physical contraception plus OCs would provide protection against pregnancy and STDs.[8]

In assisting patients to choose the appropriate contraception method, pharmacists should educate patients such that they can have an informed choice. Also, pharmacists should carry out essential screening procedures for administering OCs; act as a knowledge provider about administration methods such as management when missing pills, and finally follow-up for the OCs use as appropriate. Since most of the OCs are not prescriptions only medicine, pharmacists' input is vital as they are the only gatekeepers in ensuring the efficacy and safety of OC usage.

Author's background

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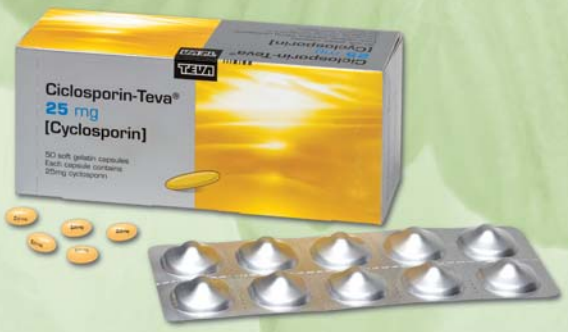

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The Annual General Meeting of the Pharmaceutical Society of Hong Kong

The Annual General Meeting of the Pharmaceutical Society of Hong Kong was held on 18 Dec 2010 at 5.30p.m at the PSHK Club House. The President, Mr. Benjamin Kwong reported on the activities for 2010 and the Treasurer, Mr. Anson Lam reported on the financial standing of PSHK. The General Council (GC) member election began at 6.15p.m. The past year's president and the 3 Pharmacy & Poisons Board Representatives automatically become GC members and 11 General Council members were elected by ballots. Six old GC members and 5 new GC members were elected for the coming term. The meeting was followed by dinner at Majesty Seafood Restaurant 〔金御海鮮酒家〕 at 7.30p.m.

All pharmacists are welcomed to join PSHK. Membership form can be downloaded from the website: **www.pshk.hk/**

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CHAN, Shirley	KWOK, Ritchie	LEE, Chris	YAN, Cadence
Pharmacy & Poisons Board Representatives			
LEUNG, Kenneth	SUEN, Peter	YAU, Rico	

Visit of Editorial Advisory Board Member from Canada

Professor Paul Li, one of the editorial advisory board members of HK Pharm J paid a visit to Hong Kong on December 23, 2010. He stopped by City University of Hong Kong to meet Dr HY Cheung, the editor-in-chief of the journal and gave some suggestions on the publication of the journal. He has promised to encourage his research staffs or students to contribute articles on their research works in this journal. The photo on the right was taken when he and Dr Cheung were having a lunch together.

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2011 Hong Kong Pharmacy Conference
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Programme:

Day 1 (26th February, 2011)

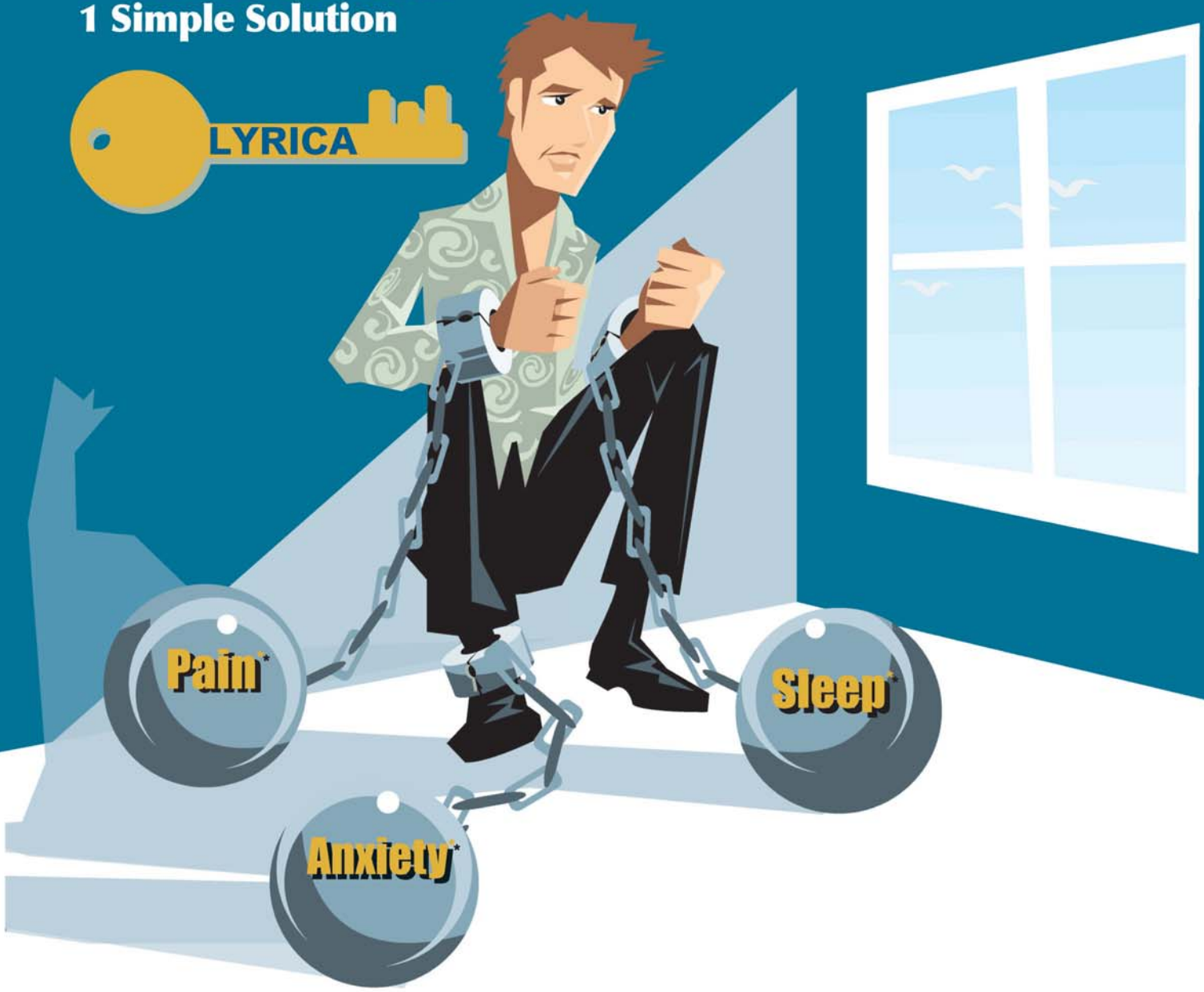
Time	Topics
1:30pm	Registration
2:30pm - 2:40pm	Opening ceremony
2:40pm - 2:50pm	Welcome speech *by the Chairlady*
2:50pm - 3:00pm	Opening Remarks *by Dr. Joseph KL Lee, Counsel Member, Legislative Counsel, HKSAR*
3:00pm - 3:40pm	Theme 1: *Role of Pharmacists in Primary Health Care by Prof. Sian Griffith, Director, School of Public Health, Chinese University of Hong Kong*
3:40pm - 4:10pm	Break, poster and exhibition
4:10pm - 4:50pm	Theme 2: In Search of the Next Ketamine -Emerging Drug of Abuse *by Dr. Man Li TSE, Consultant, Hong Kong Poison Information Centre*
4:50pm -5:30pm	Theme 3: New Expectations of the Modern Age Consumers *by Mr. KP Tsang, Chairman, Alliance for Patients' Mutual Help Organizations*
6:00pm - 6:45pm	Pre-Conference Dinner Symposium
7:00pm - 10:00pm	Conference Dinner

Day 2 (27th February, 2011)

Concurrent Session	I	II	III
Topics	**Information Technology**	**Education**	**Clinical**
8:30am -9:10am	e-Health Records: What Pharmacists are Doing to Make this Happen? *by Ms. SC CHIANG, Senior Pharmacist, Chief Pharmacist Office, Hospital Authority, Hong Kong*	360 Degree Communication with Patients *by Mr. YW SO, President, Hong Kong Society of Hospital Pharmacist & Mr. Donald CHONG, Medical Affairs Manager Pfizer Corporation Hong Kong Ltd.*	Clinical Research Ethics Application & Informed Patient Consent Approval *by Prof. Benny ZEE, Chairman, CUHK-NTEC Clinical Research Ethics Committee; Assistant Dean (Research), Faculty of Medicine, Chinese University of Hong Kong*
9:10am - 9:50am	Pharmacy Informatics & Clinical Intelligence - the Development in China *by Wen Chuanmin, General Manager* （上海大通医药信息技术有限公司）	Pharmacy Law Update *by Mr. Clive CHAN, Department of Health*, HKSAR	Provision of Visiting Pharmacist Service for Residential Care Home for the Elderly *by Mr. Billy CHUNG, Chief Operating Officer, The Hong Kong Pharmaceutical Care Foundation*
9:50am 10:10am	Coffee Break - Poster & Exhibition		
10:10am - 10:50am	Medication Error Reduction – The New Era with the Smart Pump *by Dr. Burnis BRELAND, Director of Pharmacy at Columbus Regional Healthcare System*	Update on the Chinese Medicine Ordinance *by Mr. Frank CHAN, Senior Pharmacist (TCM), Chinese Medicine Division, Department of Health.*	Role of Clinical Pharmacist in Cardiology and Nephrology Teams *by Ms. Min YANG, Deputy Director, Department of Pharmacy, & Ms. Hai Yan LAO, Chief Pharmacist, Department of Pharmacy, Guangdong General Hospital*
10:50am - 11:30am	Drug Intelligence at your Fingertips – Which finger and What Tips? *by Mr. Man Keung NG, Resident Pharmacist, Tuen Mun Hospital, Hong Kong, Mr. Johnny WONG, Pharmacist, Chief Pharmacist's Office, Hospital Authority, and Mr. Kenneth CHUNG, Pharmacist, Queen Elizabeth Hospital, Hong Kong*	Pharmacy curriculum: China Vs HK *by Ms. Xiaoli DU, Pharmacist-in-charge, Peking Union Medical College Hospital, China & Dr. Susan HO, Associate Director of Pharmacy Education, School of Pharmacy, Chinese University of Hong Kong*	Sharing of the Toxicology Detectives to ensure medication safety *by Dr. Albert CHAN, Director, Hospital Authority Toxicology Reference Laboratory and Dr. WT POON, Associate Consultant, Department of Pathology, Princess Margaret Hospital, Hong Kong*
11:30am - 12:30pm	Lunch Symposium		
12:30pm – 2:00 pm	Lunch Poster & Exhibition		
2:00pm -2:40pm	Hospital Accreditation -Inside-out *by Mr. Kim Wah NG, Vice President for Administration, Hong Kong Adventist Hospital*	Primary Health Care – Macau Perspectives *by Ms. Carolina, Ung Oi Lam, Secretary General, The Pharmaceutical Society of Macau*	Paediatric Nutrition *by Mr. Gordon Cheung*
2:40pm -3:20pm	Hospital Accreditation -Outside-in *by Mr. Michael LING, Department Manager, Department of Manager, Kwong Wah Hospital, Hong Kong*	a. 上海世博会药学服务与保障-王斌主任, 复旦大学附属华山医院 b. 广州亚运会药学服务与药房管理-叶丽卡主任, 广州医学院第二附属医院	The Role of Clinical Pharmacist in Paediatric ICU *by Ms. Amanda LI, Clinical Pharmacist, Queen Mary Hospital, Hong Kong*
3:20pm -4:00pm	LEAN management *by Dr. Theresa LI, Chief Manager(Strategy, Planning & Service Transformation)/KCC, Hong Kong*	Student Debate: Should a master degree be the minimal qualifying degree for practicing pharmacists in Hong Kong? Chinese University of Hong Kong vs. University of Hong Kong	Pharmacist's approach to complementary and alternative medicine in cancer treatment – how to make informed decision *by Dr. May LAM, Teaching Consultant, Department of Pharmacology and Pharmacy, University of Hong Kong*
4:00pm - 4:40pm	Drug information: What do Hong Kong People want to know? *by Dr. Celeste EWIG, Instructor, School of Pharmacy, Chinese University of Hong Kong*		Clinical Update on Chronic Myeloid Leukemia by Dr. Raymond WONG, Associate Consultant, Dept of Med & Therapeutics – Division of Haematology, Prince of Wales Hospital

Triad of Neuropathic Pain

3 Different Problems
1 Simple Solution



- **Advanced Treatment for Neuropathic Pain**
  Powerful pain relief as early as after the 1st full day of treatment[1]
- **A New Class for Generalized Anxiety Disorder (GAD)[2]**
  Rapid relief of both psychic and somatic symptoms at week 1[3]
- **Novel Sleep Architecture Benefits**
  Significantly reduced sleep onset latency and increased slow-wave sleep proportion compared with placebo[4]

*Symptoms of neuropathic pain

References: 1. Dworkin RH, et al. Neurology 2003;60:1274-1283. **2.** Riekels K., et al. Arch Gen Psychiatry 2005; 62:1022-1030. **3.** Montgomery SA, et al. J Clin Psychiatry 2006; 67:771-782. **4.** Ian Hindmarch, et al. Sleep 2005; Vol 28, No.2. **Full prescribing information is available upon request.**

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A New Gateway of Treatment

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- Metabolism independent of CYP2D6 pathway in the liver[1-3]
- Low potential for CYP2D6-mediated drug-drug interaction[4]

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PRISTIQ® ABBREVIATED PACKAGE INSERT: TRADE NAME: PRISTIQ® **PRESENTATION:** Pristiq is formulated as an extended-release tablet which contains 76 mg of desvenlafaxine succinate equivalent to 50 mg of desvenlafaxine. Light pink, square (pyramid-one sided) tablet debossed with "W" (over) "50" on one side. **INDICATIONS:** Pristiq is indicated for the treatment of major depressive disorder (MDD). **DOSAGE & ADMINISTRATION:** The recommended dose for Pristiq is 50 mg once at approximately the same time daily, with or without food. Pregnant women during the third trimester, child & adolescent must balance the potential risks with the clinical need; No dosage adjustment in patient with mild renal impairment but the recommended dose in patients with moderate renal impairment is 50 mg per day; The recommended dose in patients with severe renal impairment or end-stage renal disease (ESRD) is 50 mg every other day. Supplemental doses should not be given to patients after dialysis; No adjustment of the starting dosage for patient with hepatic impairment; No dosage adjustment is required solely on the elderly patients but the possibility of reduced renal clearance of Pristiq should be considered when determining the dose. **CONTRAINDICATIONS:** Hypersensitivity to desvenlafaxine succinate, venlafaxine hydrochloride or to any excipients in the Pristiq formulation. Must not be used concomitantly in patients taking MAOIs or in patients who have taken MAOIs within the preceding 14 days. **WARNINGS & PRECAUTIONS:** All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behaviour, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Not approved for use in treating bipolar depression; Serotonin syndrome or NMS-like reactions; Activation of mania/hypomania; Elevated blood pressure & abnormal bleeding; Serum cholesterol & triglyceride elevation; Narrow-angle glaucoma; Renal impairment; Seizure; Hyponatremia; Interstitial lung disease & Eosinophilic pneumonia; New symptoms and serious discontinuation symptoms were reported in discontinuation of treatment; Caution is advised to patients with cardiovascular, cerebrovascular, or lipid metabolism disorders; Co-administration of drugs containing desvenlafaxine & venlafaxine is not recommended. **SIDE EFFECTS:** Most commonly observed adverse reactions in short-term fixed-dose studies were: nausea, dizziness, insomnia, hyperhidrosis, constipation, somnolence, decreased appetite, anxiety, and specific male sexual function disorders. Hypersensitivity, effects on blood pressure, abnormal bleeding, mydriasis, hypomania & mania, serum cholesterol & triglyceride elevation, and seizure were also reported. **INTERACTIONS:** Risk in combination with other CNS-active drugs has not been systematically evaluated and caution is advised; MAOI; Serotonergic drugs; Drugs that interfere with hemostasis; Not increase the impairment of mental and motor skills caused by ethanol but advised to avoid alcohol consumption; Concomitant use with potent inhibitors of CYP3A4 may result in higher concentrations of Pristiq; inhibitors of other CYP enzymes are not expected to have significant impact on the pharmacokinetic profile of Pristiq; Minimal inhibitory effect of desvenlafaxine on CYP2D6; Not inhibit or induce the CYP3A4 isozyme; Not inhibit CYP1A2, 2A6, 2C8, 2C9 & 2C19 isozymes & not expected to affect the pharmacokinetics of drugs that are metabolized by these CYP isozymes; Not a substrate or an inhibitor for the P-glycoprotein transporter; No clinical data establishing the risks and/or benefits of electroconvulsive therapy combined with Pristiq treatment. **PREGNANCY AND LACTATION:** Pregnancy Category C. Carefully consider the potential risks and benefits of treatment when treating a pregnant woman during the third trimester, labor and delivery. Excreted in human milk, breastfeed if the expected benefits outweigh any possible risk. **DRUG ABUSE AND DEPENDENCE:** Not systematically studied in preclinical/clinical studies for its potential for abuse. Physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of Pristiq. Limited clinical experience with desvenlafaxine succinate overdose in humans. **Reference:** W10529C005-HK (04/09) **Date of preparation:** MAY2010 **Identifier number:** PRIS0510 **FULL PRESCRIBING INFORMATION IS AVAILABLE UPON REQUEST.**

References:
1. Dugan SE, Fuller MA. Ann Pharmacother 2004;38:2078-2085.
2. Patroneva A, et al. Drug Metab Disp 2008;36:2484-2491.
3. Preskorn S, et al. J Clin Psychopharmacol 2009;29:39-43.
4. Pristiq® Approved Product Information.
Further information is available upon request.

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Impact of Pharmacist Intervention on Prescribing Acarbose in a Hong Kong Hospital

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ABSTRACT

This study aimed to: (i) evaluate acarbose utilization in Princess Margaret Hospital (PMH) and (ii) compare acarbose prescribing compliance rates between the control and intervention group in cases failing to achieve HbA1c < 8% within 8 months according to Hospital Authority Drug Formulary (HADF) operation guidelines. The study was conducted at PMH during: (i) May 2006 to December 2007 as the control group and (ii) May 2007 to December 2008 as the intervention group. In the intervention group, educational bulletins and pharmacist written feedback notes were given to prescribers. Acarbose utilization pattern and impact of pharmacist intervention on acarbose prescribing were evaluated. A total of 273 subjects aged 64.8±12.2 were reviewed. Acarbose was used as an add-on therapy in 99% of subjects. Subjects achieving HbA1c goal during acarbose use was significantly higher in the intervention group than the control group (50.3% vs 33.3%, p=0.011). The HbA1c level during acarbose use was significantly lower in the intervention group compared to the control group (8.3±1.6(%) vs 9.0±1.8(%), p=0.002). Among those non-compliant cases, over 80% documented that "patient refuses insulin therapy" as the reason. A total of 57/174 (32.8%) subjects in the intervention group were intervened by sending pharmacist written feedback notes to prescribers. The response rate to the pharmacist written feedback notes was 80.7%. Acarbose was discontinued in 132.6% subjects according to pharmacist recommendation. Hence, it is concluded that the HbA1c was better controlled in the intervention group and could be attributed to pharmacist intervention to improve physicians' awareness of HADF guidelines.

Keywords: *acarbose, clinical pharmacy, drug utilization review, diabetes*

INTRODUCTION

One in 10 people has diabetes mellitus in Hong Kong.[1] The prevalence ranges from 2% in people younger than 35 years of age to more than 20% in those older than 65 years.[1] Due to insufficient local funding policy and health insurance system, the majority of diabetes patients are managed in public health sector.[2] Type 2 diabetes mellitus contributed in 2004 up to 3.9% of the total Hong Kong healthcare expenditure and 6.4% of the Hong Kong Hospital Authority's (public sector) expenditures on health.[3] In addition to lifestyle modifications, medication therapy is the mainstream of management in achieving optimal glycemic control, and this imposes a heavy economic burden on the public health care system.[2-9] In an effort to promote evidence-based, cost effective and rational drug utilization, the Hospital Authority Drug Formulary (HADF) was developed and implemented at the local public hospitals in July 2005.[10]

Acarbose, an alpha-glucosidase inhibitor, is 15 times more costly than the first line oral anti-diabetic agents, sulphonylureas and metformin. Acarbose accounts for a total yearly drug expenditure of HK $730,000 in the Princess Margaret Hospital (PMH). A number of studies showed that monotherapy with acarbose is less effective in lowering HbA1c level than metformin or sulphonylureas alone.[9,11-15] Acarbose is categorized as a special drug in the HADF, which should only be prescribed to patients under the public health care coverage for specific indications.[16-18] The specified indications are as follows: (i) an alternative to insulin after failure of optimal doses of sulphonylurea and metformin or (ii) an alternative to insulin after optimal dose of sulphonylurea if metformin is intolerable or contraindicated, and should be discontinued if HbA1c level less than 8% cannot be achieved within 6-8 months.[16] The HADF recommendation is consistent with the international guidelines, which also recommend to adjusting the drug therapy if HbA1c target cannot be met within 6-8 months.[5-9,16,19-25]

The current study aimed to compare the discontinuation rates of acarbose between the control and intervention group in cases failing to achieve HbA1c < 8% within 8 months and evaluate the drug utilization of acarbose in PMH.

METHODOLOGY

The study was conducted in PMH, a 1400-bed major acute public hospital in Hong Kong. There were two recruitment periods: (i) From May to December 2006 - Period A and (ii) From May to December 2007- Period B. Type 2 diabetes adult patients who were initiated with acarbose during the two recruitment periods and had their diabetes managed in PMH were

included. Subjects recruited in period A were the historic control group while those recruited in period B were the intervention group. A historical control was preferred to a parallel control in this study to avoid the potential effect of pharmacist intervention on physicians' prescribing practice in the control group. The same months had been chosen for the two recruitment periods in order to minimize any seasonal effects. The following subjects were excluded: (i) subjects with acarbose prescribed as self financed item, (ii) subjects defaulted follow-ups or died during the study periods.

The non-compliant cases were defined as cases in which (i) HbA1c target less than 8% cannot be achieved within eight months of acarbose initiation and (ii) acarbose has not been discontinued until the end of year 2007 and 2008 in the control group and intervention group respectively. Electronic patient medical records of all recruited subjects were reviewed. The intervention period was from May to September 2008. Pharmacist intervention in form of written feedback notes to physicians was made for the non-compliant cases in the intervention group. The feedback note included recommendations for discontinuation of acarbose (if patients insist to continue acarbose, physicians can prescribe it as a self-financed item) and therapy adjustment according to the international guidelines.[5-9,19-25] In case the physicians insisted on continuation of acarbose, they were advised to state the reasons on either the feedback notes or the electronic medical records.

Physicians were informed of this study in May 2008 prior to the implementation of the intervention program. A drug bulletin was also given to physicians for educational purpose. During the intervention period, feedback was given to the physicians in form of written notes. The feedback note was attached to the patient medical charts. Targets intervened were those cases which continued acarbose despite failure to achieve HbA1c less than 8% within 8 months. The HADF compliance rates between the intervention group and the control group were compared statistically using chi-square test. The compliance rate was measured in terms of discontinuation rate of acarbose in cases failing to achieve HbA1c less than 8% within 8 months. The drug utilization pattern of acarbose was presented in form of descriptive statistics as mean + / - SD. Unpaired t-test was used if the continuous data had a normal distribution while Mann Whitney's test was used if not. Chi-square test was used in categorical data when the expected frequencies for each category was at least 1 and no more than 20% of the categories had expected frequencies of less than 5. Otherwise, fisher's exact test was used.[26, 27] P value <0.05 was regarded as statistically significant. Statistical analysis was conducted by the SPSS 13.0 software (SPSS, Chicago, Illinois, USA).

RESULTS

The demographic data of the total 273 subjects was summarized in Table 1. Out of the 273 subjects, 99 (36%) of them were included in the control group and 174 (64%) were included in the intervention group. There were no significant differences (p>0.05) in the demographic data for subjects in the two study groups except smoking status as ex-smokers (p=0.042) and the co-morbidities involving proteinuria (p=0.004) and cerebrovascular disease. (p=0.027)

Metformin was the most common antidiabetic agent used concurrently with acarbose followed by gliclazide in both groups (Table 2). There were 71/99 (71.7%) and 132/174 (75.9%) subjects used metformin concurrently with acarbose, followed by 68/99 (68.7%) and 113/174 (64.9%) subjects used gliclazide in the control and intervention groups respectively. There were no significant differences in the concurrent use of antidiabetic agents between the control and intervention group. (p>0.05)

Table 1. Demographic Characteristics of Subjects Included in the Study

	Number of subjects (%)		p-value
	Control Group (n=99) (%)	*Intervention Group (n=174) (%)*	
Gender			0.773
Male	53 (53.5%)	90 (51.7%)	--
Female	46 (46.5%)	84 (48.3%)	--
Age *(Mean ± S.D.)*	63.7 ± 12.3	65.5 ± 12.2	0.251
Smoking status			
Non-Smokers	55 (55.6%)	84 (48.3%)	0.313
Smokers	11 (11.1%)	14 (8%)	0.453
Ex-Smokers	11 (11.1%)	32 (18.4%)	0.077
Alcohol Consumption			
Non- drinker	30 (30.3%)	64 (36.8%)	0.531
Social-drinker	6 (6.1%)	15 (8.6%)	0.61
Ex-drinker	4 (4%)	1 (0.6%)	0.042
Body Weight (kg) *(Mean ± S.D.)*	64.1± 12.6	63.4 ± 11	0.723
Co-morbidity			
Hypertension	73 (73.7%)	116 (66.7%)	0.224
Dyslipidemia	42 (42.4%)	61 (35.1%)	0.227
Retinopathy	36 (36.4%)	50 (28.7%)	0.192
Proteinuria	29 (29.3%)	26 (14.9%)	0.004
Nephropathy	26 (26.3%)	48 (27.6%)	0.813
Cardiovascular system	24 (24.2%)	48 (27.6%)	0.547
Gastrointerstional system	22 (22.2%)	42 (24.1%)	0.719
Hepatic system	13 (13.1%)	27 (15.5%)	0.592
Neuropathy	11 (11.1%)	12 (6.9%)	0.228
Obesity	9 (9.1%)	16 (9.2%)	0.977
Cerebrovascular system	4 (4%)	21 (12%)	0.027

Table 2. Number of subjects of concurrent antidiabetic agents use with acarbose in the control and intervention groups

Antidiabetic Agents	Number of subjects (%)		Total	p-value
	Control Group	*Intervention Group*		
	(n=99) (%)	(n=174) (%)	(n=273) (%)	
Metformin	71 (71.7%)	132 (75.9%)	203 (74.4%)	0.451
Gliclazide	68 (68.7%)	113 (64.9%)	181 (66.3%)	0.529
Glibenclamide	21 (21.2%)	42 (24.1%)	63 (23.1%)	0.581
Glipizide	3 (3%)	6 (3.4%)	9 (3.3%)	1.000
Tolbutamide	3 (3%)	3 (1.7%)	6 (2.2%)	0.671
Insulin	6 (6.1%)	20 (11.5%)	26 (9.5%)	0.141

Table 3 Acarbose initiation was the most prevalent in the internal medicine unit in both control and intervention groups, which accounted for 61.6% and 69% respectively. More patients in control group were initiated with acarbose by endocrinologist than intervention group (p = 0.003). There was no difference between the 2 groups in other specialties including geriatrics, cardiology, and renal.

Initial acarbose dose of 50 mg three times daily was the most common in both control and intervention group, which accounted for 75/99 (75.8%) and 135/174 (77.6%) subjects respectively. There were no significant differences in the initial acarbose dose between the control and intervention group (Table 4).

There were 54.5% subjects in the control group and 40.8% subjects in the intervention group discontinued acarbose during the corresponding study periods. Among these subjects, the duration of acarbose use was 176 ± 129 days in the control group and 223 ± 139 days in the intervention group. The duration of acarbose use in the intervention group is significantly longer than that in the control group (p=0.036).

Baseline HbA1c levels were documented in 95% subjects in the control group and 93.7% subjects in the intervention group. HbA1c levels during acarbose use were lower than that at baseline in both control and intervention groups and the difference is statistically significant. (p<0.05) Comparing the HbA1c between the control and intervention group, HbA1c level during acarbose use is significantly lower in the intervention group (p=0.002) while no significant differences in HbA1c at baseline and post discontinuation. Baseline fasting blood glucose levels were documented in 66% subjects in the control group and 75.3% subjects in the intervention group. The fasting blood glucose during acarbose use is significantly lower in the intervention group than the control group (p=0.003).

There were total 75 (75.8%) out of 99 subjects in the control group and 144 (82.8%) out of 174 subjects in the intervention group documented whether hypoglycemia episodes occurred during acarbose use. Hypoglycemia episodes occurred in only 4% subjects in the control group and 9.7% in the intervention group which is not significantly different. (p=0.133) while the remaining subjects were documented that no hypoglycemia episodes during acarbose use.

Any documentation of flatulence, bloating or gastrointestinal (GI) discomforts was regarded as presence of GI side effects. Gastrointestinal side effects occurred in 46.3% subjects in the control group which was significantly more common than 25% in the intervention group. (p=0.014) The remaining subjects were documented that no GI side effects occurred during acarbose use. Among the subjects with documented GI side effects, 73.7% subjects discontinued acarbose in the control group versus 66.7% subjects in the intervention group which was not significantly different. (p=0.619)

Out of 174 subjects in the intervention group, 90.2% of them had their HbA1c levels within 8 months of acarbose use documented. There were 78 (49.7%) subjects had HbA1c greater than or equal to 8%. Out of these 78 subjects, 57 (73%) of them did not discontinue acarbose within 8 months and all these subjects were intervened with written feedback notes. Among those 57 subjects in which acarbose was not discontinued within 8 months despite HbA1c greater than or equal to 8%, 15 (26.3%) of them discontinued acarbose subsequently within the study period. For the 73.7% subjects who continued acarbose despite the intervention, 31 (54.4%) of them responded to the intervention by documentation of reasons for acarbose continuation either in the electronic patients records or on the feedback notes. The response rate to intervention was therefore 80.7% (46/57). *"Patient refuses insulin therapy"* accounted for the top reason of discontinuation 26/31 (83.9%) followed by *"Dosage of acarbose has NOT yet been maximized"* and *"Patient waitng for insulin therapy"* which accounted for 3/31 (9.7%) and 2/31 (6.5%) reasons respectively.

Out of the 84 subjects in the control group and 157 subjects in the intervention group with HbA1c during acarbose use documented, 56 (66.7%) subjects in the control group had HbA1c ≧ 8% compared to 78 (49.7%) subjects in the intervention group which is significantly different (p=0.002).

Table 3. Acarbose initiation in different specialties

Specialties	Number of subjects (%)		Total	p-value
	Control Group	*Intervention Group*		
Internal Medicine	61 (61.6%)	120 (69%)	181 (66.3%)	0.217
Endocrinology	20 (20.2%)	14 (8%)	34 (12.5%)	0.003
Geriatrics	9 (9.1%)	21 (12.1%)	30 (11%)	0.449
Cardiology	3 (3%)	10 (5.7%)	13 (4.8%)	0.387
Renal	2 (2%)	2 (1.1%)	4 (1.5%)	0.623
Medical Infectious Disease	1 (1%)	5 (2.9%)	6 (2.2%)	0.422
Others	3 (3%)	2 (1.1%)	5 (1.8%)	0.356
Total	99 (100%)	174 (100%)	273 (100%)	--

Table 4. Acarbose initial dose in the control and intervention group

*Acarbose initial dose	Number of subjects (%)		Total	p-value
	Control Group	*Intervention Group*		
50mg tds	75 (75.8%)	135 (77.6%)	210 (76.9%)	0.73
100mg tds	15 (15.2%)	23 (13.2%)	38 (13.9%)	0.657
50mg bd	8 (8.1%)	12 (6.9%)	20 (7.3%)	0.718
50mg daily	1 (1%)	10 (5.7%)	11 (4%)	--
25mg tds	0 (0%)	3 (1.7%)	3 (1.1%)	--
100mg bd	0 (0%)	1 (0.6%)	1 (0.4%)	--
Total	99 (100%)	174 (100%)	273 (100%)	--

DISCUSSION

Among those subjects with documentation of GI side effects during acarbose use, 46.3% subjects in the control group and 25% subjects in the intervention group. The GI side effects occurrence rate was lower than that reported in the literature which flatulence occurred in 74% patients.[28] The lower occurrence rate observed in this study may not represent the actual occurrence rate as about half of the subjects did not document whether GI side effects were present or not. A study reported that

flatulence was the most common reason for premature discontinuation of acarbose therapy accounting for 9/12(75%) cases.[28] In our study, among the subjects with documented GI side effects, about 70% subjects discontinued acarbose in both groups but the correlation between the GI side effects and acarbose discontinuation rate cannot be established.

The most common acarbose initial dose in this study was 50mg three times daily, which accounted for 75.8% and 77.6% subjects in the control and intervention group respectively. Such initial dose was appropriate according to the recommendation in the product insert.[29] On the other hand, according to literatures, the recommended initial dose of acarbose is 25 mg three times daily with gradual titration to 50 mg three times daily as maintainence dose while the maximum dose is 100 mg three times daily. The "start low, go slow" approach aims to minimize GI side effects.[30-32] The initial dose of 50 mg three times daily instead of 25 mg three times daily being used most commonly in this local hospital can probably be explained by the availability of 100 mg acarbose tablets only which makes administration of 25 mg dose difficult.

There was significantly higher percentage of subjects achieving HbA1c less than 8% during acarbose use in the intervention group than that in the control group. (p=0.011)

The significant difference may be attributed to the increased awareness of the prescribers after the initiation of the intervention regarding the importance of achieving HbA1c level less than 8% within 8 months of acarbose use as stated in the HADF. Several studies had already demonstrated that educational intervention provided by pharmacists was associated with improved prescriber adherence to guidelines.[33-37]

The HbA1c level during acarbose use was significantly lower in the intervention group compared to the control group. (p=0.002) The significant difference may be explained by the increased awareness of prescribers after the intervention by the distribution of education bulletin regarding the importance of achieving target HbA1c recommended by several international guidelines in diabetes patients. HbA1c level during acarbose use was significantly lower than the baseline HbA1c in both control and intervention group. ($p<0.05$) The observed reduction in HbA1c level with acarbose use was consistent with the demonstrated effectiveness of acarbose in lowering HbA1c level in diabetes patients in other studies.[38-42]

In this study, a total of 57 intervention letters were issued. The response rate to the intervention letters was considerably high at 80.7%. Similar studies which also made intervention in an attempt to alter prescribing practice in form of intervention letters had been conducted in Texas and the response rates obtained were 71.2% in one study and 71.5% in the other one.[27,28] The studies in Texas indicated that about 20%-40% responded cases changed the prescribing practice according to the recommendation in the intervention letters. In our study, 32.6% subjects discontinued acarbose according to the recommendation in feedback notes which is consistent with the results found in Texas studies.[27,28] However, comparing with the control group, there was no significant difference in the discontinuation rates of acarbose beyond 8 months of acarbose use within the study period for those subjects with HbA1c not less than 8%. (p=0.754) As a result, acarbose discontinuation during the intervention period could not be concluded to be contributed by the impact of intervention feedback notes.

The intervention in form of written feedback notes did give us clues on the contributing factors to the prescribing non-compliance of acarbose to HADF. More than 80% (26/31) of intervened subjects with continuation of acarbose despite HbA1c $\geqq$ 8% documented that "patient refuses insulin therapy" as the reason for the acarbose continuation.[43] The high percentage of patients refusing insulin therapy was not surprising as high prevalence of diabetes patients were found unwilling to take insulin in other studies with concerns regarding hypoglycemia, permanent need for insulin therapy, less flexibility, and feelings of failure.[43-47] In this study, however, we did not make further intervention to increase patients' acceptance to insulin use and investigate whether increased acceptance rate to insulin use would increase acarbose prescribing compliance to HADF. Further studies may be needed to investigate this correlation with pharmacist intervention by proving education and self-management support to patients which were necessary for patients' decision making regarding insulin initiation.[48]

Prescribers' decision on continuation of acarbose in view of patient's reluctance to insulin use despite contradiction to HADF recommendations may be explained by the prescribers' concern of even worse control on HbA1c if acarbose was discontinued while patient refused to change to insulin or non-compliance to insulin therapy. Research showed that prescribers often delayed modification of the diabetes treatment regimen because they believed their patients would be concerned about starting insulin therapy and patient may be non-adherent to insulin therapy.[44] Another study in US reported that more than half of the patients on oral anti-diabetic agents who could not attain HbA1c less than 8% maintain the therapy for more than 3 years.[45] In spite of prescribers' concerns regarding worsening patient outcomes after discontinuation of acarbose, under the public health care system, the principles of cost-effective drug use and rational utilization of public resources should not be neglected. The HADF is formulated based on the principles of evidence-based medical practice and rational use of public resources aiming to ensure equitable access to cost effective drugs through standardization of drug policy and utilization in all HA hospitals. Prescribers are highly recommended to adhere to the HADF guideline in prescribing. Intervention by education and written feedback notes was not significantly effective to improve their prescribing compliance to HADF as shown in this study. Therefore, more direct actions are warranted to improve their prescribing compliance to HADF, for instance, by direct face-to face intervention which was shown to be more effective than written communications in past research.[49,50]

Limitations

Since the required data was retrieved from patient's medical records, similar to other drug utilization reviews, any discrepancies in interpreting laboratory data and progress notes may directly affect the accuracy of the study.

Besides, missing data due to inadequate documentation is also a typical limitation to retrospective data review. [51] Acarbose initiation between May to December was selected as the inclusion criteria for subject recruitment instead of the whole year due to the limitation of study periods as an academic project. As a result, the acarbose utilization pattern reported in this study may not be generalized to all patients in the local hospital. In addition, the sample size may not be large enough to detect significant difference for other parameter comparisons.

CONCLUSION

This study described the acarbose utilization pattern in the local hospital. Acarbose use significantly lowers HbA1c in this study, which is consistent with the efficacy of acarbose reported in the drug literatures. Besides, the initial acarbose dose and acarbose use as add-on therapy instead of monotherapy in this study are regarded as appropriate according to literature and international guideline recommendations.

This study identified patients' refusal to insulin use as the most common potential contributing factor to continuation of acarbose against HADF recommendation. The high response rate to pharmacist intervention encouraged use of similar intervention in future drug utilization review to identify the potential contributing factors to prescribing non-compliance and evaluate the prescribing practice. The high response rate also revealed that such pharmacist intervention had built up communication between pharmacists and physicians. Besides, the pharmacist intervention may have positive impact on improving physicians' awareness to guidelienss and hence, resulting in the significantly higher proportion of subjects in the intervention group achieving HbA1c less than 8% during acarbose use than the control group.

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Author's background

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Computational Study on the Molecular Inclusion of Indomethacin by *β*-Cyclodextrin for Improving Its Bioavailability

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ABSTRACT

Indomethacin (indo) is an effective non-steroidal anti-inflammatory drug. Yet its poor water solubility affects its bioavailability inside human body. To enhance the bioavailability of indo, inclusion complexation has been applied to modify the physical and chemical properties of the drug. However, no computational study concerning the stability of inclusion complexes formed between indo and β–cyclodextrin (βCD) has been reported yet. In this work, the structures of indo, βCD and their inclusion complexes are calculated at Austin Model 1 (AM1) and Density Functional Theory (DFT) using the STO-3G basis set. Four inclusion complexes between indo and βCD have been constructed and their relative stability is reported. Atoms-in-Molecules (AIM) analyses based on the B3LYP/cc-pvdz wave function are used to verify the existence of the intermolecular hydrogen bonds. It was found that the most stable complex among the four inclusion complexes was the one formed with the inclusion of methoxy phenyl moiety of indo and βCD at 1:1 ratio. Our pioneer study provided valuable information about the inclusion mechanisms and dynamics of indo and βCD in order to enhance the bioavailability of the drug.

Keywords: *indomethacin, β-cyclodextrin, molecular inclusion, computational study, hydrogen bonding, bioavailability*

INTRODUCTION

Indomethacin (indo), also known as 1-(p-chlorobenzoyl)-5-methoxy-2-methyl-indole-3-acetic acid is a non-steroidal anti-inflammatory drug commonly used to reduce fever and pain. It can effectively cure rheumatoid arthritis while acts as a non-selective inhibitor of cyclooxygenases (COX) 1 and 2,[1-4] despite its adverse effects, including damage to the gastrointestinal tract [5] and kidney.[6,7]

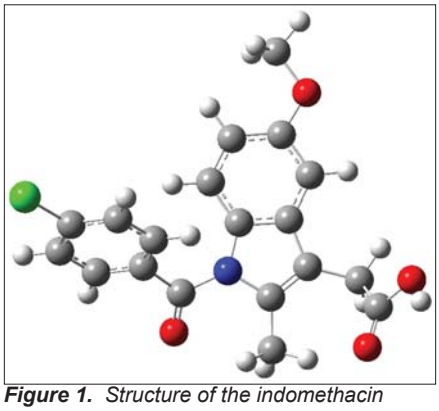

Figure 1. *Structure of the indomethacin*

However, the water solubility of indo is very poor; lowering the bioavailability, therefore hampering the efficacy of the drug. To overcome this problem, it is very common to apply molecular inclusion techniques as a method to modify the drug's physical and chemical properties, consequently enhancing the drug's efficacy.[8-10] Cyclodextrins are commonly used to form inclusion complexes with hydrophobic molecules to enhance the performance of drugs.[11-14] Many drugs currently available on the market use cylcodextrins to form molecular inclusion complexes, for instances, Brexin tablets from Chiesi Farmaceuti SpA contain piroxian-β-cyclodextrin complex and Nitropen sublingual tablets from Nippon Kayaku contain nitroglycerine – β-cyclodextrin complex.[15]

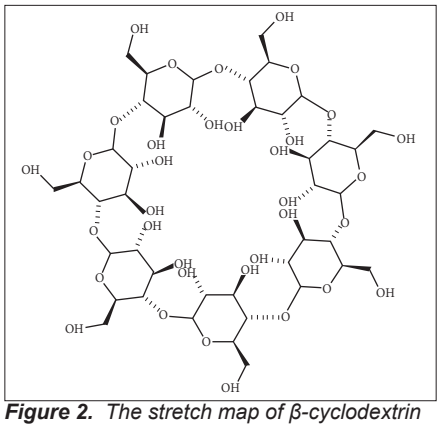

Figure 2. *The stretch map of β-cyclodextrin*

Cyclodextrin are glucopyranosides made up of 6-8 glucose units.[16] β-cyclodextrin is one of the cyclodextrins that consists of seven α-D-glucopyranosides linked together by (α-1,4)-glycosidic bonds with chair conformation. Topologically, cyclodextrins are toroids with two openings with hydrophilic primary hydroxyl groups at the smaller opening end and secondary hydroxyl groups at larger opening end, both are exposed to the external of the toroid. With the circulation hydroxyl groups, the exterior of the toroid is relatively hydrophobic making the cyclodextrin and their inclusion complexes water soluble.[17] Due to the spatial arrangement of the functional groups, the exterior of cyclodextrins is hydrophilic and the interior is hydrophobic in nature. The interior of the toroid is considerably less hydrophilic than the aqueous environment and hence the cavity of the cyclodextrin is very suitable for inclusion of small hydrophobic molecules.[18,19] Hence, cyclodextrins are capable of holding hydrophilic guest molecules and at the same time modify the physical and chemical properties of the drug.[20]

The interactions between cyclodextrins and guest molecules are usually non-covalent in nature.[21-23] Mechanism of release or degradation of cyclodextrins depends on the temperature and pH of the environment by cleavage of the bonds between the guest drug molecules and host cyclodextrins. The α-1, 4 glycosidic bonds between the glucose units are fairly stable in alkaline aqueous solution, but slowly hydrolysed by strong acids. These α-1, 4 glycosidic linkages can be cleaved by means of heating or by enzymatic actions to disrupt the cyclodextrin molecules and release the guest drugs.

In this work, considering the moderate cavity size, acceptable efficiency in drug complexation and availability, complexation between indo and βCD has been analysed. Since the shape of indo is so much larger than the cavity of βCD, it is possible that one (or more) moiety(ies) of the indo inserted into the apolar cavity of βCD rather than included as a whole. According to the results of previous primitive kneading complexation and boiling complexation on 1:1 molar ratio of molecular inclusion of indo and βCD, the successful inclusion complexes have two isomeric forms, the inclusion of p-chlorobenzyl moiety and ether moiety of indo into βCD were observed in Fourier –transform infrared spectroscopy FTIR analysis. Earlier FTIR analysis showed that the characteristic stretching bands of indo were significantly changed in the inclusion complexes, indicating some important chemical properties were significantly changed in the inclusion complexes and some important chemical interactions were taken place. Judging from the changes in absorbance of FTIR, it suggested that molecular inclusion between indo and βCD is highly possible. According to the studies conducted by Szejtli et al in 1980[24] and Beckenfeld et al in 1990,[25] they suggested that the p –chlorobenzyl and carboxylate moieties were encircled by βCD. In this work, their experimental results were verified by theoretical calculations.

Furthermore, the major stability factor of the inclusion complexes was also examined. Previous studies have indicated that the stability of the inclusion complexes contributed from the intermolecular hydrogen bonds formed between the guest and the host molecules. However, these hydrogen bonds have never been studied computationally, our preliminary theoretical study aimed to confirm these intermolecular hydrogen bonds do play an important role in the stability of the inclusion complexes.

COMPUTATIONAL METHOD

For the convenience of discussion, the complexes in which the p-chlorobenzyl moiety of indo encircled by βCD was denoted indo:βCD1, while with the methoxy phenyl moiety encircled by βCD was denoted as indo:βCD2, and with the carboxylate moiety encircled by βCD was denoted indo:βCD3, and finally with the indo associated on the top of βCD was denoted as indo:βCD4. Among the six species being investigated in this work, two were reference control molecules indo and βCD.

In spite of the number of inclusion complexes, their sizes and conformational flexibility make the full geometrical optimization very expensive and difficult to operate in reality. Therefore, theoretical analysis such as Hartee-Fock calculations and Density Function Theory were used to optimize the structures of all six species. In detail, the structures of all six species were optimized first by Austin Model 1 (AM1) method and then further optimized at B3LYP level using STO-3G basis set. The energies and wave functions of all the optimized conformations at B3LYP level using cc-pvdz basis set were subsequently calculated using Gaussian 03 package. The convergence criteria of SCF were set to 10^{-9}. AM1 calculations provided a rough estimation of the possible inclusion conformations, and a brief idea of possible inclusion modes. Density Function Theory B3LYP method with STO-3G basis set is a commonly used minimal basis set, each Slater type orbital STO is approximated by a linear combination of 3 Gaussian type orbital GTO as one-electron wave function. Unfortunately, STO-3G basis set lack the flexibility describing certain complicating molecular environment because it has only one single set of basis function for each type of atomic orbital, also the basis set is atom centred, leading to restricted ability in describing electron distribution between nuclei. Therefore inadequacy in describing intermolecular forces may occur. A larger basis set cc-PVDZ was expected to give better approximations, it was able to approximate the energy of the optimized conformations more precisely, and hence the wavefunction can be used for further investigation on existence of intermolecular hydrogen bonds.

There are two typical methods being used to estimate the intra-, intermolecular hydrogen bonds. One is energy assessment where the hydrogen bond intensity can be measured by the energy difference between the inclusion product and reactants. The other one is by electron density assessment, where the spatial electron density of the region can be used to measure hydrogen bond intensity between the associated atoms. The former one is efficient in calculations of hydrogen bonds if the energy of the molecule is precise. However for large size molecules like Indo:βCD complexes, it is nearly impossible to obtain precise energy, as a consequence unable to estimate hydrogen bond existence. Therefore, electron density assessment was used instead of energy assessment.

“Atoms in molecules” (AIM) is an appealing theory to calculate electron density using the concept of gradient path. It is based on the charge density AIM partition a molecular system and characterizes chemical bonds inside a molecule. The topological properties of hydrogen bonds in the complexes were characterized using the AIM theory of Bader[26] with AIM2000 program package.[27]

AIM is frequently used to analyse the topological properties of molecules and non-covalent interactions[28] in which it characterize the interactions based upon the topology of electron density ρ(r) to partition the molecule into atomic fragments bound by a zero flux surface of the gradient vector field of ρ(r). Electron density is a function consist of 3 spatial coordinates, it can be described in terms of topology, namely maxima, minima and saddle points. Electron density ρ(r) can be characterized by means of three eigenvalues, λi (i = 1, 2, 3), of the ρ(r) Hessian matrix. Critical points (CPs) are named and classified as (r,s) according to their rank, r (number of non-zero eigenvalues), and signature, s (the three eigenvalues algebraic sum). In molecules there are four types of CPs having special interest: (3, -3), (3, -1), (3,

+1) and (3, +3). A (3, -3) CP corresponds to a maximum in ρ(r), characterized by $\nabla^2\rho(r) < 0$ and typically appeared in nuclear positions. A (3, +3) CP or cage critical point is a decreasing of the electronic charge and it is characterized by $\nabla^2\rho(r) > 0$. (3, +1) points or ring CPs, are saddle points. Finally, a (3, -1) point ,also referred as bond critical points (BCPs), is located frequently between two neighbouring nuclei, denoting the existence of a chemical bond between them. BCPs can lie between bonded or non –bonded atoms. BCP is a minimum of electron density along the bond path, however, the BCPs are not necessarily located on a straight line connecting two nuclei, the bond path may be curved, and the degree of bending correlates with strain energy.

Laplacian of electron density $\nabla^2\rho(r)$ identifies whether the charge of the region is locally depleted or concentrated. BCPs with positive $\nabla^2\rho(r)$ typically associated with interaction between closed –shell system, for instance, ionic bonds, hydrogen and van der Waal's interaction. While BCPs with negative $\nabla^2\rho(r)$ characterize covalent bonds. The value of the ρ(r) at BCPs is also correlated with the strength of the bonds. The topological criteria of hydrogen bonds within the AIM formalism have been described in two publications by U. Koch and P. L. A. Popelier et al.[29]

RESULTS AND DISCUSSION

Identification of complex conformations

Austin model 1 (AM1) was used to roughly predict the energies and conformation of indo, βCD and their inclusion complexes.[30] More than 10 possible conformations were proposed in each complexation mode and optimized by AM1. The energies of all possible conformations were lower than the sum of energy of the two constituents alone, indicating the four proposed complexation modes are possible in energy. The optimized conformations were further modified as to maximize stability until the energy of conformations converged.

Energies of complexes

The AM1 optimized structures (two monomers and four inclusion complexes) were further optimized at the level of B3LYP/STO-3G and then followed by single point calculation at the level of B3LYP/cc-pvdz. The energies of the six species and the energy difference (ΔE) between the inclusion complex and its constituents were listed in Table 1 along with the previous obtained AM1 energies. The energy obtained at the B3LYp/sto-3G level is referred as B3LYP/STO-3G energy and energy obtained at the B3LYP/cc-pvdz level is referred as B3LYP/cc-pvdz energy.

Table 1. The AM1, B3LYP/sto-3G and B3LYP/cc-pvdz energies (in au) of the 10 species, the energy difference ΔE (in Kcal mol^{-1}) between the inclusion complex and the two molecules which form the complex

Species	Energy	Complex	Energy	ΔE (in Kcal mol^{-1})
AM1				
Indo	-0.140030	Indo:βCD1	-2.80042	-3.1
βCD	-2.645473	Indo:βCD2	-2.80251	-4.4
Indo +βCD	-2.785503	Indo:βCD3	-2.81202	-10.4
		Indo:βCD4	-2.80135	-9.9
B3LYP/sto-3G				
Indo	-1530.63670	Indo:βCD1	-5749.75491	-39.6
βCD	-4219.05535	Indo:βCD2	-5749.70554	-8.7
Indo +βCD	-5749.69172	Indo:βCD3	-5749.72424	-20.4
		Indo:βCD4	-5749.73042	-24.3
B3LYP/cc-pvdz				
Indo	-1549.58018	Indo:βCD1	-5824.82684	-76.2
βCD	-4275.12529	Indo:βCD2	-5824.83042	-78.4
Indo +βCD	-5824.70548	Indo:βCD3	-5824.80758	-64.1
		Indo:βCD4	-5824.75280	-39.7

The hydroxyl hydrogen on the βCD can rotate freely; their spatial orientations have great effect on the stability and result in very different energy estimation. Before these computational calculations were preformed, these hydrogen atoms are directed to nearby oxygen atoms, maximizing intra and inter molecular hydrogen bond formation, especially for the hydrogen atoms inside the βCD cavity and enhance the stability of the optimized inclusion complex while avoiding the indo being expelled.

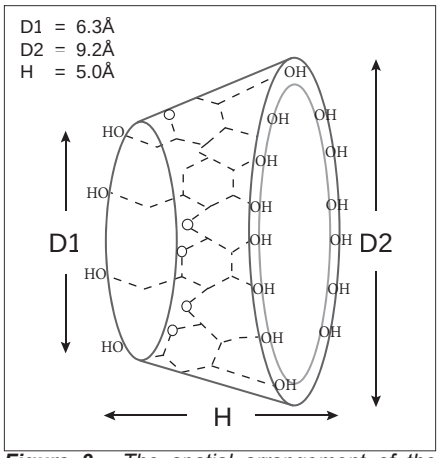

Figure 3. *The spatial arrangement of the glucose units in βCD toroid, the height and inner diameters of the cavity of βCD*

Topologically, βCD has two opening, one is larger, and the other one is smaller, the diameter is about 6.3Å at smaller opening and 9.2Å at larger opening. Encircled guest molecules oriented to a position inside the βCD as to maximize the contact and stabilization by forming non-covalent intermolecular interactions.[31] The whole indo molecule is larger than the diameter of the larger opening, matching the diameter of toroid with the width of the moieties of indo, the three moieties are smaller than the cavity in size, consequently, the entries of these three asymmetric moieties lead to the formation of several structures with different energies,[32, 33] in this aspect, only the one with the lowest energy was studied in each mode.

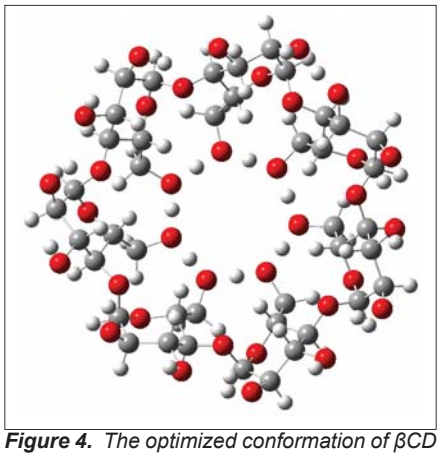

Figure 4. *The optimized conformation of βCD*

The hydrogen atoms of hydroxyl groups at the smaller opening are pointing at the oxygen bonds of the nearby hydroxyl groups, forming a ring of intra-molecular hydrogen bonds, these very strong intra-molecular hydrogen bonds contribute to the stability and shape of βCD, as well as providing the necessary non-covalent interaction with the included moiety.

The energies of all four involved complexes were lower than the energy sums of their constituents energies, demonstrated the ability of βCD to form stable inclusion complexes with indo. The relative stabilities of Indo:βCD complexes can be measured by their stabilizing energy ΔE.[34] The lower the ΔE, the more stable the inclusion complex is. Different methods show some discrepancies in conformations, energies and trend of stability, AM1 method gives longer C-H, C-C, O-H bond lengths while B3LYP method predicts hydrogens delocalized with hydrogen bond formations. AM1 semi-empirical method, also used in other previous study done by M. Pumera,[35] although primitive, is still one of the most convenient way for energy calculations of large size molecules; for example, the inclusion complexes with cyclodextrins.[36,37] The use of the calculations methods such as ab-initio or DFT on the inclusion complex will be very time-expensive because the system consists of 188 nuclei. AM1 is fast enough to make studies of inclusion complexes feasible,[38] even though the energies and structures optimized may not be accurate.

The complexation energies ranged from -39.69 kcal mol^{-1} to -78.40 kcal mol^{-1}. Among the four inclusion complexes, the ΔE of Indo:βCD2 was the lowest, indicating that it was the most stable complex; the ΔE of Indo:βCD4 was the highest, indicating that it was the least stable. The Indo:βCD4 is the least favourable energetically.

With slight derivation in stabilization energies, the inclusion of p-chlorobenzyl moiety and methoxyl phenyl moiety were dominant over the remaining two. The graphic representations of the optimised inclusion complexes show the flexibility of the ring of βCD, in which it could be changed according to the structure of the included moieties. The p-chlorobenzyl moiety was tangential to methoxyl phenyl moiety spatially; fit in either one of them left the other one associate near the smaller opening of βCD. The stabilization of these two complexation modes depended on the interaction between the included moiety and the βCD cavity as well as the interaction between the other moiety and the hydroxyl groups at the opening of βCD .

Based on the results, we can conclude that the methoxy phenyl moiety of indo was preferred in the inclusion inside βCD and the major contribution to the stability of Indo:βCD 2 was deduced to be the formation of intermolecular hydrogen bonds and this will be verified in latter section.

Hydrogen bonds in inclusion complexes

According to R. F. W. Bader, the quality of the AIM topological analysis of the electronic density depends highly on the quality of the wavefunction from which it is derived. Similar works included a work done by N. Singh which used B3LYP/6-31G calculated wavefunction to preform AIM.[39] Although it would be problematic to analyse hydrogen bonding using basis set with the absence of diffuse functions, we tried to use the wavefunction obtained at the theoretical level of B3LYP/cc-pvdz.

Hydrogen bonds inside the four 1:1 Indo:βCD complexes were identified using AIM 2000 program with all default options, the number of bond critical points BCPs, covalent bonds CVP and hydrogen bonds were listed in Table 3.

There are basically 3 types of hydrogen bonds identified by AIM. The first type is normal hydrogen bonds HB in form of X-H…Y, typically formed when partially positive hydrogen atoms associate with electronegative atom Y, X-H act as a Lewis acid awhile the Y act as Lewis base., this type of typical hydrogen bonds can be characterize

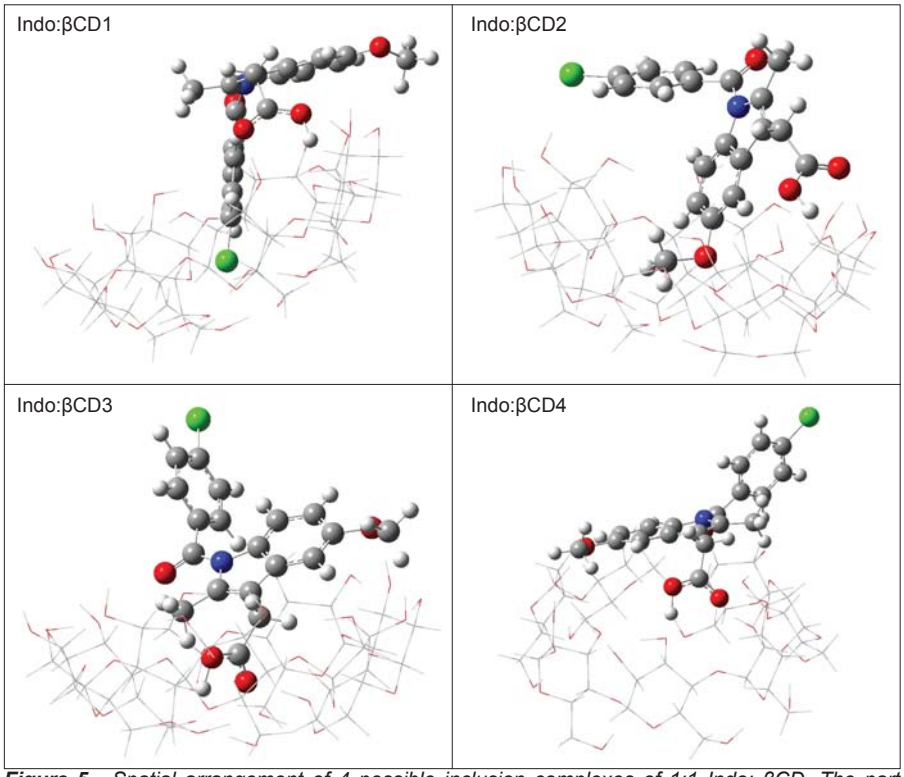

Figure 5. *Spatial arrangement of 4 possible inclusion complexes of 1:1 Indo: βCD. The part represented by wire frame is β-cyclodextrins and the part represented in ball –and –socket is indo*

Table 2. The assignment of the atomic labelling in the complexes

	Indo:βCD1	Indo:βCD2	Indo:βCD3	Indo:βCD4
βCD	1-147	1-147	1-147	1-147
Indo	148-188	148-188	148-188	148-188

Table 3. Count of bond critical points, covalent bonds and hydrogen bonds in the inclusion complexes.

	BCP	CVP	HB	Hydrogen Bond Character		
				Intermolecular	Cyclodextrin	Indomethacin
Indo:βCD 1	250	206	44	18	24	2
Indo:βCD 2	248	202	46	14	29	3
Indo:βCD 3	249	201	48	20	25	3
Indo:βCD 4	238	204	34	11	20	3

BCP: The total number of bond critical points; CVB the total number of BCP for covalent bonds; HB: the total number of BCP for hydrogen bonds; Intermolecular: the number of HBs between indomethacin and β-cyclodextrin; Cyclodextrin: the number of intramolecular hydrogen bonds inside β-cyclodextrin; Indomethacin: the number of intramolecular hydrogen bonds inside indomethacin.

by a small value in electron density and positive Laplacian of electron density $\nabla^2 \rho(r)$. Di-hydrogen bonds DHB in form of X-H…H-Y, the interaction between partially positively charged and partially negatively charged hydrogen atoms, these dihydrogen bonds process covalency, the Laplacian of electron density $\nabla^2 \rho(r)$ can be negative. The strength of interaction is weaker than typical hydrogen bonds, close to van der Waal's interaction .The major diverse from hydrogen bonds are the dihydrogen bonds have the characteristics of covalent bond. Although very weak electrostatically, the electron density, the Laplacian of electron density $\nabla^2 \rho(r)$ are very small and path length usually longer than typical hydrogen bonds. These di-hydrogen bonds, P. Hobza characterized by a strengthening of the C-H bond (for a C-H hydrogen bond donor), in contrast to proper hydrogen bonds.[40] Strong hydrogen bonds may be partially covalent hydrogen bonds introduced by G. Gilli et al.[41] these hydrogen bonds with small intermolecular distance the covalency of the hydrogen bond increase, the electrostatic interaction become less important. The Laplacian of electron density $\nabla^2 \rho(r)$ could be positive, due to the covalent character.

On the other hand, these hydrogen bonds can be divided into intermolecular hydrogen bonds and intermolecular bonds. The following discussion emphasised on the normal intermolecular hydrogen bonds.

Intermolecular hydrogen bonds in Indo:βCD1

Among the eighteen intermolecular hydrogen bonds in Indo:βCD1, there were four normal hydrogen bonds, the bond path length were in range of 3.4175 -5.5493Å, the electron density were in range of 0.0068-0.0414, correspond to weak closed shell interactions, electrostatically in nature.[42] The proton donors were usually the carbon atom connected to the hydrogen atoms involved in hydrogen bonds. The shortest BPL (3.4175Å) was for C167- H171… O47, with the largest electron density ρ, showing that it was the strongest hydrogen bond among the 6 normal hydrogen bonds. The longest BPL (5.5493Å) was for C23-H101…CL173, with the smallest electron density ρ; it was the weakest among four. There were two hydrogen bonds with the chlorine atom, C23-H101…Cl173 and C29-H108… Cl173; these two bonds were of similar strength and bond path length. The proton acceptors were the chlorine atom while the proton donors were two distinct carbon atoms. These proton donors were all carbon atoms, these hydrogen bonds were not very stable, as the proton donor was not linked to a highly electronegative atom such as oxygen, fluorine atoms, and the degree of charge separation was not high. The p-chlorobenzy moiety was not firmly grasped. Hydrogen of the methoxyl phenyl group was pointing to an oxygen atom of the hydroxyl group at the larger of opening of βCD, an intermolecular hydrogen bonds C157- H158 … O48 was formed. The bond path length was relatively short, about 3.5798Å; the interaction was quite strong as well.

Intermolecular hydrogen bonds in Indo:βCD2

Among the fourteen intermolecular hydrogen bonds, Indo:βCD2 had nine normal hydrogen bonds, the bond path length of the hydrogen bonds were in range of 2.8103-6.5617Å, with the electron density of 0.0011-0.0856, these hydrogen bonds were weak and small positive value of electron density indicated non covalent closed shell interactions. The hydrogen bond O72-H143...O156 had the shortest BPL (2.8103Å), with the largest electron density ρ (0.0856), showing that it was the strongest hydrogen bond. C41-H122...O156 had the longest BPL (6.5617Å) and the smallest electron density ρ, it was the weakest as well. A massive network of hydrogen bonds was formed between the included methoxyl phenyl group and the hydroxyl groups near the smaller opening. There were in total five hydrogen bonds in the methoxy phenyl region, C151-H154...O65, C41-H122...O156, O72-H143...O156, C157-H158...O52 and C157-H160...O62, all together they hold the indo strongly inside the βCD cavity. Carbon centre 157 was a proton donor of two of its hydrogens, formed two hydrogen bonds, C157-H158...O 52and C157-H160...O62; these two hydrogen bonds are of similar bond path length and strength, relatively stronger than the other hydrogen bonds in Indo:βCD2. While the methoxy phenyl oxygen atom acted as proton acceptor of two protons from βCD, two hydrogen bonds O72-H143...O156 and C41-H122...O156 were formed. The hydrogen H154 of the phenyl group also formed a hydrogen bond with oxygen O65. The hydrogen bond with oxygen as proton donor was stronger; besides having a shorter bond path length, the electron density was also larger.

Intermolecular hydrogen bonds in Indo:βCD3

Among the twenty intermolecular hydrogen bonds in Indo:βCD3, nine normal hydrogen bonds were found, the range of bond path length were 2.5171-6.8908Å, the electron density ρ(r) were 0.0021-0.1215, correspond to weak closed shell interactions electrostatically

Table 4. The bond path length BPL in Å, electron density in ρ(r) and Laplacian $\nabla^2 \rho(r)$ of the bond critical points for intermolecular hydrogen bonds in the inclusion complex Indo:βCD1

BCP Number	Proton Donor	HB (BCP)	Bond Path Length BPL	ρ(r)	$\nabla^2 \rho(r)$
52	C 23	H101 … Cl173	5.5493	0.0068	0.0200
58	C 29	H108 … Cl173	5.6159	0.0061	0.0192
89	C 167	H171 … O47	3.4175	0.0414	0.1392
210	C 157	H 158 … O48	3.5798	0.0321	0.1172

Table 5. The bond path length BPL in Å, electron density in ρ(r) and Laplacian $\nabla^2 \rho(r)$ of the bond critical points for intermolecular hydrogen bonds in the inclusion complex Indo:βCD2

BCP Number	Proton Donor	Nuclei	Bond Path Length BPL	ρ(r)	$\nabla^2 \rho(r)$
17	C157	H158...O52	3.4881	0.0378	0.1300
33	C157	H160...O62	3.7571	0.0285	0.0893
43	C41	H122…O156	6.5617	0.0011	0.0048
50	C151	H154...O65	5.5281	0.0039	0.0156
53	O72	H143...O156	2.8103	0.0856	0.1460
103	C3	H79…O182	6.2783	0.0016	0.0076
132	C21	H99... O167	6.5348	0.0020	0.0060
208	O59	H134..Cl173	4.5051	0.0175	0.0484
222	C178	H143... O179	2.8660	0.0772	0.1732

in nature. Seven proton donors were carbon and the remaining two were oxygen. O72-H141…O179 was the strongest hydrogen bond among the 9 normal hydrogen bonds as its BPL was the shortest (2.5171Å) with the largest electron density ρ (0.1215). C20-H151…O58 was the weakest, having the longest BPL (6.8908Å) for, with the smallest electron density ρ (0.0021).A hydrogen bond was formed between O52 and H86, one of the methyl hydrogens, and the proton donor was C184. The methyl hydrogen was pointing to the hydroxyl groups at the smaller opening, as the distance between O52 and H86 is quite large, this hydrogen bond is weak, with 0.0029 electron density ρ(r). The hydrogen atom of the p-chlorobenzyl ring was pointing to the hydroxyl groups at the larger opening, the proton donor was the C165 at the ortho position of the p-chlorobenzyl moiety, having a relatively short bond path length, and the interaction was strong. There were three hydrogen bonds formed between the carboxylic group and the cavity; C175-H176…O70, O67-H141…O179 and C41-H122…O182. The strength of these three hydrogen bonds were O67-H141…O179> C41-H122…O182 > C175-H176…O70. All three hydrogen bonds together made the carboxylic group included very firmly, while the methoxyl group was hanging on the top of larger opening. Two hydrogen bonds O64-H57…O156 and C157- H160…O63 was formed, apparently, these two hydrogen bonds were quite strong electrostatically.

Intermolecular hydrogen bonds in Indo: βCD4

Among the eleven intermolecular hydrogen bonds, nine of them were normal hydrogen bonds in Indo: βCD4. The bond path length were ranging from 2.6145 to 5.8246Å, the electron density were ranging from 0.0511 to 0.1071. The shortest BPL (2.6145Å) was detected with the hydrogen bond formed between the carboxylic oxygen and hydroxyl hydrogen, C21-H134…O183 with the largest electron density ρ, it was the strongest hydrogen bond among the nine normal hydrogen bonds. C151-H160…O68 had the longest BPL (5.8246Å) with the smallest electron density ρ, it was the weakest. These nine intermolecular hydrogen bonds were quite intense, the electron density and the Laplacian of electron density were generally larger than that of other Indo:βCD inclusion complexes. Although having many strong intermolecular hydrogen bonds, it is the least stable, because the distortion of βCD conformation at smaller opening lead to breaking of the intramolecular hydrogen bonds in βCD, the loss of the delocalized hydrogen bond ring resulted in a great drop in stability. The magnitude of stabilization is therefore lowered the resulting inclusion complex is the least very stable.

Table 6. The bond path length BPL in Å, electron density in ρ(r) and Laplacian $\nabla^2\rho(r)$ of the bond critical points for intermolecular hydrogen bonds in the inclusion complex Indo: βCD3

BCP Number	Proton Donor	Nuclei	Bond Path Length BPL	ρ(r)	$\nabla^2\rho(r)$
18	C184	H186…O52	5.8478	0.0029	0.0126
54	C175	H176…O70	6.0032	0.0021	0.0092
56	O72	H141…O179	2.5171	0.1215	0.0264
65	C41	H122…O182	3.7643	0.0270	0.0964
112	C15	H82…O163	3.6705	0.0252	0.0860
125	C20	H151…O58	6.8908	0.0025	0.0088
207	C165	H168…O59	3.3307	0.0452	0.1564
216	O64	H57…O156	3.0331	0.0637	0.1736
236	C157	H160…O63	3.1078	0.0589	0.3648

Table 7. The bond path length BPL in Å, electron density in ρ(r) and Laplacian $\nabla^2\rho(r)$ of the bond critical points for intermolecular hydrogen bonds in the inclusion complex Indo: βCD4

BCP Number	Proton Donor	Nuclei	Bond Path Length BPL	ρ(r)	$\nabla^2\rho(r)$
58	C151	H160…O68	5.8246	0.0051	0.0224
91	C184	H187…O53	3.5728	0.0332	0.1156
140	C152	H155…O44	4.5944	0.0116	0.0392
163	C151	H154…O73	3.1113	0.0583	0.1956
186	O74	H143…O156	3.7741	0.0881	0.1464
197	C20	H133…O183	2.9629	0.0669	0.2008
214	O49	H129…O163	2.7844	0.0857	0.1580
216	C165	H168…O48	2.9526	0.0710	0.2116
222	C21	H134…O183	2.6145	0.1071	0.0816

Comparing the intermolecular hydrogen bonds in the four inclusion complexes, Indo:βCD2 had the largest number of intermolecular hydrogen bonds and the hydrogen bonds were more electrostatically stable. The presence of the intermolecular hydrogen bonds significantly lowers the energy of the Indo:βCD2 and stabilizes the inclusion complex in the lowest-energy conformation.

CONCLUSION

In this work, we carried out AM1 and DFT optimizations on two monomers (indo and βCD) and four (1:1) Indo:βCD inclusion complexes formed. AIM theory of Bader was applied to carry out the topological analyses on the six inclusion complexes, we concluded that: (1) The stabilization energy of Indo:βCD2 is the lowest and it is the most stable among the four inclusion complexes. (2) Indo:βCD2 has more and stronger intermolecular hydrogen bonds than the others. (3) Topological analyses of Indo:βCD2 showed that the methoxy phenyl group was included into the hydrophobic cavity of βCD, while the hydrophilic carboxyl and p-chlorobenzyl moiety are preserved for increasing the solubility of inclusion complex in aqueous solution.

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Author's background

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Great News ....

Continuing Education Units (CEUs) for Authors of Articles in the HKPJ. At the most recent meeting of the Pharmacy Central Continuing-education Committee (PCCC), it was decided that CEU would be awarded to authors of articles published in the HKPJ. For each issue, the Editorial Committee will choose an article from all the published articles in that issue, for PCCC to use for CE purposes. The author(s) is(are) responsible for setting questions for the approved CE article. Primary authors are entitled to receive 6 CEUs and other co-authors of the same CE article are entitled for 4 CEUs granted by PCCC. For details on how to get CEU, please refer to the article named "PCCC Continuing Education Units (CEU) Accrediting System" [HKPJ 2002;11(2):79-80] or visit the PCCC Website at www.pccchk.com

Great news to boost the professional standard and recognition of the contributions to the HKPJ!

Seed Extract of Horse Chestnut (*Aesculus hippocastanum* L., 七葉樹) as Effective Medication for Chronic Venous Insufficiency and Other Health Benefits

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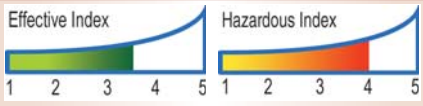
Botanical Name: Aesculus hippocastanum L.
Chinese Name: 七葉樹 [qīyèshù]
Plant Family: Hippocastanaceae
Part Used: Nuts, leaves, flowers, bark, seeds
Other Name: Chestnut, marron europeen, escine, aescin, conker, T'ien-shih-li (Chinese)
Brand Name: BENEX®, EDEVEN™, Venenkraft N™, Venal™, Henna & Horse Chestnut Conditioner™ - Boots, Aesculus Horse Chestnut Tincture™ - *A. Vogel*, VeinFactors™ - *Futurebiotics*

ABSTRACT

For centuries, extracts of horse chestnut (Aesculus hippocastanum), have been used to support vascular functions as a dietary supplement in Europe. Horse chestnut contains a mixture of triterpenoid saponins known as escin or aescin. These compounds have many health benefits like neuroprotective, anti-inflammatory and antitumor effects. The efficacy of horse chestnut seed extract against chronic venous insufficiency (CVI) was confirmed in some clinical trials. However, horse chestnut seed extract (HCSE) should be used cautiously in patients with hepatic or renal impairment. Patients who have bleeding disorders or are anticipating surgery are recommended to avoid taking horse chestnut. This article reviews the different aspects of its health benefits.

Keywords: *Aesculus hippocastanum, neuroprotective, anti-inflammatory, antitumor, chronic venous insufficiency*



Contraindications:
Use with caution in pregnant or breast-feeding patients. Use also cautiously in patients who are hypersensitive to other members of the horse chestnut family and those with bleeding disorders.

Undesirable Effects
Isolated cases of contact dermatitis have been reported. Muscle twitching, weakness, lack of coordination, dilated pupils, vomiting and diarrhea have occurred after taken the extract of horse chestnut.

Interaction with Conventional Drugs
May interact with anticoagulants. When taking aspirin, may increase risk of bleeding because of aesculin

INTRODUCTION

Aesculus hippocastanum L., commonly known as horse chestnut, is one of the most frequently used herbal medicine. It is a member of the Hippocastanaceae family. It belongs in an entirely different botanical family from *Castanea vesca* the well-known sweet chestnut tree. It exists in nature as both a shrub and a tree. It is believed to have originated in the Balkan region of Eastern Europe but is now grown in every country in the Northern Hemisphere. Today, it can be found in all temperate regions of North America, Europe, and Asia. Horse chestnut has 15 recognized species. This includes also the related species Chinese horse chestnut *(Aesculus chinensis)*. The seed is known to have antirheumatic and emetic effects. Its seed is also used in the treatment of contracted limbs due to rheumatism or palsy, and even used to treat stomach aches. Different aspects of this plant are reviewed in this article.

DESCRIPTION AND IDENTIFICATION:

a) Macroscopic appearance

Aesculus hippocastanum (Fig. 1) is a large and tall (about 60 feet in height)

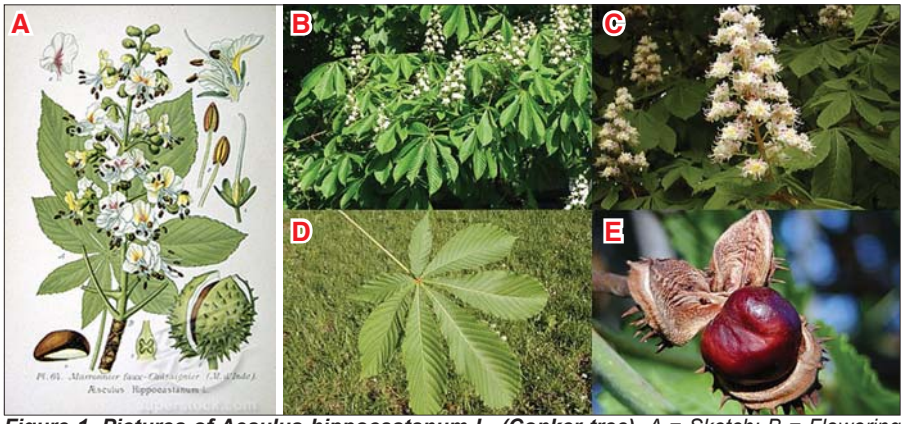


Figure 1. Pictures of Aesulus hippocastanum L. (Conker tree). *A = Sketch; B = Flowering branches; C = Flower; D = Leaf; E = Fruit. (taken from Amedee Masclef Atlas des Plants de France & from photo album of Jirovec-Madal)*

spectacular tree belongs to the Hippocastanaceae family. It has widely spreading branches, forming round or oblong crown. The tree has an erect and columnar trunk, and stout. Old tree normally has outer branches that are curled up. Horse chestnut wood is being of little value for timber because it is soft and spongy.[9]

The arrangement of the leaves of the Common Horse chestnut is opposite; they are made of 5-7 leaflets of 10-25 cm long which spread from a petiole like fingers from the palm. It has sticky substance that covers the buds of the tree, which serves as a protection against winter frosts and dampness.[9]

The Horse chestnut flowers are incredibly beautiful erect panicles. Each panicle is made up of 20-50 white flowers having a small red spot. The height of the panicles can be 10-20 cm tall due to a number of flowers in them.[9] They give rise to green, softly spiky capsules of chestnut fruits being pollinated with insects. However, only about 5 of them usually develop on every panicle. One to 3 glossy brown seeds 2-4 cm in diameter are contained in capsules. This is commonly known as “concers”. Each concer is attached to the capsule as a whitish scar at the base.[9]

The tree of the Horse chestnut preferably grows through sandy loam but can grow practically in any type of soil. The trees grow very tall and have a large crown usually in open places. It can tolerate different climatic conditions. It reaches about 35 m in height in the majority of countries of the northern hemisphere.[9]

The name *Aesculus* originated from the word esca, which means food. Its other name *hippocastanum*, may refer to its ability to heal respiratory illnesses of horses and cattle. The small horseshoe-like markings present on its branches may be another possibility where it obtained its name.[10]

The bark is colored grayish brown or grayish green in color. It has corky, elongated, wart-like eruptions with ribbing appearance. It has pinkish brown interior having fine lines running its length. It has very bitter, astringent taste and odorless.[10]

It has dark brown smoothed surfaced nut approximately 2 in (5 cm) in diameter. It is usually polished in appearance except for its dull tan scar which is connected to the seed vessel. It has a light green spine covered coating encasing the chestnuts that drops away before it drops from the tree.[10]

The seeds are somewhat flattened, maybe oval to round with the diameter of approximately 2-4 cm, covered with a dark brown skin, when fresh it appears shiny and have a large roundish brown light spot or scar. A very large embryo with large slightly yellow cotyledons occupies the entire area beneath the skin.[11]

b) Microscopic description

The brown walled polygonal cells that extend radially along the cross section of the seed, arranged in palisade fashion comprise the epidermis of the skin. Many layers of sclerenchymatic cells are found beneath this, with thick coarsely stippled, yellowish to brownish cell walls. It is directly adjoined with a colorless parenchyma rich in intercellular spaces. It consists of a few layers of coarse walled, unclearly stippled cells and a small number of spiral and annular vessels. The colorless, thin walled cells tightly filled with starch and fat comprise the tissue of the cotyledons.[11]

BIOACTIVE CONSTITUENTS

a) Saponin (Aescin/Escin)

According to French pharmacopoeial standard, the plant contains not less than 3% aescin (3–10%; Fig. 2) which is a mixture of saponins. Major glycosides include α- and β-escin. Yoshikawa *et al*. (1999) isolated a new acylated polyhydroxyoleanene triterpene oligoglycosides, escins IIIb, IV, V, and VI and isoescins Ia, Ib, and V, from the seeds of horse chestnut tree *(A. hippocastanum* L.*)*. Their structures were elucidated on the basis of chemical and physicochemical evidence. The four principal saponin constituents, such as escins Ia, Ib, IIa, and IIb, isolated from the seeds of European horse chestnut trees *(A. hippocastanum L., Hippocastanaceae)* were isolated using high performance liquid chromatography (HPLC). Escins were found to be contained only in the seeds.[12]

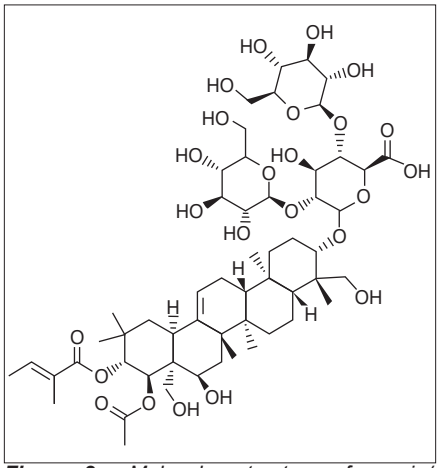


Figure 2. *Molecular structure of aescin/ escin, $C_{55}H_{86}O_{24}$; MW = 1131.26 g mol^{-1} (primary bioactive constituent in the seed of A. hippocastanum)*

b) Flavonoids

Isolated from the seeds of *A. hippocastanum L.* (Hippocastanaceae) were nine flavonol oligosides of quercetin and kaempferol with glucose, xylose, and rhamnose as sugars. There were five of them which are new compounds (2 trisaccharides, 1 bisdesmoside, a nicotinic and an indolinone hydroxyacetic acid ester of the bisdesmoside). Other Flavonol (kaempferol, quercetin) glycosides isolated included astragalin, isoquercetrin, rutin, and leucocyanidin. (1)H- and (13)C-NMR techniques were used to elucidate their structures.[13] Kapusta et al 2007 isolated the main flavonoids from horse chestnut seeds and their structures were established with spectral methods. A new tamarixetin 3-O- [β-d-glucopyranosyl (1→3)]-O-β-d-xylopyranosyl-(1→2)-O-β-d-glucopyranoside were isolated and identified. Using a new ultraperformance liquid chromatographic (UPLC) method for profiling and quantitation of horse chestnut flavonoids, thirteen compounds were identified in the profile, the acylated forms of the dominant di and triglycosides quercetin and kaempferol occurred in just trace amounts. In the powdered horse chestnut seed, the total concentration of flavonoids was 0.88% of dry matter. After purification on C18 solid phase, the alcohol extract containing 3.46% increased to 9.40% of dry matter. Kapusta *et al*. 2007 also measured the flavonoid profile and their content in the horse chestnut wastewater obtained as byproduct in industrial processing of horse chestnut seeds. It was found out that the total flavonoid concentration in the powder obtained after evaporation of water was 2.58%, while after purification on solid phase, this increased to 11.23% dry matter. Their study concluded that flavonoids are present in a horse chestnut extract in a relatively high amount and have the potential to contribute to the overall activity of these extracts. Industrial horse chestnut wastewater can be used to obtain quercetine and kaempferol

glycosides for cosmetic, nutraceutical, and food supplement industries.[68]

c) Lectin

Using affinity chromatography, 95 mg of lectin per 1 kg of fresh horse chest nut seeds were obtained. It has a molecular weight of 132 KDa and was determined by gel-filtration on tojopearl HW-55. One component with molecular weight of 33 kDa was revealed using SDS-polyacrylamide gel electrophoresis. Disc-electrophoresis was also used and revealed another band in acidic (pH 4.5) and alkaline system (pH 8.9). There was no sugar detected in the lectin. Amino acid composition of the lectin has been determined. Purified lectin did not interact with monosaccharides, but interacted with O-glycans. [14]

d) Sterols

The bark of the horse chestnut has been examined and was found to contain sterols. The most abundant sterols were stigmasterol, alpha-spinasterol and beta-sitosterol.[15]

e) Coumarins

The coumarin constituent of horse chestnut includes aesculetin, fraxin (fraxetin glucoside), and scopolin (scopoletin glucoside).[16]

f) Tannins

Its tannin content is most likely to be condensed in view of the epicatechin content which is formed during hydrolysis of condensed tannins.[16]

g) Other bioactive components

Other constituents include citric acid, phytosterol, allantoin, amino acids (adenine, adenosine, guanine), and choline. [16]

h) Esters of indole acetic acid

Domagalski *et al.* (1987) found out that there were 12 chromatographically distinct esters of indole-3-acetic acid extracted and purified from the liquid endosperm of immature fruits of various species of the horse chestnut *(A. parviflora, A. baumanni, A. pavia rubra, and A. pavia humulis)*. These compounds were purified and characterized as an ester of indole-3-acetic acid and myo-inositol, an ester of indole-3-acetic acid and the disaccharide rutinose (glucosyl-rhamnose) and another compound was partially characterized as an ester of indole-3-acetic acid and a desoxyaminohexose.[17]

PHARMACOLOGICAL EFFECTS

a) Anti-inflammatory/immune modulation

Saponins (aescin) have been documented for their anti-inflammatory actions. It is known to increase venous tone by increasing the vasoconstrictor, prostaglandin F2 alpha. It also acts in the reduction of transcapillary filtration of water and protein. It limits the release of enzymes, which is typically increased in chronic pathologic conditions of the vein and stabilizes cholesterol-containing membranes of lysosomes. It also aids in toning of vein walls and improves vascular resistance.[18] The triterpene glycosides and steroid saponins decrease venous capillary permeability and appear to have a tonic effect on the circulatory system[19] while aesculetin (esculin), a hydroxycoumarin, may have its effect in increasing the bleeding time. The absorption half-life of orally administered aescin is about 1 hour and about 20 hours of elimination half-life.[20]

Both fruit extract and the saponin fraction showed anti–inflammatory activity in rats.[27] The anti-inflammatory effect of total horse–chestnut extract compared to aescin has been reported to be greater in the rat.[27] It was proposed that aescin exerted a 'sealing' effect on capillaries and thereby reducing the number and/or the diameter of capillary pores. It therefore affected the initial phase of inflammation.[27]

In vitro studies showed that HCSE (horse chestnut seed extract) prevented histamine-induced edema of the skin, cerebral edema provoked by cold injury post-ischemic edema of the muscle.[34] Intravenous administration of aescin did not reduce traumatic edema in one study using the rat ear model.[35] However, the increase of vascular permeability induced by acetic acid in mice, histamine in rats, and serotonin in rats was inhibited by aescin.[36] Aescin increased acid protease activity levels and improved the rate of edema resolution and reduced the maximum swelling volume.[37-38] A decreased lymphatic edema occurred among post-mastectomy patients receiving topical 1-thyroxine and aescin (Somatoline®).[39] An increase in hand temperature was observed in patients undergoing hand surgery treated with aescin (Reparil® 10 mg I.V. twice daily for six days).[40] A single application of topical 2% aescin gel decreased tenderness at the site of experimentally induced injection hematomas in a double blind, randomized trial.[41]

b) Anti-exudative

The horse-chestnut saponin aescin is also known as an anti-exudative compound. It induces isolated portal vein contraction in rat and rabbit. Prostaglandins of F alpha type appear to mediate this effect. The stimulation and release of prostaglandins has been demonstrated in isolated lung of the rat known to be generated by aescin. When aescin is perfused through this organ, the release of PGF2alpha is increased as shown in mass-fragmentographic analysis of the lung effluent.[21]

c) Anti-aging

Fujimura *et al.* (2006) found that an extract of horse chestnuts *(Aesculus hippocastanum)* is able to generate contraction forces in fibroblasts. Cell morphology, vasoconstriction, and/or wound healing is determined by contraction forces generated by non-muscle cells, such as fibroblasts. Significant decreases in the wrinkle scores at the corners of the eye or in the lower eyelid skin were observed. Therefore, Fujimura *et al.* (2006) suggest that an extract of horse chestnuts can generate contraction forces in fibroblasts and is a potent anti-aging ingredient. [22] Two percent of solution of synthetic sunscreen incorporated into extracts of horse chestnut seed increased the SPF value.[31] It can be used as a sunblock. In another study by Gasbarro and Vetorello (1992), it was found out that it can reduce cellulite formation after using the test product of a multi- ingredient cream containing aescin.[32]

d) Microcirculatory effects/effects on venous tone/antithrombotic effects

The major microcirculatory effects that have been shown by Wollina *et al.* (2006) are the reduction of capillary filtration rate and improvements in levels of transcutaneous partial pressures of oxygen and carbon dioxide (TcPO(2) and TcPCO(2)) using flavonoids from horse chestnut seed extracts. Their data suggest that there may be some additive effects in the combination of pharmacologic and compression therapy.[23]

Chronic venous insufficiency, edema,

and hemorrhoids were some of the common ailments treated by the extracts of *Aesculus hippocastanum* (horse chestnut) seed. Its principal component beta-escin or aescin is attributed to most of its beneficial effects. Other effects like anti-inflammatory, anti-hyaluronidase, and anti-histamine properties are possessed by beta-escin as suggested by recent studies.[24] The inhibitory effect on the catalytic breakdown of capillary wall proteoglycans is the probable reason of the efficacy of preparations that contain horse chestnut seed extract (HCSE).[25] Suter *et al.* (2006) demonstrated the effectiveness of these preparations through the objective measure of reduction in lower leg edema and the subjective alleviation of leg pain, heaviness, and itching.[4-6, 25]

Contraction studies done by Felixsson *et al*. (2010) showed that horse chestnut extract dose-dependently contracted both veins and arteries, with the veins being the most sensitive (Fig. 3). They also noted that horse chestnut significantly reduced ADP-induced human platelet aggregation. In the presence of ketanserin, a further reduction was seen with the extract. They finally concluded that horse chestnut contraction of both veins and arteries is, at least partly, mediated through 5-HT_{2A} receptors. Another finding was that horse chestnut reduced human platelet aggregation (Fig. 4).[26]

Intravenous aescin (Reparil®) decreased the rate of subclinical thrombosis from 27% to 16% in one controlled study in 200 post-operative patients;[42] however, in postoperative gynecological patients, eight other randomized, controlled studies failed to show any thrombotic prophylactic effect from aescin.[43]

Essaven gel, which contains aescin, heparin and essential phospholipids, decreased pain, edema, warmth and flushing of the involved area with thrombotic inflammation of tibial superficial veins.[44] Vasotonin N forte® (HCSE and mofebutazone) relieved subjective complaints after three weeks of treatment in patients with superficial thrombophlebitis.[45]

Contractions in isolated bovine and human veins were induced by horse–chestnut extract (16% aescin, 0.2 mg/mL) and also aescin (0.1 mg/mL).[27] Isolated canine veins concentration–dependent contractions were observed with a horse–chestnut extract (16% aescin, 5 × 10−4 mg/mL).[27] Increased femoral venous pressure in anaesthetised dogs, and decreased cutaneous capillary hyperpermeability in rats (200 mg/kg, given orally) were observed using standardised extract (16% aescin, 50 mg, given intravenously).[27] Ointments containing HCSE are used topically for hemorrhoids, but there are no data on the transdermal absorption of aescin, or the effectiveness of local HCSE in the treatment of hemorrhoids. [33]

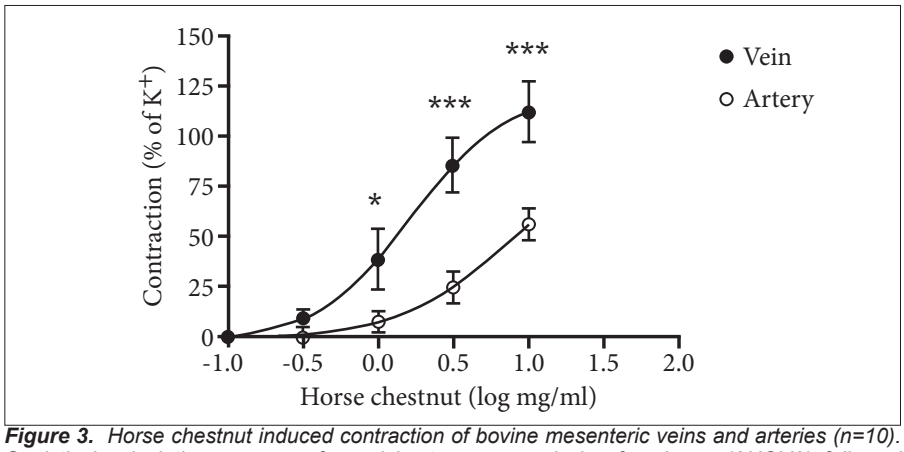


Figure 3. *Horse chestnut induced contraction of bovine mesenteric veins and arteries (n=10). Statistical calculations were performed by two-way analysis of variance (ANOVA) followed by Bonferroni's post test between venous and arterial contraction for each concentration. Significance is denoted as *p<0.05 and *** p<0.001. [Felixsson et al. (2010)]*

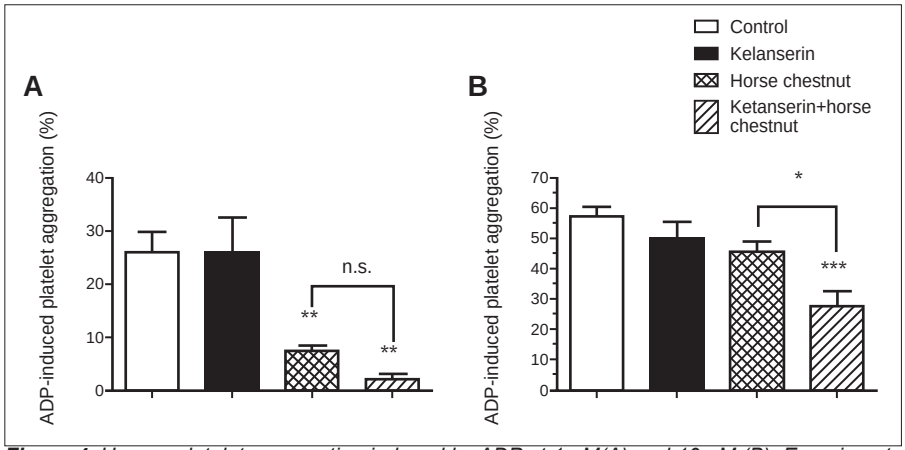


Figure 4. *Human platelet aggregation induced by ADP at 1 μM(A) and 10 μM (B). Experiments were performed with ADP alone (A, n =17; B, n = 18) or together with 1 mg/ml horse chestnut extract (A, n = 10; B, n = 12), 10−5 M ketanserin (A, n = 5; B, n =6) as well as horse chestnut extract (1 mg/ml) and ketanserin (10−5 M) combined (A, n = 5; B, n = 6). Statistical calculations were performed by one-way ANOVA followed by Bonferroni's post-test compared to control. Signifi cance is denoted as n.s. =not signifi cant, * p < 0.05, ** p < 0.01 and *** p < 0.001. [Felixsson et al. (2010)]*

e) Anti-cancer

Patlolla *et al.* (2006) treated HT-29 human colon carcinoma cell lines with various concentrations of beta-escin and analyzed by flow cytometry for apoptosis and cell cycle progression. Their results showed that Beta-escin treatment in HT-29 cells induced growth arrest at the G1-S phase, which was associated with the induction of the cyclin-dependent kinase inhibitor p21(WAF1/CIP1), and this correlated with reduced phosphorylation of retinoblastoma protein. Besides, their results also indicated that beta-escin inhibited growth of colon cancer cells with either wild-type or mutant p53. According to them, this novel feature of beta-escin, a triterpene saponin, may be a useful candidate agent for colon cancer chemoprevention and treatment.[24]

In the study conducted by Tan *et al.* (2010), they found out that β-escin is a novel blocker of STAT3 (signal transducer and activator of transcription 3) activation and therefore may have potential in the suppression of proliferation and chemosensitization in HCC (hepatocellular carcinoma).[2,28] In the study of Harikumar *et al*. (2010), they noted that escin also chemosensitizes human tumor cells through inhibition of nuclear factor-kappa B signaling pathway.[3]

f) Antimicrobial activity

It was found out that Aescin has antiviral activity against *influenza virus*[29] and

has *in vitro* fungistatic activity against *Trichoderma viride* G.[30] Wei *et al.* (2004) isolated two new flavanoids, along with eight known ones through a bioassay-guided fractionation of an ethanol extract of the seeds of *Aesculus chinensis.* Spectroscopic methods including 2D NMR were used in their study to elucidate the structures of the new compounds. Significant antiviral activities on Respiratory syncytial virus (RSV), parainfluenza virus type 3 (PIV 3), and influenza virus type A (Flu A) were demonstrated using the said compounds.[69]

g) Adrenal stimulation/hypoglycemic effects

A 10-fold increase in plasma ACTH and a 20-fold increase in plasma corticosterol levels in rats were attributed to Beta-aescin. However, it did not have an anti-inflammatory effect in adrenalectomized or hypophysectomized animals.[46] The anti-inflammatory effect of aescin may be due to its adrenal stimulating effect.

Glucose absorption was inhibited by oral aescin by suppressing the transfer of glucose from the stomach to the small intestine and by inhibiting the glucose transport system at the small intestinal brush border in glucose-loaded rats.[47] It had neither an insulin- like nor an insulin-releasing activity.[47] Serum glucose levels were not decreased.[47-48] It had an inhibitory effect on ethanol absorption in rats.[47]

h) Neuropsychiatric effects

Treatment with high-dose IV aescin (20 mg every 8 hours for 3 days) caused a significant drop in intracranial pressure (ICP) in patients with pseudotumor cerebri.[49] In another study of Zhang *et al.* (2010), they found out that escin attenuates cognitive deficits and hippocampal injury after transient global cerebral ischemia.[1]

Intravenous treatment with sodium aescinate administered over several days considerably reduced the rise in intracranial pressure, shortened the duration of unconsciousness, and decreased total mortality among accident victims with severe cranio-cerebral trauma. Two to three years of follow-up examinations showed a significantly higher rehabilitation rate in the group treated with aescinate.[50]

Comparison of the use of Apoplectal retard® (a formulation of buphenine, etofylline and HCSE) to placebo in a double-blind trial in geriatric patients suffering impaired cerebral function due to stroke was conducted. There was a significant improvement of cerebral and psychic functions in the group receiving Apoplectal retard (two capsules given three times daily for four weeks) while the placebo group worsened.[51]

i) Antilipemic

Horse Chestnut Seed Extract (HCSE) given to hypercholesterolemic rats lowered serum blood cholesterol in a dose-dependent manner.[52] A related species of common horse chestnut named Aesculus turbinata or Japanese horse chestnut was found to have antiobese effects due to its saponin content in its edible seeds.[70]

j) Antispasmotic effects/ effects on gastric ulcers

Aescin significantly inhibited the increased gastric acid secretion normally induced by histamines and carbachol in rats.[53] Aescin prevented ethanol-induced gastric ulceration in rats; the protective effect was not associated with an increased amount of gastric mucus or glycoproteins.[53] Oral pre-treatment with aescin reduced the number and severity of gastric ulcers induced by pylorus- ligation and absolute ethanol in rats.[54] There is a reversal of the protective effects of aescin in rats upon pretreatment with indomethacin before aescin administration, suggesting an inhibition of prostaglandin biosynthesis.[53-54] HCSE applied to guinea-pig ileum significantly reduced the spontaneous contractions of circular smooth muscle and inhibited acetylcholine and barium chloride- induced contractions of longitudinal smooth muscle.[55]

k) Diuretic

In saline-loaded rats, aesculin had a moderate diuretic effect, significantly increasing the renal loss of sodium, chloride and potassium. Only high doses of aescin had the same diuretic effect as aesculin.[56]

SIDE EFFECTS/ADVERSE EFFECTS/ TOXICITY

a) Hypersensitivity reactions:

Following topical application of horse chestnut seed extract, there were isolated cases of contact dermatitis have occurred.[57] Following IV administration of aescin there was a case of anaphylactic reaction that occurred.[58]

b) Potent toxic constituents in horse chestnut:

Quercetin, quercitrin, rutin, alkaloids, aesculin, saponins, and shikimic acid.[59,71]

c) Acute toxic effects:

Cases of poisoning are rare due to the bitterness of the seed and the large quantity required, although there are few cases of poisoning and death have occurred after ingestion of whole chestnut seeds.[58] Muscle twitching, weakness, lack of coordination, dilated pupils, vomiting, diarrhea, depression, paralysis, and stupor are symptoms of its poisoning.[58] Gastric lavage, activated charcoal, diazepam for spasms, atropine for colic, electrolyte replenishment, and sodium bicarbonate infusions for acidosis are possible treatment for poisoning.[7] It is also necessary to include intubation and oxygen therapy as treatments.[7] Gastrointestinal symptoms, dizziness, nausea, headache and pruritus in 0.9% to 3.0% of subjects are some side effects from therapeutic doses of HCSE in eight placebo-controlled studies.[7] Side effect rates were not significantly different from the placebo group in three of these studies.[7] However, overdose of aescin may be nephrotoxic. Children who received high doses of aescin (two to three times the recommended dose for an average of four days) post-operatively developed acute renal failure.[60] High doses of aescin may contribute to existing nephrotoxicity only if the aescin is displaced from albumin as suggested in animal and *in vitro* studies.[61] In acute toxicology tests in animals, HCSE and aescin had no adverse effects with doses as high as eight times therapeutic levels.[20] Also, Phenopyrazone appears to be responsible for several cases of pseudo-lupus. It is one of the constituents of the drug Venocuran®, which also contains HCSE and cardiac glycoside-containing plant extracts.[62-63] Another adverse effect reported was the case of drug- induced hepatic injury of a man two months after receiving one 65 mg Venoplant® IM injection.[64]

d) Chronic toxic effects:

There are no data on mutagenicity or carcinogenity. No chronic toxic effects, teratogenicity or embryotoxicity from HCSE have shown in animal studies over 34 weeks.[20,65]

e) Limitations:

Hepatotoxicity or nephrotoxicity has not been demonstrated in toxicology studies.[61] HCSE should be used cautiously in patients with hepatic or renal impairment as suggested by some herbalists.[29,71] Patients who have bleeding disorders or are anticipating surgery are recommended to avoid horse chestnut because the constituent aesculin may theoretically increase bleeding times.[66,71]

f) Other herbs or pharmaceuticals interactions:

The antithrombin activity of aesculin, a coumarin derivative is theorized to interact with anticoagulant therapy resulting in increased bleeding time.[29,66] Aescin may affect the binding of other drugs as it binds to plasma protein.[71]

g) Pregnancy and/or childhood safety:

It has not been established the safety of HCSE during pregnancy and lactation.[29] There were neither cumulative effects nor any evidence of embryotoxic or teratogenic effects in animal tests.[65]

DOSAGE AND METHODS OF ADMINISTRATION

a) Availability of standardized preparations

Horse chestnut seed extract is standardized to a triterpene glycoside content of 16-21%, calculated as anhydrous aescin. Controlled release preparations cause less stomach upset than standard forms.[20]

b) Dosages used in herbal combinations

Variable.[8]

c) Proprietary names

Common European preparations include Reparil® (aescin) and Venoplant® or Venostasin® (whole chestnut seed extracts).[60] American brands include GNC Herbal Plus Standardized Horse Chestnut, Nature's Way Standardized Horsechestnut Extract, and Natrol Horse Chestnut, all standardized to 20% aescin. Horse chestnut seed preparations are also available in gels and ointments for external use on varicose veins; European products include Venostasin N® ointment (containing HCSE).

d) Multi-ingredient preparations containing horse chestnut seed extract

Many horse chestnut seed products also contain other ingredients including rutin and B vitamins. The European preparation Veno-Reparil® contains aescin and bioflavonoids. Essaven gel contains aescin, heparin and essential phospholipids.[60] Other products include Apoplectal, Bioglan Fingers & Toes, Bioveinal, Climaxol, Ginkgo Plus, Hemorrogel, and Herbal Capillary Care.

e) Adult doses

Powdered root extract: 250-500 mg of standardized powdered extract three times per day.[20] Most studies have used oral doses of 600 mg per day of HCSE (equivalent to 100 mg/day of aescin), in two divided doses.[8] Beta-aescin is given intravenously in Europe; adult doses are not to exceed 20 mg per day. This preparation is not available in the United States.[60]

Topical use: 1% to 2% aescin gel may be applied several times daily.[60]

Tea: 1-2 tsp. of dried seed infused for 10-15 minutes in 1-2 cups water, drunk three times per day or used as a lotion.[67]

Tincture: 1-4 ml three times per day.[67]

f) Pediatric dosages

Intravenous beta-aescin is used in pediatric patients in Europe. The daily maximum dose of IV beta aescin for children up to three years is 0.1 mg/kg/day; for children ages 3 to 10 years it is 0.2 mg/kg/day.[60]

FUTURE DIRECTIONS

Aesculus hippocastanum was found to have numerous potential uses in the human health supported by several studies mentioned in this review. The different bioactive constituents of this plant may have other health benefits yet to be discovered. No studies were done on its antimicrobial (only a few), pulmonary, rheumatologic, reproductive, nutritional and antioxidant effects. More studies on the contraindication and toxicity of this plant have to be conducted for future reference.

Author's background

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Active Ingredient
Gefitinib

Presentation:
250mg tablet

Pharmacological Properties:
Gefitinib is a selective inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase, commonly expressed in solid human tumours of epithelial origin. Inhibition of EGFR tyrosine kinase activity inhibits tumour growth, metastasis and angiogenesis and increases tumour cell apoptosis.

Indications:
IRESSA is indicated for the first line treatment of patients with locally advanced or metastatic Non Small Cell Lung Cancer (NSCLC) who have activating mutations of the EGFR TK.

IRESSA is indicated for the treatment of patients with locally advanced or metastatic Non Small Cell Lung Cancer (NSCLC) who have previously received chemotherapy.

Dosage & Administration:
The recommended dose of IRESSA is one 250 mg tablet once a day, taken with or without food. If a dose of IRESSA is missed, it should be taken as soon as the patient remembers. If it is less than 12 hours to the next dose, the patient should not take the missed dose. Patients should not take a double dose (two doses at the same time) to make up for a forgotten dose.

The tablet can also be dispersed in half a glass of drinking water (non-carbonated). No other liquids should be used. Drop the tablet in the water, without crushing it, stir until the tablet is dispersed (approximately 10 minutes) and drink the liquid immediately. Rinse the glass with half a glass of water and drink. The liquid can also be administered through a naso-gastric tube.

Patients with poorly tolerated diarrhoea or skin adverse drug reactions may be successfully managed by providing a brief (up to 14 days) therapy interruption followed by reinstatement of the 250 mg dose

Forensic Classification:
P1S1S3

Active Ingredient
Trabectedin

Presentation:
Each vial contains 1mg of trabectedin.

Pharmacological Properties:
Trabectedin is an antineoplastic agent that binds to the minor groove of DNA, bending the helix to the major groove. This binding to DNA triggers a cascade of events affecting several transcription factors, DNA binding proteins, and DNA repair pathways, resulting in perturbation of the cell cycle. Trabectedin has been shown to exert antiproliferative in vitro and in vivo activity against human tumor cell lines and experimental tumors, including malignancies such as sarcoma, breast, non small cell lung, ovarian and melanoma.

Indications:
Trabectedin is indicated for the treatment of patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. Efficacy data are based mainly on liposarcoma and leiomyosarcoma patients.

Dosage & Administration:
The recommended dose is 1.5mg/m² body surface area, administered as an intravenous infusion over 24 hours with a three-week interval between cycles. Administration through a central venous line is strongly recommended. All patients must receive 20mg dexamethasone intravenously 30 minutes prior to trabectedin: not only as anti-emetic prophylaxis, but also because it appears to provide hepatoprotective effects. Additional anti-emetics may be administered as needed.

The following criteria are required to allow treatment: ANC ≥1,500/mm³, platelet count ≥100,000/mm³, bilirubin ≤ ULN, Alkaline phosphatase ≤ 2.5 ULN, albumin ≥ 25g/l, ALT & AST ≤ 2.5 x ULN, Creatinine clearance ≥ 30ml/min, CPK ≤ 2.5ULN and Haemoglobin ≥ 9g/dl. These criteria must be met prior to re-treatment. Otherwise, treatment must be delayed up to 3 weeks until the criteria are met.

Additional monitoring of haematological parameters are recommended weekly during the first two cycles of therapy and at least once between treatments in subsequent cycles.

Contraindications:
Hypersensitivity to trabectedin or to any of the excipients
Concurrent serious or uncontrolled infection
Breast-feeding (during treatment and 3 months thereafter)
Combination with yellow fever vaccine

Precautions:
- Patients must meet specific criteria on hepatic function parameters to start treatment. Active chronic hepatitis must be closely monitored and the dose adjusted if needed. Those with elevated bilirubin must not be treated with trabectedin.
- Creatinine clearance must be monitored prior to and during treatment and patients must not be treated if creatinine clearance is ≤ 30ml/min.
- Grade 3 or 4 neutropenia and thrombocytopenia have been very common. Full blood count should be performed, those who develop fever should promptly seek medical attention.
- If rhabdomyolysis occurs, treatment should be discontinued until the patient fully recovers. Caution should be taken if medicinal products associated with the conditions (e.g. statins), are administered together with trabectedin since the risk is increased.
- Co-administration of trabectedin with potent inhibitors of the enzyme CYP3A4 should be avoided, if this is not possible close monitoring of toxicities and dose reductions is required.
- Concomitant use with phenytoin may reduce phenytoin absorption leading to an exacerbation of convulsions
- Effective contraception during treatment and 3 months thereafter are required for women and 5 months after treatment for men.

Pregnancy:
Trabectedin should not be administered during pregnancy unless clearly necessary. If it is used during pregnancy, the patient must be informed of the potential risk to foetus and be monitored carefully. If used at the end of pregnancy, potential adverse reactions should be monitored carefully in the newborns.

Drug Interactions:
Since trabectedin is metabolized mainly by CYP34A, co-administration of substances that inhibit this isoenzyme e.g. ketoconazole, fluconazole, ritonavir or clarithromycin could decrease metabolism and increase trabectedin concentrations. If such combinations are needed, close monitoring of toxicities is required. Likewise co-administration with potent inducers of this enzyme (e.g. rifampicin, Phenobarbital, Saint John's Wort) may decrease the systemic exposure to trabectedin. Alcohol consumption should be avoided due to hepatotoxicity. Preclinical data have demonstrated that trabectedin is a substrate to P-gp. Concomitant administration of inhibitors like cyclosporine and verapamil, may alter trabectedin distribution and/ or elimination.

Side Effects:
Raised blood creatinine phosphokinase & blood creatinine, decreased blood albumin, weight reduction, neutropenia, thrombocytopenia, anaemia, leucopenia, febrile neutropenia, headache, peripheral sensory neuropathy, dizziness, paraesthesia, dsypnoea, cough, vomiting, nausea, constipation, diarrhoea, stomatitis, abdominal pain, dyspepsia, upper abdominal pain, alopecia, myalgia, arthralgia, back pain, anorexia, infection, hypokalaemia, hypotension, flushing, fatigue, asthenia, pyrexia, oedema, oedema peripheral, hepatobiliary disorders and insomnia.

Forensic Classification:
P1S1S3

CRESTOR™
rosuvastatin
冠脂妥™
妥善控制·冠脂妥

心血管病高危人士*請注意

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Reference : 1. Grundy SM. et al. Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. Circulation 2004; 110:227-239

冠脂妥™ **CRESTOR**™ 化學名稱：瑞舒伐他汀，屬他汀類藥物(STATIN)，適合關注膽固醇人士服用。低密度「壞」膽固醇(簡稱LDL-C)，容易積聚在動脈內壁，令血管變窄。《**美國國家膽固醇教育計劃》建議曾患心血管疾病及有其他高危因素的病人*如高血壓、糖尿病、「好」膽固醇水平較低、家人有早發性心臟病、吸煙、年齡(男性:45歲或以上/女性:55歲或以上)**應把低密度「壞」膽固醇保持於1.8mmol/L以下[1]，能有助減低「壞」膽固醇過高所引致的風險。

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