

HONG KONG PHARMACEUTICAL *JOURNAL*

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News & Short Communications

Chinese Medicine Can Help Realize
the Potential of Four Economic Areas

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Hong Kong Pharmacy Conference 2010
(23 – 24 January 2010) Pharmacist in the
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RECORD 3

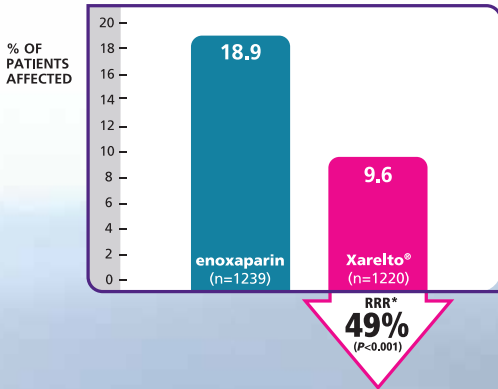
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Reshaping the future of clot prevention**

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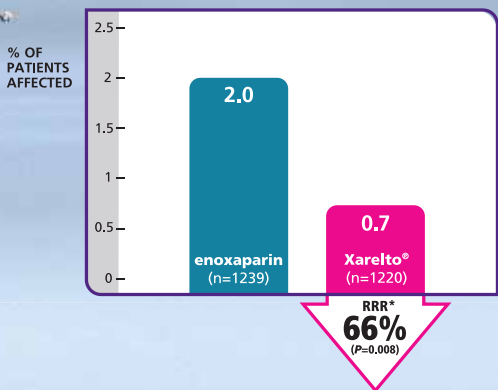
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Study Design:

RECORD3 Study was to compare a once-daily tablet of the direct Factor Xa inhibitor, rivaroxaban, with the current standard of care, enoxaparin, in patients undergoing elective total knee arthroplasty.

- The **primary efficacy end point** was the composite of any deep vein thrombosis (DVT), non-fatal pulmonary embolism (PE), and all cause mortality within 13 to 17 days after surgery.
- **Secondary efficacy end points** included major VTE (the composite of proximal DVT, non-fatal PE, and VTE-related death), and symptomatic VTE.
- The **main safety end point** was the incidence of major bleeding events while on treatment, and up to 2 days post-treatment.

Total VTE: any DVT, nonfatal PE, and all-cause mortality

RECORD = REgulation of Coagulation in major Orthopaedic surgery reducing the Risk of DVT and PE

Reference:

1. Lassen MR, Ageno W, Borris LC, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. N Engl J Med. 2008;358(26):2776-2786.

Abbreviated SmPC

Xarelto 10 mg film-coated tablets.

Composition: Active ingredient: 10 mg rivaroxaban. **Indication:** Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients; clinically significant active bleeding; hepatic disease associated with coagulopathy and clinically relevant bleeding risk, pregnancy and lactation. **Warnings and Precautions:** Treatment with rivaroxaban is not recommended in patients: - concomitantly treated systemically with strong concurrent CYP3A4- and P-gp-inhibitors, ie, azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (eg, ritonavir), - with severe renal impairment (creatinine clearance <15 ml/min), and due to lack of data: - below 18 years of age, - undergoing hip fracture surgery. The following sub-groups of patients are at increased risk of bleeding and are to be carefully monitored for signs of bleeding complications after initiation of treatment: patients with severe renal impairment (creatinine clearance 15 - 29 ml/min), patients with moderate renal impairment (creatinine clearance 30 - 49 ml/min) **Undesirable effects:** Common: increased GGT, increase in transaminases (incl. increased ALT, AST), anaemia (incl. respective laboratory parameter), nausea, post-procedural haemorrhage (incl. post-operative anaemia, and wound haemorrhage). Uncommon: increase in: lipase, amylase, blood bilirubin, LDH, alkaline phosphatase, tachycardia, thrombocytopenia (incl. platelet count increased), syncope (incl. loss of consciousness), dizziness, headache, constipation, diarrhoea, abdominal and gastrointestinal pain (incl. upper abdominal pain, stomach discomfort), dyspepsia (incl. epigastric discomfort), dry mouth, vomiting, renal impairment (incl. blood creatinine increased, blood urea increased), pruritus (incl. rare cases of generalised pruritus), rash, urticaria (incl. rare cases of generalised urticaria), contusion, pain in extremity, wound secretion, haemorrhage (incl. haematoma and rare cases of muscle haemorrhage), gastrointestinal tract haemorrhage (incl. gingival bleeding, rectal haemorrhage, haememesis, haematuria (incl. blood urine present), genital tract haemorrhage (incl. menorrhagia), hypotension (incl. blood pressure decreased, procedural hypotension), nose bleed, localised oedema, peripheral oedema, feeling unwell (incl. fatigue, asthenia), fever.



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- Society Activities
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- Pharmaceutical Technique & Technology
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- New Products

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A Time to Celebrate and to Reflect



It is my great pleasure to present another issue of the HK Pharm J to our readers. In this issue, there are quite a few exciting news items and good articles that should not be missed.

First of all, the global spread of H1N1 flu in the last few months has generated a lot of queries and questions amongst the public. Being pharmacists, we may be prompted to respond to these questions. Dr Huang has compiled some commonly asked questions and provided health professionals with the most appropriate answers. His article is informative, useful and can be found in page 88. In a recent study conducted by a group of Canadian Doctors, it was revealed that treatment of pandemic flu H1N1 with neuraminidase inhibitors is safe during pregnancy, lactation, and breast-feeding (p. 81).⁽¹⁾ This news is certainly welcome for women and babies as they are the most susceptible patients. However, the best approach to preventing colds and flu infection is to keep our body strong. A report published recently in *Pediatrics* indicated that colds and flu-like problems in kids could be prevented by the daily intake of a probiotic food component in the diet (p. 82). Further studies will be required to confirm these results.

Perhaps, the best and most effective way for handling a health problem is to thoughtfully investigate the etiology of a disease, to compare the pros and cons of a therapeutic agent and to understand the mechanistic action of a drug. Two mini reviews published in this issue exemplify how important they are from these different aspects. Mak's article on one of the adverse reactions to the use of heparin as an anticoagulant requires careful interpretation and proper handling as revealed by recent molecular studies (p. 93). An article written by Leung in page 96 describes how an effective drug has been introduced after the etiology of renal cell carcinoma was revealed, while Cheung and his associates in page 100 systematically demonstrated that whenever chlorhexidine is used for

disinfection, different types of microbes are attacked differently by the chemical. These data will definitely benefit drug manufacturers to produce a better formula for disinfectants.

On the other hand, Chinese medicine, which has been applied for more than 4 thousand years by the Chinese, could be a goldmine of novel therapies for human beings and also a driving force behind economic growth if it could be modernized with some incentive schemes from government.⁽²⁾ This speculation is not without foundation as two recent studies on herbal substances have turned out to be economically beneficial (page 82).^(3, 4) Meanwhile, herbal substances to be used as a remedy have also been accepted by the USP Pharmacopeia Convention that has included some standard herbal monographs in the new USP Dietary Supplements Compendium (page 81). Hence, Dr Wong has presented a pledge (p. 85) to our government for proper action in response to these exciting developments in the nearby countries.

The year 2009 is a year of jubilation for the Pharmaceutical Society of Hong Kong. This is because in the October of 1949, when it was still less than a month after the proclamation by Mao Tze-Tung of the liberation of Mainland China by the Communists, an Ordinary Meeting attended by only a dozen of practicing pharmacists was held in Hong Kong in order to form a professional society. The purpose of this society was to promote standards and the interest of pharmacists. And this was the birth of the Pharmaceutical society of Hong Kong. This year will mark the Diamond Jubilee of its inauguration. By the time you receive this copy, members of the society will be ready to celebrate its 60th Anniversary in the form of lecture delivery and banquet dinner at the Hong Kong Jockey Club on Hong Kong Island, followed by a two day conference in January, 2010 (p. 112). If you haven't registered for these special functions, you still have a chance to sign up.

As the society badge says "*Menor et Fidelis*", all pharmacists should devote themselves mindfully and faithfully to their profession. Although throughout its growth, there was a lot of political and social turbulence, we have witnessed that members of the society stuck with these

virtual values and although the path was filled with many stumbling blocks from outside or crises from within, the current status and achievements of this society are actually the result of joint efforts of all members no matter the veteran or the new. Their contribution and devotion deserve our tribute. All these events and person deserve our recognition and acknowledgement at this historical moment. Besides, pharmacy practice and education in Hong Kong will inevitably be influenced by the policy in mainland China after more than a decade of reunification with mainland China. Therefore, "From Today Onwards" is the theme chosen for the 60th Anniversary celebration. As a way to commemorate the 60th anniversary of the founding of the Hong Kong Pharmaceutical Society, we have decided that the next issue will be devoted to recapture and reflect some milestones in modern pharmacy practice and education in the past hundred years in China and in Hong Kong as well as to project their trends in the next twenty to forty years. We will also take this opportunity to express our heartfelt thanks to those who have done so much for so long to promote the growth of this profession in the region.

At the moment of writing this editorial, Chinese people, no matter whether they dwell on mainland China or overseas, are going to celebrate the National day in October. May I take this opportunity to suggest to our people, wherever they are, that we can be proud of our motherland only because we have a government who really cares for people's rights, joy, wealth, harmony, fairness and freedom under rule by law.

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Cheung Hon-Young
 Editor-in-Chief
 31st September, 2009

Infliximab and Other TNF Blockers Linked to Risks for Histoplasmosis and HSTCL

Date: June 3, 2009

Clinicians are reminded that patients receiving treatment with TNF blockers, including infliximab, are at increased risk for the development of serious infections, particularly when receiving concomitant treatment with immunosuppressants such as methotrexate or corticosteroids. In a new section added to the boxed warning, the FDA reports that invasive fungal infections have included histoplasmosis,

coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Healthcare professionals are advised to closely monitor patients for signs and symptoms of potential fungal infection both during and after treatment with anti-TNF drugs. Patients in whom fever, malaise, weight loss, sweats, cough, dyspnea, pulmonary infiltrates on chest radiographs, or serious systemic

illness (including shock) develops should undergo a complete diagnostic workup appropriate for immunocompromised patients. The FDA notes that patients with histoplasmosis or other invasive fungal infections may present with disseminated vs localized disease.

Source: The US Food and Drug Administration (FDA)

Neuraminidase Inhibitor for Treatment of Novel H1N1 Influenza in Pregnant and Breast-feeding Women is Safe

Date: July 4, 2009

The safety of neuraminidase inhibitors for treatment of novel H1N1 influenza in pregnant and breast-feeding women is summarized and reported in the June 15 online by the *Canadian Medical Association Journal*. Using the MEDLINE database from 1950 to week 2 of May 2009 and EMBASE from 1980 to week 19 of 2009 through the OVID system, the reviewers searched the literature for reports of the use of oseltamivir or zanamivir during pregnancy, lactation, and breast-feeding. In addition, the

reviewers collected pertinent data through the network of teratogen information services in Japan. Even before the current pandemic, the use of oseltamivir and zanamivir for patients with confirmed influenza was fairly common in Japan. Limited evidence to date suggests that oseltamivir is not a major teratogen in humans. Because more data concerning the safety of use during pregnancy are available for oseltamivir vs zanamivir, use of oseltamivir in pregnant women is preferred vs use of zanamivir. Both of

these drugs are thought to be compatible with breast-feeding, and continuing breast-feeding when the mother is taking either medication is not likely to cause significant drug exposure in the infant. It was concluded that in pregnant women at risk for novel influenza H1N1, the recommended treatment is oseltamivir. In breast-feeding women who need treatment of novel influenza H1N1, oseltamivir and zanamivir are compatible.

Source: Medscape Medical News CME

Coinciding with the Release of GMP Regulations by FDA for Small Dietary Manufacturers, USP Introduces Dietary Supplements Standards

Date: August 5, 2009

The U.S. Pharmacopeial Convention (USP) has introduced a collection of standards designed to help dietary supplement manufacturers comply with current good manufacturing practices (cGMP). The release of the USP Dietary Supplements Compendium is timely, because smaller supplement manufacturers face implementation of cGMP regulations in less than a year, a

USP official said. The document, which draws from the USP National Formulary (USP-NF) and the USP Food Chemical Codex, provides quality specifications for more than 500 dietary supplements and ingredients, along with guidance documents and images to simplify the analysis of ingredients of botanical origin. The U.S. FDA is introducing cGMP mandates to the supplement industry in a

tiered fashion. In June 2008, companies with more than 500 employees were required to become compliant. This June, mid-sized (20 to 500 employees) companies followed, and in June 2010 the smallest companies will be required to do the same.

Source: <http://www.usp.org/products/dietarySupplementsCompendium>

Pfizer and Fudan University Announce Joint Graduate Program in Clinical Research

Date: August 10, 2009

Pfizer announced a partnership with Fudan University to establish a graduate program in Clinical Data Management and Statistical Programming. This three year Masters Degree program, a first of its kind in China, is designed

to develop qualified professionals to support clinical research which is rapidly increasing in China. "Pfizer is committed to creating and expanding our partnerships in China," said Jeff Kindler, chief executive officer of Pfizer.

"We believe that making a commitment to both research and training is the most effective way to foster development in China's pharmaceutical industry.

Source: www.newsrx.com

Probiotics May be Useful as Prophylaxis Against Colds, Flu-like Symptoms

Date: August 12, 2009

The effects of probiotic intake on incidence and duration of cold and influenza-like symptoms during the winter season were evaluated in healthy children aged 3 to 5 years. Selected strains of probiotics, such as *Lactobacillus acidophilus* NCFM, or *Lactobacillus acidophilus* NCFM

in combination with *Bifidobacterium animalis* subsp *lactis* Bi-07, have been found useful as prophylaxis in children but much less in healthy populations. The study concluded that daily probiotic dietary supplementation during the winter months was a safe effective way to

reduce episodes of fever, rhinorrhea, and cough, the cumulative duration of those symptoms, the incidence of antibiotic prescriptions, and the number of missed school days attributable to illness

Source: *Pediatrics*, 124:e172-e179.

Iron Supplementation May be Harmful During Pregnancy

Date: August 18, 2009

Simona Bo and colleagues from the University of Turin in Italy examined the association between iron supplementation and metabolic or hypertensive abnormalities during mid-pregnancy in 1,000 women. They reported that 500 of the women had gestational diabetes mellitus and 212 used iron supplements. The researchers

found that iron supplement users had a higher prevalence of gestational diabetes mellitus (70.8 versus 44.4 percent), hypertension (25.0 versus 9.8 percent), and metabolic syndrome (25.9 versus 10.4 percent). After adjusting for multiple confounders, the risk was two- to three-fold higher for each condition. Women in both groups who took iron supplements

had significantly higher values on the glucose tolerance test. Hence, it is concluded that iron supplementation during mid-pregnancy is linked to higher risk of gestational diabetes, metabolic syndrome and hypertension.

Source: *American Journal of Obstetrics & Gynecology*, 201(2):158e1-158e6.

Herb Eases Rheumatoid Arthritis Pain

Date: August 24, 2009

A 400-year-old Chinese herbal remedy was found effective to relieve inflammation and joint pain in patients with rheumatoid arthritis, says a US study of 121 sufferers funded by the National Institute of Arthritis

and Musculoskeletal and Skin Diseases. About two-thirds of the patients who took a purified extract of the herb *Tripterygium wilfordii* Hook F (雷公藤) for about six months showed at least 20% improvement

in their symptoms, compared with about one-third of those who took the anti-inflammatory sulfasalazine.

Source: *Annals of Internal Medicine*

Oral Drug Injected in Error at Public Hospital

Date: August 29, 2009

A terminal breast cancer patient at North District Hospital was mistakenly injected with morphine. On August 19, a nurse was about to give the patient 2.5 milligrams of morphine orally when family members visiting her asked it be delayed. The nurse put down the bottle without labelling it and

about 25 minutes later another nurse went to attend the patient and injected the morphine as saline solution. The blunder was the third error at public hospitals in less than two weeks. Ten days ago, two babies at Queen Elizabeth Hospital were swapped at birth and nursed by the wrong

mothers for five days before the mix-up was resolved. On August 9, a nurse at the same hospital injected five newborns with an expired vaccine for protection against tuberculosis.

Source: The South China Morning Post

Pfizer to Pay Record \$2.3B Penalty for Illegal Drug Promotions

Date: September 2, 2009

Federal prosecutors of the USA government hit Pfizer Inc. with a record-breaking \$2.3 billion in fines Wednesday and called the world's largest drugmaker a repeating corporate cheat for illegal drug promotions that plied doctors with free golf, massages, and resort junkets. Announcing the penalty as a warning to all drug manufacturers, Justice Department officials said the overall settlement is the

largest ever paid by a drug company for alleged violations of federal drug rules, and the \$1.2 billion criminal fine is the largest ever in any U.S. criminal case. The total includes \$1 billion in civil penalties and a \$100 million criminal forfeiture.

Authorities called Pfizer a repeat offender, noting it is the company's fourth such settlement of government charges

in the last decade. The allegations surround the marketing of 13 different drugs, including big sellers such as Viagra, Zoloft, and Lipitor. As part of its illegal marketing, Pfizer invited doctors to consultant meetings at resort locations, paying their expenses and providing perks, prosecutors said.

Source: The Associated Press

US Pharmacopoeia Takes First Step in Program to Verify Ingredients in TCM

Date: September 3, 2009

In moves that could ultimately help elevate quality standards for traditional Chinese medicines (TCM) sold in the U.S. and worldwide, the United States Pharmacopoeial Convention began verifying individual ingredients in these medicines. The verification by USP recently has been completed.

For the first time ever one ingredient in a TCM produced by a Hong Kong-headquartered pharmaceutical company was voluntarily tested under an agreement reached between USP and the Modernized Chinese Medicine International Association (MCMIA). The move to verify ingredients in TCM fulfil

an enormous gap in terms of measuring these medicines against certain scientific standards. Through this verification programme, the quality of individual herbal ingredients could be certified by an independent and reputable organization.

Source: PharmAsia News

British Schoolgirl Dies after HPV Vaccination

Date: September 29, 2009

Health authorities in Britain are investigating after a 14-year-old girl, Natalie Morton, dies a few hours after she was injected with Cervarix vaccine which protects against two strains of the human papilloma virus that cause cervical cancer. Caron Grainger, director for public health at Coventry city council,

said an autopsy will be conducted to investigate if the vaccine played any role in Morton's death. The batch of vaccine administered at the school has been quarantined for two days. A number of other girls at the school reported mild symptoms such as dizziness and nausea after receiving the shot.

"What we don't know at this stage is whether her sad death and her feeling unwell is in any way connected to the immunization itself," said Mike Attwood of the public health department in Coventry.

Source: CBC News

Recall of a Herbal Dietary Product due to Exceed Content of Microbes

Date: September 12, 2009

On September 11, the Department of Health of the Hong Kong Government SAR ordered a lot of herbal dietary product, called “Strong Hepomine”, to

be immediately recalled because of its’ excess amount of microbial cells. It was found that one batch labeled as L0020605 exceed the maximal allowance of microbial

cells by three times in the dietary product.

Source: Department of Health of HKASR, China

Success of India’s Pharmaceutical Sector Creates New Opportunities to Advance Quality, Availability of Medicines

Date: September 19, 2009

India has been highly successful in promoting its pharmaceutical manufacturing sector, thanks in part to a less stringent patent policy beginning in the 1970s, with now literally thousands of small, medium, and large companies exporting medicines and their ingredients to all parts of the world, including the United States. In 2006, 20 percent of the abbreviated new drug applications (ANDAs) at the U.S. Food and Drug Administration (FDA) came from Indian

manufacturers and approximately 1,200 drug master files from these manufacturers were on file at FDA. Indian manufacturers receive oversight from four Ministries—Health and Family Welfare, Chemicals and Fertilizers, Commerce, and Finance. Regulatory scrutiny comes from the first of these, with India advancing a Food and Drug Administration similar to the United States. India also advanced to more modern patent protection in 2005 with increasing compliance to World

Trade Organization (WTO) approaches to protect intellectual property.

USP developed its activities in India over the past decade in recognition of the remarkable success of the Indian manufacturing community and the increasing knowledge that scientific and technical members of this community have about global standards.

Source: The Standard of Quality 6(3): 2-3. (www.usp.org)

Errata for Volume 16(2) Apr-Jun, 2009

Correct references cited in an article entitled “Overview on the International and Local Situation of Smoking Cessation” Vol. 16(2), p.54-60, are as follow:

Page	Column/Table	Line	Wrong Reference No.	Correct Reference No.
58	First column	4	26	22
58	First column	23	25	23
58	First column	31	26	24
58	Second column	4	29	26
58	Third column	15	30	27
58	Third column	15	31	28
58	Third column	15	32	29
58	Third column	16	33	30
58	Third column	22	34	31
59	Table 4	1	27	25

Chinese Medicine Can Help Realize the Potential of Four Economic Areas

WONG, Albert B.

Modernized Chinese Medicine International Association, Hong Kong G.P.O. Box 5301

ABSTRACT

Four of the six Economic Areas with High Potential (EAHP) recommended by the Task Force on Economic Challenges (TFEC) in April for further evaluation are actually associated with Chinese medicine (CM). They are testing and certification, medical services, innovation and technology and educational services. Therefore, the government should assess the merits of developing these 4 EAHP within the CM context. We believe that once these 4 EAHP are successfully developed, not only will Hong Kong (HK) gain a new emerging knowledge- and technology-based CM industry cluster, it will also help create numerous high-paying jobs while delivering social and healthcare benefits to the society.

Keywords: Chinese medicine; Modernization; Hong Kong; Future economic growth; Applied research

INTRODUCTION

Few HK political and business leaders are aware of the great stride CM has made toward *modernization* during the last decade. Even fewer know that the Ministry of Science and Technology has predicted that China's TCM healthcare will grow into a 400 billion RMB market in 10 years, hence offering a potentially huge opportunity for HK's CM industry. This lack of understanding of CM's past and future prospects results in CM's great potential as a dynamic HK industry cluster being largely unrecognized. At a time when HK's traditional economic pillars are being eroded by the *Financial Tsunami*, new emerging industries, such as CM, should be re-evaluated and developed in order to safeguard HK's prosperity.

CM DEVELOPMENT IS A NATIONAL POLICY

In 2002, 7 ministries and committees of the Central Government formally called

for the *modernization* of CM. Since then, numerous legislations and policies were promulgated to provide a framework to foster the improvement of CM quality and effectiveness, to encourage scientific R&D and to invite international parties to participate in the CM development.

In 2008, the Central Government, in overhauling the national healthcare system, incorporated CM's tenets on "life nurturing 養生" and "pre-disease treatment 治未病" as the bulwark of preventive healthcare into the system. Government officials projected that, in the future, 1/3 of the patients in Mainland would be under the care of CM practitioners.

Modernization in CM science and technology

China's recent economic surge, together with the implementation of the national CM development policy, has drastically transformed CM's status and ushered it into an age of modernization and scientific development. Scientific methods are now commonly used in the development of new CM products and their quality assurance. Many CM products now meet international requirements and are being tested or registered as therapeutic agents or as nutraceuticals.

In the area of innovative research, large scale scientific collaborations are underway among mainland, HK and international scientists. For example, Harvard University and HK's Baptist University are working together to screen for anti-cancer agents from dozens of Chinese herbs. Stem Cell Biology Laboratory of UK's London University is also collaborating with a Shanghai hospital to seek fractions isolated from CM that can help promote stem cell growth.

The CUHK (Chinese University of Hong Kong), supported by US's NIH (National Institute of Health), is identifying immunomodulators from CM. NIH also funded Guangzhou Bai Yun Shan Pharmaceutical Co., Ltd. (廣州白雲山和黃中藥公司) to engage in the R&D of *Radix Isatidis* 板藍根 as an anti-viral agent to

resist pandemics such as SARS and avian flu. Fudan University 復旦大學 is leading a national effort to investigate the mechanisms of a number of effective classical CM decoctions.

Recently, Pfizer, the world's largest pharmaceutical company, after consultation with HK scientists, MCMIA's experts and others, decided to engage in the development of novel CM-based pharmaceuticals and nutraceuticals.

In the area of *testing and certifications*, The Shanghai TCM University is working on a national system of CM standards while several HK universities, funded by the HK government, are collaborating to develop what is known as "Hong Kong Standards" for CM. In 2006, USP (US Pharmacopoeia) and MCMIA signed an agreement to promote the USP Dietary Supplement Verification Program (USP DSVP) as a means to help CM companies promote their products internationally with USP's endorsements for their quality.

Modernization in CM practice

The modernization of CM practice is expected to be more difficult and it will proceed more slowly than its herbal decoction counterpart. It is because tradition, culture and philosophy are more difficult to change. Its principal tool, clinical trials, is generally time-consuming, costly and arduous. Even so, considerable progress has been made in the Mainland, HK and Taiwan in the computerized instrumentation quantification of the 4 CM diagnostic methods. Adaptation of western style clinical trials and pharmacological methods has met with considerable success. The use of pharmacokinetics techniques to gain insight into CM formulation theory is also ongoing in CUHK.

In many clinics, the use of standardized granules 顆粒 have replaced processed herbs 中藥材飲片 to enhance accuracy and consistency in dispensing the decoctions. This is often accompanied by the computerization of the clinics to better handle patient and prescription data. Many new CM doctors' offices now

assume a modern appearance. In spite of these improvements, unfortunately, HK's young CM graduates' modernization endeavor continues to be hampered by the prohibition to use modern instruments in their practice and by the lack of sufficient internship opportunities because there is no CM hospital in HK.

The accelerating pace of the modernization of CM both as a science and as a practice has led the Ministry of Science and Technology to predict in June 2009 that China's TCM healthcare will be a 400 billion RMB industry in 10 years.

HK's CM advantages and potentials

HK enjoys many advantages over Mainland cities in the CM arena. When the forces of CM *modernization* are set in motion, not only will these advantages become magnified, other latent potentials can also be activated and energized.

Even after 3 decades of *economic reform* 改革開放, HK continues to maintain its unique position as Mainland's largest trading partner for CM herbs. The international networks that have been in place for decades will now become ready channels for the newly modernized decoctions and high quality herbs cultivated under GAP (Good Agricultural Practice) guidelines. To facilitate the *internationalization* of these new products, MCMIA and HKTDC (HK Trade Development Council) jointly created the world's only international trade and conference platform for modernized CM, ICMCM (International Conference & Exhibition of the Modernization of Chinese Medicine). It is now a seasoned and well known annual event that has been held in HK for the last 8 years.

Besides the explicit business advantages, HK has a number of latent advantages and potentials as well. Some of them are inherent and systemic while others are recently established. The inherent advantages include the well-known rule of law, transparency, western business acumens, international networks and reputation and logistics etc., which are conducive to the development of trade as well as testing and certifications.

HK's mature and advanced healthcare system could readily provide an ideal incubating environment for "life nurturing 養生" and "pre-disease treatment 治未病" practices. The 14 CM Training & Research Centers run in conjunction with

HK's public hospitals have taken some initial steps in this direction. Experiences gained in this process could be shared with the Mainland the international healthcare professions, both of which also emphasize integrative medicine. The recent MOU signed between the hospital authorities of HK and Paris on CM collaboration illustrates such a trend.

There are also many recently established advantages. In the past decade, with the founding of the 3 TCM medical schools and the establishment of a number of CM research programs in 6 universities and JCICM (Hong Kong Jockey Club Institute of Chinese Medicine), a sizeable contingent of CM scholars and scientists have been assembled in HK. They engage in a wide range of research activities from neurological, cardiovascular and anti-rheumatoid agents to TCM classical literatures. The research environment in HK was deemed favorable enough that CGCM (Consortium For Globalization of Chinese Medicine), a federation of over 100 universities and research institutions collaborating in international CM research, chose HK as its headquarters. ICMCM is another recently established HK advantage to advance international CM trade and information exchanges.

CM Industry Cluster
1. Herbal plantation
2. R&D
3. Manufacturing
4. Trading/marketing
5. Informatics
6. Education
7. Insurance
8. Medical/health Tourism
9. Wellness & Treatment
10. Rehabilitation & Palliation

PRACTICAL CM PROJECTS FOR THE FOUR ECONOMIC AREAS

The CM community comprises of a collection of industries and groups. For convenience sake, we call them a *CM Industry Cluster*. The members of the cluster are listed in the table below. Being a cluster of industries, they encompass many economic areas, four of which are identical to those that are recommended by TFEC. Hence developing these 4 *EAFP* on a *CM Industry Cluster* platform could quickly yield tangible and measurable contributions to the economy.

Below is a discussion on the practical ways CM can enable these *EAFP* to fully realize their potential for the benefits of HK.

Testing and certification

Currently, the Department of Health is reviewing over 12,000 CM products for licensing. Few of these products have their ingredient markers identified or tested for quality control. Therefore we suggest that a *Chinese Medicine Applied Research Institute* be established to coordinate this task in conjunction with the *Hong Kong CM Standards* project. The business of these projects alone will enable this *EAFP* to take off quickly as a major industry in the CM cluster.

The *Institute* itself could perform some of the essential research and methodology development while the routine analyses and tests could be done by HKLAS accredited commercial and institutional laboratories. The *Institute* can then issue certificates based on the merits of the data generated by these laboratories. The *Institute* should also be given the mission to seek scientific solutions to CM problems and to provide technological supports to the industry's product development.

HA (Hospital Authority) and HKBU (HK Baptist U) are creating an herbal fingerprint database for individual CM herbs, which could later be used to support testing and certification. In parallel, MCMIA is evaluating the feasibility to establish a global CM chemical marker marketing center in HK. Chemical markers are indispensable in quality control and in the quantification of research results. Both of these are keys to CM modernization. The *Institute* and the accredited laboratories can help certify the purity of the markers in support of this important and unique service.

Once the above projects are fully developed, HK will undoubtedly become an international *Testing and Certification Center* by its own right.

Medical services

HK's primary healthcare system can assimilate the CM preventive approach mentioned above by first including CM in the ongoing healthcare reform consultation and financing process. It is obvious that the incorporation of CM into the HK primary healthcare system could help alleviate many of the current problems in areas such as human resources, costs and accessibility.

With the establishment of

"evidence- based" CM in the Training & Research Centers and with clinical standards supported by our world-renown western medical practitioners, HK is well positioned to build a world class CM hospital, staffed with top CM practitioners, to attract both local and international patients. This hospital could also act as a referring hospital for Mainland facilities when special medical services are required. It can serve both as a medical/ health tourism destination and a bridge to the motherland.

Innovation and technology

HK has some of the best CM scientists in the world. The CM classical texts are full of clues to treat common and difficult diseases. The Chinese Academy of Chinese Medical Sciences as well as universities and companies in HK have been digitally compiling contemporary and ancient CM medical cases. This growing library affords an important depot for data-mining to discover treatment methods and new drugs using modern pharmacological approaches.

In the past years, UGC (University Grant Committee) has supported consecutive *Area of Excellence* grants for HKUST (HK U of Science and Technology) to develop drugs for Alzheimer's disease and Parkinson's disease etc., some of these drug candidates are from CM sources. Meanwhile, ITF (Innovation Technology Fund) funded the CGCM partners to develop a drug for stroke treatment. HKU also has a Center of Excellence in Neuro-science while HA is establishing a Clinical Center for Neuro- science. Government funding also supports other CM research centers in all the major universities. HK Science Park recently opened its Biotech Centre

providing large research space and facilities to the CM and biotech industries with favorable financial incentives and instrument support.

Besides these existing research centers, HK has always been an ideal location for managing large scale multi- center clinical trials for new CM drugs because HA has a Standard for Institution Review Board that meets FDA requirements. These existing infrastructures offer fertile soil for the development of novel CM products and they allow a large part of the CM R&D to be conducted locally, hence providing high-paying job opportunities and creating high-value intellectual properties.

CM R&D employs a set of paradigm and approaches that are quite different from many western sciences. To facilitate its effective development, a **Chinese Medicine Research Council** should be established to strategize, coordinate, direct, fund and monitor the CM R&D and its innovations.

Educational services

HK universities have high world ratings. With this prestige, language advantage and international network, the HK universities are well placed to attract international CM students to receive regular or specialty CM training while others can come to engage in CM R&D. When the graduates return home, they could serve as medical, cultural and commercial "CM ambassadors".

In recent years, TCM is gaining popularity among the progressively health- conscious HK citizens. Therefore

more extracurricular CM courses should be opened to the people in their own community so as to empower them with common sense and common knowledge to take care of their own health. A knowledgeable and health-conscious population is the key to primary healthcare success and the best way to effect lower public medical expenditure.

CONCLUSION

We believe this is an opportune time for the government to lead and to lend strong support to the development of the CM industry cluster so that it can become a driving force to propel the 4 *EAHP* to their full potential. This will best be carried out by a new, dedicated pan-departmental agency (namely, a **Chinese Medicine Development Commission**).

At the end of this process, HK could gain a group of vigorous emerging industries, create many high-salaried employment opportunities and strengthen its healthcare system. In addition, the HK CM industries could participate fully in the thriving 400 billion RMB mainland CM market. If nothing else, a robust CM industry cluster will clearly be one of the best insurance HK can buy to withstand future *financial crises*.

Author's background

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Call for Contributions

To commemorate the 60 anniversary of establishment of Hong Kong Pharmaceutical Society, the next issue of this journal will be dedicated to the modern pharmacy educations and practices in China during the twenty century. The Editors would be particularly pleased to receive papers and contributions in these areas of pharmacy. We would also be pleased to consider other papers in any area of pharmacy for publication in next volume during 2010. Areas covered range from brief communications, pharmacy practices, drug and therapeutics, over-the-counter medications, nutraceuticals and herbal medicines, pharmaceutical technique and technology, and reports on society activity as well as new products.

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認識及預防H1N1新流感

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摘要

自今年四月首宗人類豬流感病毒(H1N1)在墨西哥爆發令108人死亡以來, 已擴散傳播世界各地。專家警告, 感染個案正不斷在上升, 感染的人在未來數個月會更多, 將取代季節性流感。一般市民對H1N1新流感認識不多, 經常向醫護人員查詢。本文就經常提問的十個問題作扼要的回應, 希望對藥劑師在執業中遇到同類問題時有幫助。

關鍵詞: 人類豬流感; H1N1病毒; 季節性流感; 傳染途徑; 特敏福; 流感疫苗

引言

前一陣子講了好幾場有關H1N1新流感的演講, 還有日復一日病人甚至醫師的詢問, 我實在有點累了, 決定將最常見的十個問題寫成文章與各位分享, 希望大家能得到幫忙。

流感的傳染途徑

A. 流感的傳染途徑主要分為兩類:

1. 飛沫傳染 2. 接觸傳染

◆ 飛沫傳染: 一般飛沫傳染的定義, 是飛沫由口中噴出後, 飄行約一公尺左右就落地的飛沫。因此, 不會因為一個房間裡有一個人得到流感, 其他人都中標, 不會這麼恐怖。但是如果是在密閉的捷運車廂裡, KTV裡, 兩個人相隔一公尺內, 這些飛沫就有可能會傳染。

☆ 飛沫的量由多到少: 打噴嚏 >> 咳嗽 = 唱歌 = 大聲演講五分鐘 > 輕聲說話

◆ 接觸傳染: 雖然飛沫傳染力只在前方一尺處, 但是我們的手卻是強力的病毒散播器。當我們打噴嚏, 咳嗽, 雖然我們用衛生紙擤住, 然而這些病毒顆粒會存在我們手上。這時候如果我們用手去摸其他物品, 病毒就有可能會散播到被觸摸的物品上, 比如說:

門把, 水龍頭, 電梯按鈕, 握手。當下一個人去觸摸這些物品後, 又用手摸鼻子, 揉眼睛, 這時候病毒就會造成感染。衛生署最近公布不要用手擤住口鼻咳嗽打噴嚏, 要用衛生紙, 或是使用“吸血鬼姿勢”擤住口鼻, 就是這個道理。

☆ 病毒在無生物上可存活的時間:

- + 光滑表面如門把手水龍頭: 甚至可達一天以上。
- + 不光滑的衛生紙或毛巾, 以及人類的手: 約15分鐘到一小時。

流感症狀跟其他感冒的分辨

A. 事實上是很難分辨。以之前美國的案例統計, 發燒佔94%, 咳嗽佔92%, 喉嚨痛佔66%, 腸胃道症狀則有25% (包括吐或腹瀉)。其中9%病人需住院治療。一般流行性感冒病毒造成的感冒比普通鼻病毒或RSV病毒引起的感冒會嚴重許多, 可以算是流感的特色之一。

到醫院檢查能否證實得到H1N1新流感?

A. 原則上有發燒與咳嗽的病人來到醫院, 我們就會用棉棒在喉嚨或鼻咽抹一下, 送做流感的快速檢測。流感的快速檢測是有學問的, 因為並不是做了就非常準確。原則上病毒量越大, 敏感度就越大; 因此, 症狀很明顯的時候病毒量高, 陽性的機會比較高; 另外抹的檢體越多, 挖喉嚨越用力, 陽性率也比較高。那種才剛發病的輕微咳嗽, 或是蜻蜓點水式的沾一下喉嚨, 是比較不準確的。

H1N1新流感是屬於A型流感的一種。如果檢測出來是A型流感, 快速檢測並不能告訴你是不是H1N1新流感, 只能知道你得到A型流感。要進一步知道是不是H1N1新流感(圖一), 必須靠分子生物學的方法才能分辨。現在疾病管制局只針對“重症(或住院病患)”與“群聚感染”兩種狀況, 才會進一步分析是否

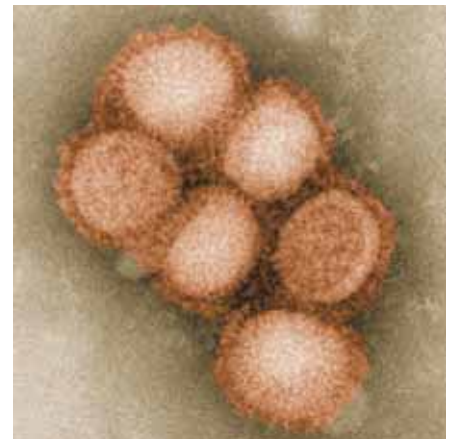
為H1N1新流感, 其他門診病人不會特別檢驗。

根據目前的流行病學統計, A型流感當中90%都是H1N1新流感。所以如果在門診驗出A型流感陽性, 病人有九成的把握是得到H1N1新流感。雖然還有10%可能是其他舊型的A型流感, 然而比例不高, 因此可以忽略之。(請看快速檢驗的敏感度)

為什麼年輕人與兒童生病的人比較多?

A. 在本世紀的三次大流行當中, 兒童總是感染率最高的族群; 學齡前兒童佔感染族群的 24% ~ 30%左右, 在學兒童則佔30% ~ 35%, 兩個年齡層加起來高達五成以上。每次流行的過程都是先由在學的兒童感染人數先上升, 請假學童的比例升高; 經過一兩週之後, 成人感染人數開始也上升, 最後嬰兒與老人因流感相關疾病的住院率才開始上升。

除了兒童之外, 軍營, 因風災而群聚的災民, 擁擠的辦公室雇員, 這些人也都是大流行前期率先感染的族群。這些人共同的特徵就是: 頻繁密集的與人接觸, 猶如一個病毒的大培養皿。病毒在學生或這些社會行為頻繁的人口大浪繁殖以後, 才能進一步感染其他不常與人接觸的族群, 也因此疫苗應該優先接種在這個族群的人身上。



圖一. H1N1流感病毒

年輕族群真的比較容易併發重症死亡嗎？

A.事實上本世紀三次大流行裡，只有第一次1918年大流感是W型的死亡曲線，也就是年輕人死亡人數爆增；其他兩次都還是U字型的死亡曲線，以老人與嬰幼兒死亡為多。小孩與青年人得到流感的人數眾多，簡單的說，如果有1000個小孩或青年人得到流感，其中一人死亡；而只有10個老人得到流感，無人死亡，請問，誰的死亡率高？這還很難說呢！然而媒體只會報那一人死亡的年輕人案例，不會知道感染的族群總數有多少，讓民眾以為死亡都是小孩年輕人，不是老人。另外還有一些死亡的案例雖然年紀不大，但是本身有先天性免疫不全，心臟病，慢性肺病等等，這些人不應該算在健康的年輕族群，當我們在看媒體報導的時候要特別注意。

請記得1918年西班牙大流感正值一次世界大戰，有群聚的軍人，後勤人員，還有當時落後的醫療環境，對疾病的無知，都不是現今的醫療水準可比擬。

流感病人是因為甚麼原因而導致重症甚至死亡？

A.流感病人導致重症甚至死亡的原因。

1. 本身疾病惡化（如：氣喘，慢性肺病，心臟病...）
2. 病毒本身造成的肺炎
3. 重要器官的感染（如：心肌炎，腦炎）
4. 繼發性細菌感染（如：繼發細菌性肺炎或敗血症）。

上述四種以此項最為重要也最為常見。流感病毒與肺炎鏈球菌或是金黃色葡萄球菌都有某種相輔相成的關係，會讓流感病人更容易被細菌攻擊，感染，進而重症或死亡！

為什麼要吃“特敏福”藥物？吃了會不會有抗藥性？

A.吃特敏福（Tamiflu）對病人有兩個好處：1.可以縮短病程；2.可以減少併發重症的機率。之前對於特敏福的藥效都著重在第一點縮短病程，所以有48小時內服用藥物才有用之說。然而，即便是感染48小時以後使用特敏福，仍然可以減少併發症。因此現階段政府給付的特敏福並不限於48小時內，只要有症狀，快速檢驗A型流感陽性，就可以免費使用克流感治療。

家人接觸者若屬於危險族群，比如說老人或者幼兒，免疫不全，氣喘等等，可以使用**特敏福**做預防性藥物，但吃藥的時間要延長到10天。吃了克流感10天只能預防這10天不要被感染，一但停藥，下次又有別的流感病人與您接觸，還是會被傳染，所以我們需要疫苗，而不能單靠**特敏福**。

很多人擔心吃了**特敏福**後，對病毒會有抗藥性。的確在藥物的壓力下，病毒有可能產生抗藥性，那是在被治療的人身上，比較不會是在使用預防性藥物的健康個體身上。抗藥性是全國甚至全世界的問題，不會是個人的問題，因此這方面應由負責公共衛生的人去傷腦筋，個人不需要想太多。

新流感的預防

A.剛剛已經說過新流感的傳染途徑有飛沫傳染與接觸傳染兩種。因此，預防新流感有兩個重要的步驟：戴口罩，勤洗手。

戴口罩不需要24小時都戴著，這樣一天下來就算沒有得到流感，應該也會得濕疹。只需要在人群擁擠，距離你一公尺左右常常會有人晃來晃去的公共場所，才需要戴口罩。外科口罩有三層式結構，可以阻擋近90%的飛沫，與N95相去並不會太遠，所以戴外科口罩就可以了。至於其他市面上的可愛圖樣口罩，貴得要命的活性炭口罩，防護效果反而比外科口罩還差。

很多人覺得在醫院裡容易感冒，沒錯，但是那不是因為空氣中飄滿著病毒，而是因為你摸的批價櫃檯，診間門把，電梯按鈕，上面的病毒被你摸下來自己放到鼻孔或嘴巴裡的。我在醫院不看診的時候，都不戴口罩的。

所以勤洗手才是預防新流感的王道。人不知不覺摸鼻子揉眼睛這種動作實在太多了，不如隨身帶一瓶乾洗手液，接觸別的物品之後就洗手一下，這樣才能減少手上的病毒帶給自己的機會。

為什麼疫苗先給災民，醫護人員，孕婦，兒童與學生注射，最後才是老人？

A.簡單來說，要阻止流感傳播，要先從上游著手，而不是下游。災民與兒童是上游，他們是群聚的生活，很容易大量繁殖病毒，所以要先打。醫護人員常常要面對免疫不全的老人與小孩，所以不能得到流感，否則會傳染給死亡率高的這群人，因此要先打。

再來就是孕婦，因為孕婦是所有危險族群當中，唯一有行動能力，會叭叭走，搭地鐵，坐巴士的人。有行動能力意味著她們自己就可以到外面得到流感回來，不需要等家裡的小孩得到才傳染給她們。因此不要讓孕婦得到流感進而變成重症，是國家社會的責任，所以要先打。

得了流感後是否以後就可不用再打新流感疫苗

A.理論上是沒錯。但是有個盲點，就是快速陽性只有90%是新流感，也就是你只知道你90%是得了新流感，還是有10%可能不是。你願意冒這10%的風險嗎？這沒有答案。我個人對於已經得到A型流感的病人是建議：9月的季節性流感疫苗照打，而11月的H1N1新流感疫苗可以先觀望一下，如果一個月都沒有傳出疫苗有甚麼副作用，那麼就還是可以打。不過這是作者個人的建議，並不一定符合社會的政策，當參考即可。

總結

新流感疫情預計全球會有1/3的人感染，這趨勢是不可能擋得住，停課也沒用，檢疫也沒用，總之這一天就是會發生。因此這一切的政策目的不是為了擋住新流感的流行，而是延長疫情。如果一個社會同時1/3的人生了病，那麼整個地區不就完蛋了，經濟活動一定受影響或停擺，醫療院所一定不堪負荷。但是如果這1/3的人分四年慢慢感染，那麼社會就不會被拖垮，醫療資源也可以得到喘息，這就是我們的目標。

另一個目標是減少併發重症與死亡的病人，這一部分就要靠藥物與醫療水準來輔助。總之延長戰線，減少死亡，以時間換取空間，才可能在這場流感戰爭獲勝。

What is Available to Benefit Hair Loss Sufferers?

CHOW, Derrick

Community Pharmacist

ABSTRACT

Androgenic alopecia is a common hair loss problem that occurs in men and women. Dihydrotestosterone plays an important role in the pathophysiology of androgenic alopecia. Currently there are two effective and safe pharmacological treatments available and pharmacists play an important role in providing advice and counseling in managing hair loss problems.

Keywords: *Androgenic alopecia; Minoxidil; Finasteride; Miniaturization; Benign prostatic hyperplasia; Hypetrichosis*

INTRODUCTION

Hair loss is a stressful problem both in men and women. Among the various hair loss problems, androgenic alopecia (also called male pattern baldness in men or female pattern baldness in women) is commonly seen in community pharmacy. Community pharmacists often face customers asking questions on how to regrow their hair back or stop losing hair. This article aims to discuss the drug options available in the pharmacy.

Normal growth of hair

The hair cycle ensures that periodically, entirely new hair shafts are produced. It also serves as an intrinsic regulator of maximum hair length. Each hair follicle has its own cycle. Hair growth cycle consists of three phases, anagen (growth), catagen (involution) and telogen (rest). Anagen is a growing phase which lasts for 2 to 6 years. Then it enters a 1 to 2 week phase in which the hair follicle contracts. Finally it enters the resting telogen phase for 2 to 3 months. The hair follicle in this phase is dormant and mitotic activity is arrested. This phase lasts for 2 to 3 months. The old hair is then replaced by a new hair as a new cycle begins. On the scalp, about 90% to 95%, 1% and 5 to 10% of scalp hairs are in anagen, catagen and telogen phases respectively.⁽¹⁾

Pathogenesis of androgenic alopecia

Androgenic alopecia presents differently in men and women. In men, there is a bitemporal recession of the hair line followed by diffuse thinning of the vertex, producing a M-shaped hair line. It then progresses to baldness in the vertex, leaving behind the occipital hair. Norhood-Hamilton classification clearly describes how the baldness progresses.⁽²⁾ In women, the hair thinning is more diffuse and is more marked on the central and parietal area of the scalp. The frontal hair line is less affected. The Luwning scale has a clear definition of this.⁽³⁾

In androgenic alopecia, the hair follicle growth cycle is altered. Large, pigmented terminal hairs gradually change into tiny, fine and non-pigmented vellus hairs. This leads to miniaturization of the hair follicle. It is found that the duration of anagen slowly decreases over several cycles. Since the anagen phase determines the length of the hair, the length of the hair becomes shorter and shorter with a shortened anagen phase. Also, the telogen phase becomes longer, and hence the number of hairs on the scalp decreases.⁽¹⁾

As the name implies, this type of alopecia is related to androgens in the body. It is found that while androgens stimulate hair growth effect on the face and chest area in men, they have an opposite impact on scalp areas, where terminal hairs are reversely transformed slowly into slowly/tiny vellus. Among the androgens, dihydrotestosterone (DHT) is the most potent one. 5 α -reductase in the scalp changes the circulating testosterone into DHT which binds to the androgen receptor and causes the miniaturization process.⁽⁴⁾

PHARMACOLOGICAL TREATMENT

Two treatments are approved by the US Food and Drug Administration (FDA) for the treatment of androgenic alopecia: topical minoxidil and oral finasteride.

1. Topical Minoxidil

Minoxidil was first marketed as a systemic treatment for hypertension. This peridinopyrimidine derivative is a potassium channel agonist which causes vasodilation.⁽⁵⁾ Hypetrichosis later was found to be a common side effect systemically. This led to the development of topical use for treatment of hair loss. However, its exact mechanism of action in androgenic alopecia is unknown.

Minoxidil is currently available as 2% and 5% solution in Hong Kong. A 2% gel formulation has also been marketed in recent years. These formulations are available over-the counter under the supervision of a pharmacist. While the 2% formulation can be used for both men and women, the 5% formulation is indicated for men only. It is believed that minoxidil extends the anagen phase and reverses miniaturization of hair follicles.⁽⁶⁾ Hence minoxidil can halt the baldness and even cause a dense to medium regrowth of hair. In a randomized, placebo-controlled trial comparing topical minoxidil 5% and 2% solution in men, 5% solution was significantly superior to 2% minoxidil and placebo in increasing hair growth in men with androgenic alopecia in terms of changing from baseline in nonvellus hair count, patient rating of scalp coverage and investigator rating of scalp coverage. Five percent topical minoxidil produced more hair regrowth in 48 weeks compared with 2% minoxidil as determined by target area hair counts. The 5% solution was able to cause an earlier and more robust response than the 2% formulation.⁽⁶⁾ In another randomized, placebo-controlled trial in women, 2% topical minoxidil was statistically superior to placebo in terms of changes in nonvellus hair and investigator rating of scalp coverage.⁽⁷⁾

The dosage of topical minoxidil is one mL twice daily on dry scalp. Different applicators are available on different products and the user has to follow instruction in order to apply the exact quantity on the scalp. Patients should be reminded to apply it on the scalp but not on the hair. The solution

can be spread evenly on the scalp with a fingertip outward. It is better not to leave any solutions on the hair because the solution can make the hair flaky and greasy, thus patient compliance may be reduced. Wash hands thoroughly after application. For maximal efficacy, patients should avoid wetting the scalp within 4 hours to allow sufficient time for absorption. Hair gel or hair spray is permitted at least 20 minutes after topical minoxidil application.

The patient should also be informed that temporarily increased shedding may occur at the beginning of minoxidil therapy because minoxidil stimulates resting follicles to enter the anagen phase which induces detachment of the old club hair. Visible hair growth is usually seen in 4 to 6 months.⁽⁸⁾ To maintain effectiveness, continuous daily application is necessary. The scalp will return to baseline after discontinuing the medicine for 4 to 6 months.⁽⁹⁾

In general, topical minoxidil is well-tolerated and any side effect of topical minoxidil is usually mild. However, dose-dependent local scalp irritation (e.g. pruritus, itching and burning) may occur. Facial hair growth also occurs in some women.

2. Oral Finasteride

Finasteride is an aza-steroid compound which acts as a 5 α -reductase type 2 inhibitor. It binds to 5 α -reductase isoenzyme 2 and inhibits the conversion of testosterone to DHT. It was originally marketed as a 5 mg tablet for treating benign prostatic hyperplasia. Since DHT has a well-known role in androgenic alopecia, finasteride was further studied and later the 1 mg tablet was approved for the treatment of androgenic alopecia.

Finasteride 1mg daily reduces DHT concentrations by 64.1% – 71.4% in serum and scalp respectively.⁽¹⁰⁾ In a clinical study aimed to determine the optimal dose of finasteride in androgenic alopecia, finasteride 1 mg was determined to have efficacy similar to that observed at a higher dose but superior to lower doses.⁽¹¹⁾ In a randomized, placebo-controlled study which followed subjects up to 5 years, treatment with finasteride led to scalp hair improvement in all endpoints such as hair count and photographic assessment, while the placebo group resulted to progressive hair loss. Concerning the hair count, the finasteride group had significant increased in hair counts over five years, and the maximal increase occurred in month 12.⁽¹²⁾

The usual dosage of finasteride for treating androgenic alopecia is 1mg daily taken with or without meals. The medicine is usually taken daily for at least three months before any response can be seen. If successful response occurs, the medicine should be taken indefinitely. It is because once the treatment stops, the DHT levels will return to pre-treatment levels and shedding continues. There will be a return to the pre-treatment hair loss stage in 12 months.⁽¹³⁾

Finasteride is indicated for the treatment of androgenic alopecia in men only. It is contraindicated in women who are or may become pregnant (Pregnancy Category X) because 5 α -reductase may cause abnormalities of the external genitalia of male fetuses. Women of child-bearing age should not handle any broken or crushed tablet to avoid absorption of drug through the skin. Thus the medicine should be kept out of reach of other people.⁽¹³⁾

Finasteride is generally well-tolerated. The incidence of sexual side effects of finasteride was slightly higher than that of placebo in a 1-year study which showed decreased libido (1.9% vs 1.3%), erectile dysfunction (1.4% vs 0.9%) and ejaculation disorder (1.4% vs 0.6%). The side effects are reversible when the drug is stopped.⁽¹⁰⁾

PHARMACIST'S ROLES

Hair loss can affect one's appearance. In a community setting, it is not difficult for a pharmacist to identify patient with hair loss problems. Appropriate questioning such as duration and pattern of hair loss, family history, concomitant medical illness or current medication can help identify the underlying cause of hair loss. For androgenic alopecia, early intervention is important so that the hair follicle is not completely miniaturized.⁽¹⁴⁾ Appropriate advice can be provided to the patient about the available pharmacological options. It is important to let the patient fully understand the medication, especially the how it works and its limitation, to ensure compliance. Wigs and hairpieces are also good choices to cover the scalp. To maintain healthy growth of hair, protein-and iron-rich diets can be recommended to patients. Patients should avoid alkaline shampoos, as alkaline media reduce the strength of hair. Excessive toweling or blow drying after washing is not recommended. Dying hairs, waving and straightening hairs are also discouraged.

Author's background

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INTRODUCING



Pariet for the Management of Acid-Related Diseases

Heparin-induced Thrombocytopenia (HIT) – An Interesting Immune-mediated Adverse Drug Reaction That Can Cause Paradoxical Thrombosis

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ABSTRACT

It is well recognized that one of the adverse reactions associated with the use of heparin is thrombocytopenia. This is usually a mild, transient, non-immune-mediated reaction that spontaneously resolves even without treatment. There is, in fact, a distinctly separate though rarer form of thrombocytopenia associated with heparin that is immune-mediated and more severe. With heparin being a widely used anticoagulant in regular clinical practice, it is important that awareness to these reactions to heparin is heightened.

Keywords: Heparin; Thrombocytopenia; Anticoagulants; Direct thrombin inhibitors; Heparinoid, Heparin-induced-thrombocytopenia

INTRODUCTION

Heparin is a widely used anticoagulant in the prophylaxis and treatment of many clinical situations, such as thromboembolism, different types of surgeries, atrial fibrillation and haemodialysis. It was estimated that as much as a third of hospitalized patients in the USA used heparin.⁽¹⁾ With such wide spread use of heparin, any serious adverse drug reaction associated with it, even though uncommon by rate of occurrence, could pose a significant management problem in reality.

It is well known that thrombocytopenia may be associated with the use of heparin. There are, however, two distinct forms that are recognized: the first and the more common form, is a mild, non-immune-mediated thrombocytopenia

affecting approximately 10 to 20% of patients, usually within the first 48 – 72 hours of heparin initiation, with a platelet count rarely $< 100 \times 10^9/L$, and which gradually returns to pre-treatment levels within a few days even if heparin is continued.^(2,3) This mild and transient form of thrombocytopenia is non-progressive, nor is it associated with bleeding or thrombosis, and no specific treatment is required. It is thought to be caused by the direct adhesion of heparin to platelets, promoting platelet binding to fibrinogen with subsequent aggregation leading to a decrease in platelet count.⁽⁴⁾ This more common form has been previously referred to as Type I heparin-induced thrombocytopenia but may be better described as heparin-associated thrombocytopenia, to distinguish it from the more severe immune-mediated form.

The aim of this article is to highlight the more severe, immune-mediated heparin-induced thrombocytopenia (referred to as HIT), to describe its pathophysiology, incidence of occurrence, clinical presentation and briefly outline the management strategies.

PATHOPHYSIOLOGY OF HIT

The immune-mediated reaction to heparin is in fact directed against an antigenic complex of heparin and a platelet-derived molecule called platelet factor 4 (PF4), a small positively charged molecule of uncertain biological function found in the α -particle of platelets. The steps leading up to thrombocytopenia and possibly thrombosis are described and illustrated in Figure 1.⁽⁵⁾

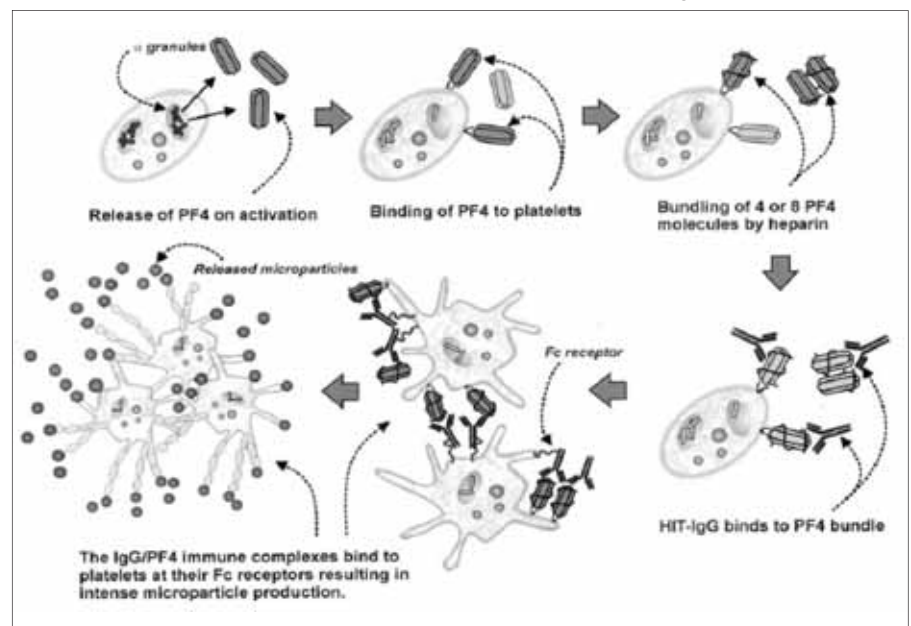


Figure 1. Diagrammatic illustration of steps leading up to HIT. Starting from top left, the release of PF4 on activation; top middle, PF4 then binds to platelet surface; top right, the bundling of several PF4 molecules and heparin with associated conformational changes; bottom right, IgG binds to heparin/PF4 complexes; bottom middle, the Fc fraction of IgG activates own or adjacent platelet; bottom left, activated platelets release prothrombotic microparticles leading to platelet consumption, thrombocytopenia and possibly thrombotic events. (Adapted from ref.5)

INCIDENCE OF OCCURRENCE

When discussing the incidence of events, it is important to distinguish the presence or development of antibodies to heparin/PF4 complexes, from heparin-induced thrombocytopenia (HIT), and HIT with thrombosis (HITT). It had been estimated that 8% up to some 50% of patients receiving heparin might develop antibodies to heparin/PF4 complexes.^(6,7) Only 1 – 5% of all patients on heparin will progress to develop HIT,⁽⁸⁾ amongst whom one third would suffer from arterial and/or venous thrombosis.⁽⁹⁾ It was said that the overall risk for thrombosis in patients with HIT is 38 – 76%.⁽¹⁰⁾ This higher than one third estimation would be due to the fact that, up to 50% of patients with HIT who have not had a thromboembolic event will have one within the next 30 days when taken off heparin and not continued on any anticoagulant therapy.⁽¹¹⁾ In general, the risk to develop HIT depends upon various factors, the incidence of HIT is greater: with bovine versus porcine heparin, with unfractionated heparin (UFH) versus low molecular weight heparin (LMWH), and in post-surgical (cardiac > orthopaedic > vascular > general) versus medical or obstetric patients.⁽²⁾

CLINICAL PRESENTATION

The thrombocytopenia of HIT is typically of moderate severity, with a drop of $\geq 50\%$ from baseline values or to $< 150 \times 10^9/L$. The median platelet count is around $50-80 \times 10^9/L$ but rarely $< 15 \times 10^9/L$. The fall in platelet count typically occurs between 5 – 14 days after heparin initiation, and this is the most common first clinical sign that alerts suspicion of HIT. Occasionally there are exceptions to this, if a patient has heparin/PF4 antibodies from a recent heparin exposure (within past 100 days), the platelet count may drop

within minutes or hours, resulting in rapid-onset HIT. Conversely, some cases might present as delayed-onset HIT, up to 3 weeks after heparin exposure and usually when heparin treatment has already been stopped.⁽²⁾ If heparin was stopped, the platelet count starts to rise within 2 to 3 days and usually returns to normal within 4 – 10 days.⁽²⁾ It takes, however, up to 3 months for antibodies to disappear from the body.⁽⁸⁾

Despite thrombocytopenia, HIT is rarely associated with bleeding. It is, however, strongly associated with venous and/or arterial thromboembolic complications, venous more so than arterial by a ratio of 4:1.⁽⁵⁾ Complications such as the following have been reported: deep venous thrombosis, pulmonary embolism, myocardial infarction, thrombotic stroke, and occlusion of limb artery requiring amputation.⁽¹²⁾ Other complications of HIT include necrotizing skin lesions at the injection site in 10 – 20% of patients, disseminated intravascular coagulation, acute systemic reactions such as fever, chills, hypertension, tachycardia, chest pain and dyspnoea.^(2,3) HIT with associated thrombosis carries a mortality of 20 – 30%, with approximately 10% of cases requiring a limb amputation.^(2,3)

Laboratory tests for HIT are available; examples include immunoassay (ELISA) for HIT antibodies for the heparin/PF4 complex, and functional test that measures platelet activity in the presence of patient's serum and heparin. However, the former is not sufficiently specific to distinguish HIT from a mere presence of antibodies, while the latter is rather labour-intensive for the average laboratory to perform or to report in a timely manner. The diagnosis of HIT is primarily a clinical one, supplemented by confirmatory laboratory test as they become available. Some clinical indicators that should be

linked with a high index of suspicion for HIT are listed in Table 1.

OUTLINE OF MANAGEMENT STRATEGIES

The conventional strategy to tackle HIT before the availability of alternative anticoagulants had been to stop all sources of heparin. These must include treatment or prophylaxis with heparin by any route, heparin flushes, heparin-coated catheters, heparinized dialysate, and heparin in extracorporeal circuit. Upon heparin discontinuation, the platelet usually will start to rise within 2 to 3 days and only around a third of the patients would present with thrombosis initially. However, the strategy of heparin cessation alone in the management of HIT is only partially adequate. This is for reason that in nearly as big a proportion of patients with HIT who did not have a thromboembolic event initially, will have one within the next 30 days when taken off heparin.⁽¹¹⁾ It does mean that to prevent thromboembolic events adequately, treatment with an alternative anticoagulant should be instituted.

As LMWH can cross-react with HIT antibodies,⁽¹³⁾ substitution of heparin by LMWH is not an option. The use of warfarin is also not recommended in the initial stage of HIT but deferred to a later stage (after an alternative anticoagulant has been started, and/or the platelet levels have recovered), because venous limb gangrene and skin necrosis have been reported subsequent to early use of warfarin. The probable mechanism is a disturbance in procoagulant and anticoagulant balance: HIT causes greatly increased thrombin generation, while warfarin produces depletion in the vitamin-K dependent natural anticoagulant, protein C, such that thrombin in the

Table 1. Clinical indicators that should be linked with a high index of suspicion for HIT²

⇒ A drop in platelet count of $\geq 50\%$ from baseline values or to $< 150 \times 10^9/L$.
⇒ Onset of thrombocytopenia typically 5 – 14 days after initiation of heparin treatment. Beware of possibility of early-onset or late-onset HIT (see text).
⇒ Acute thrombotic events, not forgetting atypical presentation such as necrotic skin lesion, especially if on adequate heparin therapy.
⇒ Other causes of thrombocytopenia are excluded. e.g. sepsis, drugs.
⇒ Laboratory-confirmed HIT antibody seroconversion.
⇒ The resolution of thrombocytopenia only after cessation of heparin.

Table 2. Some key points regarding drug management to note whenever HIT is suspected:^(2, 15)

- Stop heparin from all possible sources including heparin flushes, heparin-coated catheters, heparinized dialysate, and heparin in extracorporeal circuit.
- It is highly desirable to initiate alternative anticoagulant treatment where available. This is usually continued for 2 to 3 months.
- Warfarin should be deferred until after an alternative anticoagulant has been started and platelet count has returned to at least $100 \times 10^9/L$. Warfarin should overlap with the alternative agent for 5 days and therapeutic INR has been reached before discontinuation of the latter.
- LMWH is not an alternative option

microvasculature is not controlled.⁽¹⁴⁾

Other alternative anticoagulants available include, the direct thrombin inhibitors (DTIs): *Lepirudin*, *Argatroban*, *Bivalirudin*; a heparinoid: *Danaparoid*; and a pentasaccharide: *Fondaparinux*. Both bivalirudin and fondaparinux have not been approved for use in HIT, so will not be discussed further here. Danaparoid is not FDA-approved for HIT, but is approved in the European Union. It is a mixture of heparin sulphate, dermatan sulphate and chondroitin sulphate, and exerts its effect predominantly by inhibiting factor Xa. Although there have been claims of equivalence in efficacy to lepirudin, it is believed that some 10 – 20% cross-reactivity with HIT antibodies is possible.^(2,4)

Lepirudin is recombinant hirudin produced from the medicinal leech. It is a direct, irreversible thrombin inhibitor binding both free and clot-bound thrombin. Argatroban, on the other

hand, is an arginine-based synthetic direct thrombin inhibitor that reversibly binds with the catalytic site of thrombin. There has been no direct comparative trial between the two DTIs, but a critical comparative appraisal between the two agents based on individual respective studies, reported that both lepirudin and argatroban are effective in preventing new thrombosis and in reducing the composite end-points (of all-cause mortality, new thrombosis and limb amputation) in patients with thrombosis complicating HIT.⁽¹⁵⁾

The relative risk reduction (RRR) in new thrombosis for lepirudin from studies ranged between 0.63 and 0.81, whereas for the argatroban studies, the values were 0.44 and 0.62.⁽¹⁵⁾ It would appear that lepirudin was more effective in controlling thromboembolism due to HIT. However, it was argued that this must be balanced against considerations against lepirudin, such as higher incidents of bleeding, formation of antibodies that

bind with lepirudin prolonging its half-life and action, contraindication of its use in renal failure, and a small possibility of anaphylaxis following first and subsequent exposure.⁽²⁾

SUMMARY

Despite the seemingly low percentage incidence in occurrence, the threat posed by HIT is a significant one given the wide spread use of heparin in clinical practice. Successful management is dependent on sufficient awareness; early recognition and prompt institution of appropriate interventions (see Table 2).

Author's background

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Oral Targeted Therapy of Renal Cell Carcinoma

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ABSTRACT

Renal cell carcinoma (RCC) is the most common malignancy arising from the kidney. RCC is generally refractory to traditional cytotoxic drugs and patients with metastatic RCC have a poor prognosis. Until 2006, cytokines including interferon- α and interleukin-2 were the mainstay of treatment for patients with metastatic RCC and they resulted in an overall median survival of 13 months. However, cytokines were effective only in less than 20% of the patients treated and were associated with considerable toxicities. With a better understanding of the pathogenesis of RCC, newer molecular pathways have been identified and are targeted for the treatment of advanced RCC. Sorafenib and sunitinib are two orally active tyrosine kinase inhibitors approved by the FDA for the treatment of advanced RCC. The efficacy of sorafenib and sunitinib in the treatment of advanced renal cell carcinoma has been demonstrated in clinical trials with tolerable adverse effects. Targeted therapy has become the treatment of choice for metastatic renal cell carcinoma.

Keywords: Renal cell carcinoma; Targeted therapy; Srafenib; Sunitinib

INTRODUCTION

Cancer of the kidney and upper urinary tract accounts for approximately 3% of adult cancers and occurs in a male to female ratio of 1.5:1. Most cases of kidney cancer occur in persons aged 50 to 70 years. However, it has been observed in children as young as 6 months old.⁽¹⁾ In Hong Kong, there were 411 new cases of cancer involving kidney and other urinary organs (except bladder) in 2006, and the age-standardized incidence rate (adjusted to the new world standard population) was 4.3 per 100,000 persons.⁽²⁾

Renal cell carcinoma (RCC) is the most common malignancy arising from the kidney, and accounts for approximately

85% of all kidney cancers. Although RCC is classified further by different histology types, the majority of RCC are of the clear cell subtype (70-85%). Clear cell RCC is strongly associated with inactivation of the von Hippel Lindau (VHL) gene through mutations, deletions, or hypermethylations of the gene.⁽³⁾

Cigarette smoking has been found to be a significant risk factor for the development of kidney cancers. About 30% of kidney cancers in men and 24% in women may be directly related to smoking. Obesity and analgesic abuse are associated with increased risk of developing kidney cancers. The increased risk is observed primarily in patients who develop analgesic nephropathy associated with the use of phenacetin-containing analgesics. Environmental and occupational factors include long-term exposure to high levels of trichloroethylene, an industrial solvent, and exposure to cadmium. Leather tanners, shoe workers, and workers exposed to asbestos are associated with an increased incidence of kidney cancers. An association between gasoline exposure and kidney cancers has been observed in animal studies. Workers exposed to gasoline for prolonged periods may have an increased risk. There is an increase in incidence of kidney cancers in patients with end-stage renal disease who develop acquired cystic disease of the kidneys. The risk is 30 times higher in patients on long-term dialysis with cystic changes in the kidney than in the general population.⁽¹⁾

RCC is generally refractory to traditional cytotoxic drugs. For tumors that are localized in the kidney, nephrectomy is the mainstay of treatment and offers 5-year survival rates from 90% to 95%.⁽⁴⁾ At presentation, up to 30% of patients with RCC have metastatic disease and recurrence develops in approximately 40% of patients treated for localized disease and these patients have a poor prognosis.⁽³⁾

Until 2006, cytokines including interferon- α (INF- α) and interleukin-2 were the mainstay of treatment for

patients with metastatic RCC. Findings from randomized trials have shown that treatment with cytokines results in an overall median survival of 13 months (range 6-28 months). However, cytokines were effective only in less than 20% of the patients treated and were associated with considerable toxicities.⁽⁵⁾ With a better understanding of the pathogenesis of RCC, newer molecular pathways have been identified and are targeted for the treatment of advanced RCC.

Pathogenesis of RCC^(4,6,7)

The VHL gene is a renal cancer tumor suppressor gene. The VHL gene encodes the VHL protein, which binds to hypoxia inducible factor (HIF) and results in degradation of HIF. When the VHL tumor suppressor gene is inactivated (e.g. by mutation), HIF accumulates and results in increased production of hypoxia inducible growth factors, including vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). VEGF and PDGF bind to several tyrosine kinase receptors on the surface of endothelial cells and vascular pericytes, resulting in tumor cell proliferation and angiogenesis.

Another pathway which promotes angiogenesis is mediated by the mammalian target of rapamycin (mTOR). Increased activity of mTOR (e.g. by mutation), results in an upregulation of HIF activity, which leads to tumor cell proliferation and angiogenesis.

These molecular pathways are targeted in the treatment of advanced RCC. New targeted therapeutic agents include sorafenib, sunitinib, bevacizumab, and temsirolimus. Sorafenib and sunitinib are multitargeted tyrosine kinase inhibitors which target the VEGF and PDGF receptors and inhibit the tyrosine kinase portion of the receptors. Bevacizumab is a monoclonal antibody that binds and neutralizes circulating VEGF. Temsirolimus targets the other pathway by inhibiting mTOR and reducing HIF activity. The two orally active agents – sorafenib and sunitinib will be discussed in this article.

Sorafenib

Sorafenib (Nexavar®) was approved by the FDA for the treatment of advanced RCC in Dec 2005. Sorafenib is an inhibitor of multiple intracellular and cell surface tyrosine kinases, inhibiting tumor cell proliferation and angiogenesis of RCC. Sorafenib inhibits cell surface kinases in tumor vasculature, preventing angiogenesis. Within cancer cells, sorafenib inhibits the Raf kinase pathways, which normally regulates cell proliferation.⁽⁸⁾

In a phase II randomized discontinuation trial, 202 patients with metastatic RCC initially received oral sorafenib 400mg twice daily during the initial run-in period of 12 weeks. Sixty five patients with stable disease (tumor shrinkage less than 25% from baseline) were randomly assigned to either continuation of sorafenib or placebo. 50% of the patients in the sorafenib group were progression free versus 18% in the placebo group ($p=0.0077$). Median progression-free survival (PFS) from randomization was significantly longer with sorafenib (24 weeks) than placebo (6 weeks) ($p=0.0087$).⁽⁹⁾

In a phase 3, randomized, double-blind, placebo-controlled trial (TARGET), 903 patients with RCC resistant to standard therapy received either continuous treatment with oral sorafenib 400mg twice daily or placebo. Sorafenib showed a statistically significant benefit in PFS over placebo. The median PFS was 5.5 months in the sorafenib group and 2.8 months in the placebo group (hazard ratio (HR) for disease progression 0.44; 95% confidence interval (CI), 0.35 to 0.55; $p<0.001$). Sorafenib reduced the risk of death as compared to placebo, although the benefit was not statistically significant. The Response Evaluation Criteria in Solid Tumors (RECIST) was utilized to identify objective response. Partial responses were reported as the best response in 10% of the patients receiving sorafenib and in 2% of those receiving placebo ($p<0.001$). The median overall survival was 19.3 months in the sorafenib group and 15.9 months in the placebo group (HR 0.77; 95% CI, 0.63 to 0.95; $p=0.02$).⁽¹⁰⁾

The reported adverse effects of sorafenib were predominantly of CTCAE (Common Terminology Criteria for Adverse Events) Grade 1 or 2. The most common were diarrhea, rash, fatigue and hand-foot skin reactions. Hypertension and cardiac ischaemia were rare serious

adverse events that were more common in patients receiving sorafenib than in those receiving placebo.⁽¹⁰⁾

The recommended dosage of sorafenib for the treatment of advanced RCC is 400mg orally twice daily, at least 1 hour before or 2 hours after meal. Treatment is continued until disease progression or unacceptable toxicity occurs. No dosage adjustment is required in patients with renal impairment and patients with mild to moderate hepatic impairment. Temporary interruption or dose reduction may be necessary in the management of adverse drug reactions. The dose may be reduced to 400mg once daily, or reduced to 400mg once every other day if additional dose reduction is required.⁽¹¹⁾

Sorafenib is metabolized primarily in the liver, undergoing oxidative metabolism mediated by CYP3A4, and glucuronidation mediated by UGT1A9. Sorafenib metabolism is unlikely to be altered by CYP3A4 inhibitors. However, inducers of CYP3A4 (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital and dexamethasone) are expected to increase metabolism of sorafenib and decrease sorafenib concentrations.⁽¹¹⁾

Sunitinib

Sunitinib (Sutent®) was approved by the FDA for the treatment of advanced RCC in Jan 2006. Sunitinib is a multi-targeting tyrosine kinase inhibitor, which targets several receptor tyrosine kinases including VEGF receptor and PDGF receptor, thus inhibiting tumor cell proliferation and angiogenesis.⁽¹²⁾

The efficacy of sunitinib as second-line therapy in cytokine refractory RCC was demonstrated by the result of two phase II open-label, single-arm, multicenter clinical trials.^(13,14) In both trials, patients with cytokine-refractory metastatic RCC received repeated 6-week cycles of sunitinib (50mg orally once daily for 4 weeks, followed by 2 weeks without treatment). The RECIST criteria were used to identify objective response. In the first trial of 63 patients, partial response was observed in 25 patients (40%). Stable disease of 3 months or more was observed in 17 patients (27%). Median PFS was 8.7 months (95% CI, 5.5 to 10.7 months) and median overall survival was 16.4 months.⁽¹³⁾ In the second trial of 106 patients, partial response was observed

in 36 patients (34%). Stable disease of 3 months or more was observed in 30 patients (29%). Median PFS was 8.3 months (95% CI, 7.8 to 14.5 months).⁽¹⁴⁾

In a multicenter, randomized phase 3 trial, 750 patients with previously untreated, metastatic RCC were randomized to receive either sunitinib (50mg orally once daily in a repeated 6-week cycles of 4 weeks on, followed by 2 weeks off) or INF- α (at a dose of 9 million international units given subcutaneously three times weekly). The median PFS in the sunitinib group and in the INF- α group were 11 months and 5 months respectively (HR 0.42; 95% CI, 0.32 to 0.54; $p<0.001$). The objective response rate assessed using the RECIST criteria, was higher in the sunitinib group than in the INF- α group (31% versus 6%; $p<0.001$). Patients in the sunitinib group reported a significantly better quality of life than did patients in the INF- α group ($p<0.001$) (assessed with the Functional Assessment of Cancer Therapy – General (FACT-G) and FACT-Kidney Symptom Index (FKSI) questionnaires). The results demonstrate a significant improvement in PFS and objective response rate for sunitinib over INF- α in first-line treatment of metastatic RCC. Based on the results of this study, sunitinib was approved by FDA for the first-line treatment of metastatic RCC.⁽¹⁵⁾

Most general adverse events of all grades occurred more frequently in the sunitinib group than in the INF- α group. The proportion of patients with grade 3 or 4 adverse events was relatively low in both groups. The most common adverse effects experienced by patients treated with sunitinib were fatigue, diarrhea, nausea, stomatitis and dyspepsia. The most common treatment-related laboratory abnormalities reported were lymphopenia, neutropenia, anemia, hyperlipasemia, and thrombocytopenia.⁽¹⁵⁾

The recommended dosage of sunitinib for the treatment of advanced RCC is 50 mg orally once daily for 4 weeks on followed by 2 weeks off. The cycle may be repeated every 6 weeks. Sunitinib may be taken with or without food. The dose may be adjusted in 12.5 mg increments as needed for individual safety and tolerability.⁽¹⁶⁾

Sunitinib is metabolized primarily by the cytochrome P450 enzyme CYP3A4. CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, indinavir,

nefazodone, voriconazole) may increase sunitinib plasma concentration. If concomitant use of strong CYP3A4 inhibitor is required, a dose reduction for sunitinib should be considered. CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital and dexamethasone) may decrease sunitinib plasma concentration. If concomitant use of strong CYP3A4 inducer is required, a dose increase of sunitinib should be considered. No clinical studies were conducted in patients with impaired hepatic function or impaired renal function.⁽¹⁶⁾

CONCLUSION

Renal cell carcinoma is generally resistant to chemotherapy. Cytokines including INF- α and interleukin-2 have limited efficacy and are associated with considerable toxicities. The increased understanding of the pathogenesis of RCC has led to discovery of newer molecular pathways and subsequently novel targeted therapy in the treatment of metastatic renal cell carcinoma. The efficacy of tyrosine kinase inhibitors - sorafenib and sunitinib in the treatment of advanced renal cell carcinoma have

been demonstrated in clinical trials with tolerable adverse effects. Further clinical trials are required to compare the efficacy and safety of different targeted therapies, and to determine the proper sequencing of these agents in treating metastatic RCC.

Author's background

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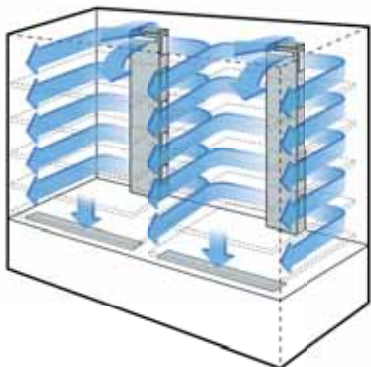
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Questions for Pharmacy Central Continuing Education Committee Program

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

1. Which of the following statements concerning kidney cancers is FALSE?

- a. approximately 3% of adult cancers are contributed by kidney cancers
- b. clear cell renal cell carcinoma is the most common kidney cancer
- c. most cases of kidney cancers occur in persons aged 50-70 years
- d. kidney cancers occur more frequently in female than in male
- e. clear cell renal cell carcinoma is strongly associated with inactivation of the von Hippel Lindau gene

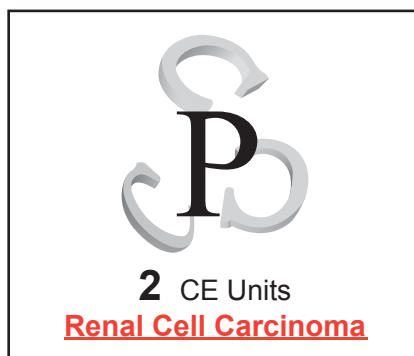
2. Which of the followings is NOT a risk factor for development of kidney cancers?

- a. cigarette smoking
- b. patient on long-term dialysis with cystic changes in the kidney
- c. use of opioid analgesics
- d. obesity
- e. long term exposure to high levels of asbestos, cadmium and trichloroethylene

3. Which of the following statements about treatment of renal cell carcinoma is INCORRECT?

- a. surgery is the drug of choice for treatment for localized renal cell carcinoma
- b. renal cell carcinoma is generally refractory to cytotoxic drugs
- c. treatment with cytokines results in an overall median survival of 13 months
- d. treatment with interleukin-2 was associated with considerable toxicities
- e. interferon- α was effective in 40% of the patients treated

4. What is the mechanism of action of sorafenib?



- a. binds and neutralizes circulating VEGF
- b. increases the action of circulating VEGF
- c. inhibits mTOR and reduces HIF activity
- d. inhibits the tyrosine kinase portion of the VEGF and PDGF receptors
- e. stimulates the tyrosine kinase portion of the VEGF and PDGF receptors

5. Which of the following drugs is NOT an approved targeted therapeutic agent for the treatment of renal cell carcinoma?

- a. sorafenib
- b. erlotinib
- c. bevacizumab
- d. temsirolimus
- e. sunitinib

6. Which of the followings is NOT the common side effect of sorafenib?

- a. hypertension
- b. rash
- c. diarrhea
- d. hand-foot skin reactions
- e. fatigue

7. Which of the following statements about sorafenib is INCORRECT?

- a. no dosage adjustment is required in patients with mild to moderate hepatic impairment

- b. dosage adjustment is required in patients with renal impairment
- c. sorafenib should be taken on an empty stomach
- d. treatment should be continued until disease progression or unacceptable toxicity occurs
- e. dose reduction may be necessary in the management of adverse drug reactions

8. The following drugs may interact with sorafenib EXCEPT:

- a. phenytoin
- b. dexamethasone
- c. rifampicin
- d. carbamazepine
- e. clarithromycin

9. Which of the following statements about sunitinib is INCORRECT?

- a. sunitinib may be taken with or without food
- b. in the first-line treatment of metastatic renal cell carcinoma, the progression free survival and objective response rate of sunitinib were significantly better than interferon- α
- c. fatigue, diarrhea, nausea, stomatitis and dyspepsia are the common side effects of sunitinib
- d. sunitinib may cause lymphopenia, neutropenia, anemia and thrombocytopenia
- e. dosage adjustment is required in patients with impaired renal function

10. The following drugs may interact with sunitinib EXCEPT:

- a. clarithromycin
- b. antacids
- c. dexamethasone
- d. ketoconazole
- e. rifampicin

Answers will be released in the next issue of HKPJ.

Overview on the International and Local situation of smoking cessation

Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
C	C	E	C	B	D	E	E	E	B

Acting Sites of Chlorhexidine on Cells of *Escherichia coli* and *Bacillus subtilis* are Different

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ABSTRACT

The effect of chlorhexidine (CHX) on the growth of Gram (+) and (-) bacteria was achieved by growth study and susceptibility test. With the aid of scanning electron microscopy together with transmission electron microscopy, morphological changes and the acting site of CHX were identified. Alterations in cell integrity as well as biomolecular alterations were monitored by energy-dispersive analysis of X-ray. It was found that bacteria exposed to CHX had lots of dented spot on cell surface similar to the effect of cerulenin. Transmission electron microscopic examination revealed that the damages in *B. subtilis* occurred mainly at the hemispherical caps of a cell while the damages in *E. coli* were retained to the cylindrical part as well as the growing tips of a cell. Leakage of cellular contents was found in cells after prolonged exposure to CHX, leading to the formation of ghost cells in a culture. A higher loss of lipids also took place in cells when a higher concentration of CHX was used. These results indicate that the cytoplasmic membrane of bacteria was disrupted by CHX, causing the leakage of cellular content and the formation of ghost cells. Based on the distributions of collapse in cells of *B. subtilis* and *E. coli* and the perturbation of phospholipid content, it is concluded that CHX attacked the cytoplasmic membrane of Gram (+) and (-) bacteria in different ways.

Keywords: Chlorhexidine; Lipid; *Escherichia coli*; *Bacillus subtilis*; Acting site, Cytoplasmic membrane

INTRODUCTION

Disinfection is a process in which an agent is used for the destruction, inactivation or removal of infectious microorganisms on inanimate objects and surfaces. Although sometimes it is achieved by physical procedures such as pasteurization and tyndallization, the most common practice is to use chemical

agents. Chemicals that are used for this purpose are called disinfectants. Amongst all the disinfectants currently in use, chlorhexidine (CHX) is one of the most favorable choices. It has been reported that CHX is effective to prevent and control infectious diseases of the mouth⁽¹⁾ and to kill bacteria in saliva and tongue; yet it has little undesirable effects.⁽²⁾ In addition, it is a broad-spectrum biocides against both Gram (+) and (-) bacteria⁽³⁻⁷⁾ and against yeast and fungi.⁽⁸⁻¹³⁾ Given that CHX has high levels of antimicrobial activity but relatively low levels of toxicity to mammalian cells,^(14,15) it is regarded as the most useful and safe disinfectant.⁽¹⁶⁾ Hence, it is widely used in hospitals and at home as a hygienic product purchasable over-the-counter in pharmacy store.

CHX has a strong affinity for skin and mucous membranes because of its cationic chemical nature. Its uses as a topical disinfectant for wounds, for skin prepping, and for protection of damaged mucous membranes have been reported to be very effective. Its proclivity to bind to the tissues offers a long lasting antimicrobial activity.⁽¹⁷⁾ The long lasting antimicrobial activities of CHX also make it suitable for use as a preservative in some pharmaceutical or medical products, such as ophthalmic solutions in the former category, and as a disinfectant of medical instruments and hard surfaces in the later category.

Different disinfectants, however, may have different ways and required different conditions to exert their maximal activity.^(18,19) The effect of CHX on bacteria has been studied a lot in recent years. These include investigation of its efficacy in cleaning and disinfection program,^(17,20) in periodontal disease prevention^(21,22) and so on. Though the *in vivo* and *in vitro* antimicrobial activities of CHX and its beneficial effects have been frequently reported, the exact sites by which CHX kills bacteria, in particular, the differences between Gram positive and negative bacteria are still ill-defined. Mechanistic study of its activities continues to be the focus of numerous investigations because it is still incompletely understood.⁽²³⁾ It is generally thought that the positively

charged molecule of CHX interacts initially with the negatively charged membrane in cell by absorption onto phosphate compounds on bacterial surface. It has been postulated that CHX bypasses the cell wall exclusion mechanism, and perfuse towards cytoplasmic membrane to cause leakage of low molecular weight components in cell membrane and precipitate cytoplasm through the formation of complexes with phosphate moieties.^(24,25) However, no distinction has been made between its action on Gram positive and negative cells.

Although its effect on the cell envelope and elemental composition of *P. stutzeri* has been described by Tattawasart and his associate,⁽²⁶⁾ the underlying actions of CHX on cell membrane has not been described in detail. In this study, the pattern of actions of CHX on Gram (+) and (-) bacterial cells was explored and we found that the acting sites of CHX on cells of *Escherichia coli* and *Bacillus subtilis* were different.

MATERIALS AND METHODS

Bacterial strains and growth conditions

E. coli ATCC 10536 and *B. subtilis* 60015 provided by Dr. H. Y. Cheung, City University of Hong Kong, were used throughout this study. Starter cultures of *E. coli* or *B. subtilis* were prepared as described previously by Cheung (1994) with some modifications by inoculating 50 µl of stock cells kept frozen at -80°C in the presence of 30% v/v glycerol into 25 ml nutrient broth in a reciprocating shaker water bath set at 120 rpm.⁽²⁷⁾ The cultures were incubated overnight, harvested by centrifugation and used for inoculation.

Chemicals and biocide solutions

Chlorhexidine (CHX), cerulenin and hexamethyldisilazane (HMDS) were purchased from Sigma-Aldrich (Saint Louis, Missouri, USA). Stock solution of CHX (75 mg/L) was prepared by dissolving in absolute ethanol. Nutrient agar and nutrient broth were obtained

from Oxoid Chemical Company (Basingstoke, Hampshire, UK). Glutaraldehyde (Electron Microscopy Grade) was from Mallinckrodt Specialty Chemicals Company (Paris, KY). Osmium tetroxide, Spur's resin, uranyl acetate and lead citrate were purchased from Electron Microscopy Sciences (Hatfield, Pennsylvania, USA).

Susceptibility tests

A series of medium with different concentrations of CHX were prepared by mixing appropriate volume of stock CHX solution and nutrient broth with a total volume of 4 ml. Ethanol concentration of each tube was kept at 1% v/v which did not exhibit any inhibitory effect on bacterial cells. After adding bacterial seedling culture, they were incubated at 37°C in shaking water bath at 120 rpm and the optical density at 600 nm (OD₆₀₀) readings were measured at 4 and 24 h.

Growth study

Growth of bacterial cultures was monitored by measuring the OD₆₀₀. Overnight seedling culture was harvested and resuspended in an aliquot of fresh nutrient broth before it was inoculated into 25 ml of the same medium containing different concentration of CHX. Growth was monitored at 37°C by measuring OD₆₀₀ at 1-h intervals over a 24-h period.

SEM and EDAX studies

The procedure of SEM was done as described by Khunkitti *et al.*⁽²⁸⁾ but with some modifications. Cells harvested at different concentrations of CHX or cerulenin were filtered through a 0.2 µm syringe membrane filter and were fixed for 24 h at 4°C in 2% v/v glutaraldehyde in 0.1 M sodium cacodylate buffer, pH 7.2. Cells were washed with cacodylate buffer in decreasing concentrations of 0.1 M, 0.05 M and 0.025 M for 15 min each and washed once in distilled water for 15 min. Samples were then dehydrated through a graded ethanol series of 50, 70 and 90% v/v for 15 min each and then three times in 100% ethanol for 15 min each. The dehydrated samples were washed by hexamethyldisilazane (HMDS) twice for 30 s each time. They were then blotted dry with filter paper and quick air-dry until all the HMDS were removed. With the use of carbon tape, the samples were stuck on aluminium stub and kept in a desiccator overnight. The dehydrated samples could be observed under Philips XL30 ESEM-FEG (Philips Electronics, Netherlands, Europe) after coated with carbon.

Determination of cellular content of chlorine and phosphorus

Elemental content of chlorine and

phosphorus in individual cell was determined by an energy-dispersive X-ray detector equipped with a multichannel analyzer (Links 860 EDAX) associated with the ESEM. The microscope was operated at voltage of 15-20 KV and the magnification was between 15000 and 30000. Cellular content of chlorine and phosphorus of bacterial specimen encircled within an area was recorded and then outputted as an EDAX spectrum. The percentage composition of the detected elements was calculated. The weight percentage of chlorine and phosphorus could reflect the cellular content of chlorine (Cl) and phospholipids in cells respectively.⁽²⁶⁾

TEM studies

The procedure of TEM was done as described previously by Cheung and Vitkovic⁽²⁹⁾ but with some modifications. Cells under exposure of different concentrations of CHX for 4 h were harvested and rinsed three times by centrifugation at 6000 g. The cell pellet was then fixed in 3% v/v glutaraldehyde solution and incubated for overnight at 4°C. After fixation, the glutaraldehyde solution was removed and the cell pellet was washed for three times with cacodylate buffer by centrifugation at 2000 g for 15 min. Each pellet was resuspended in a small volume of buffer and mixed with molten agar on a clean glass slide rapidly. Once the agar was solidified, the agar was cut into approximately 1 mm³ blocks and transferred to small glass vials containing 0.1 M cacodylate buffer. The cubes were washed once with the buffer and then postfixed in 1% v/v osmium tetroxide (OsO₄) in 0.1 M cacodylate buffer at room temperature in darkness for 2 h. After postfixation the cubes were rinsed in 0.1 M cacodylate buffer for 10 min, following by 0.05 M cacodylate buffer and deionized water. Samples were then dehydrated through a graded ethanol series of 10, 30, 50, 70, 80, and 90% v/v for 15 min each and then washed two times for 15 min each in 100% ethanol. The cell pellets were further dehydrated in a ratio of ethanol to acetone with 100% ethanol-acetone (3:1), 100% ethanol-acetone (1:1), and 100% ethanol-acetone (1:3) for 15 min each and finally washed two times for 15 min each in 100% acetone. The cell pellets were resin-infiltrated at room temperature through a graded 100% acetone to Spur's resin ratio at 4:1, 3:2, 2:3, and 1:4, at which the time of the infiltration was 1 h, overnight, and half day respectively. The pellets were continuous infiltrated with pure Spur's resin for three days. After infiltration the samples were embedded in plastic molds. The molds were then taken to 60°C oven to dry off for 2 days. The blocks were trimmed using a sharp knife under the LEICA S6E (Leica Microsystems, Wetzlar,

Germany), following by thin-sectioning on Leica Ultracut UCT with a glass knife. Sections should be 80 nm of thickness and the sections were picked up and mounted on copper grids coated with Collodion (Parlodion) purchased from Electron Microscopy Sciences (Hatfield, PA). Sections were counter-stained with lead citrate for 5 min, washed with 0.01 M sodium hydroxide, followed by three washes with water. Finally they were stained with 0.2% uranyl acetate for 10 min in the dark and washed three times with water. Stained sections were examined and photographed using a Philips Technai 12 Transmission Electron Microscope (Philips Electronics, Netherlands, Europe) operating at 80 kV under standard conditions with liquid-nitrogen cold trap in place.

Counting of dented spot

With the aid of environmental scanning electron microscope, the number of dented spots at different parts (trunk and tip) in 50 cells of *B. subtilis* and *E. coli*, respectively was counted. The tip is defined as the hemispherical caps of a rod-shaped bacterial cell while the trunk is defined as the remaining part of bacterial cell, i.e. cylindrical zone, of a bacterial cell (Figure 1).

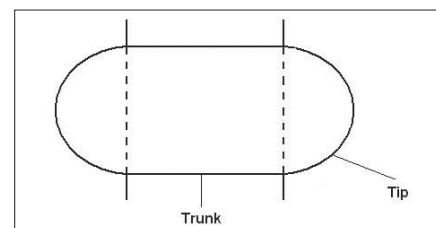


Figure 1. Definition of trunk and tip of a bacterial cell. The two hemispherical caps are the tips while the middle cylindrical zone is the trunk of a rod-shaped bacterial cell as described in the Materials and Methods.

RESULTS

Effect of CHX on the growth of *B. subtilis* and *E. coli*

Since ethanol was used to prepare the stock solution of CHX, its antimicrobial activity had to be checked. Growth of both types of bacteria was affected only when the final concentration of ethanol in a culture was more than 4% v/v (data not shown). In order to eliminate the antimicrobial effect of ethanol on these bacterial cells, ethanol concentration was always kept at 1% v/v in all studies. Figure 2 shows that the growth of both *B. subtilis* and *E. coli* was affected after the addition of CHX. The inhibitory effect of CHX on cell growth was enhanced when the concentration of CHX was increased. In comparison to the control culture (untreated cells), growth pattern was a sigmoid curve that consist of a short lag phase, followed by a long exponential phase before entering into stationary

phase. As CHX concentration increased, cell growth was inhibited and there was a long lag phase (Figure 2). When CHX concentration was around 0.5 mg/L, significant inhibitory on the growth of both *B. subtilis* (Figure 2a) and *E. coli* (Figure 2b) was observed. The inhibitory effect lasted for 6 h before both bacterial cells regained their ability to grow for another 5-6 h to reach the stationary phase. This phenomenon indicates that CHX at 0.5 mg/L concentration was bacteriostatic rather bactericidal. In addition, it was found that at this concentration of CHX, *B. subtilis* entered the log phase earlier but grew slower than *E. coli*. The minimum inhibitory concentration (MIC), which is the smallest concentration of an antibiotic / a drug required to inhibit or stop the growth of a culture, was 0.3 mg/L and 0.4 mg/L, and 0.6 mg/L and 0.7 mg/L for *B. subtilis* and *E. coli* after 4 h and 24 h, respectively (Table 1). From these results, it suggests that *B. subtilis* was more susceptible to CHX than *E. coli*.

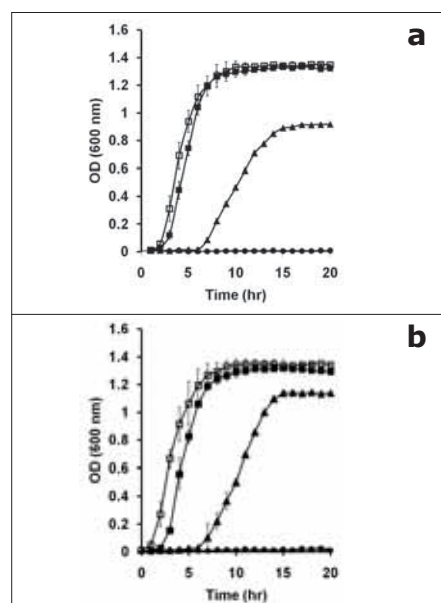


Figure 2. Effect of chlorhexidine on bacterial growth. Growth curves of *B. subtilis* (a) and *E. coli* (b) were performed as described in Materials and Methods. Cell culture was harvested at particular time points and monitored by measuring OD at 600 nm against medium as blank. Cells treated with different concentrations of chlorhexidine: open rectangle = 0 mg/L; filled rectangle = 0.25 mg/L; triangle = 0.5 mg/L; Circle = 0.75 mg/L. Each plot of the curve represents the mean of reading from two replicates and standard deviation is shown.

Microorganism	MIC (mg/L)	
	4 hour	24 hour
<i>B. subtilis</i>	0.3	0.6
<i>E. coli</i>	0.4	0.7

Uptake of chlorhexidine and loss of phosphorus by cells

With the three working concentrations of CHX, the uptake of CHX and the phosphorus content by cells could be

revealed by measuring their weight percentage of the detected elements using EDAX. The cellular contents of Cl and P against time are shown in Figure 3. It was found that the amount of CHX in cells was increased with time and the uptake of CHX by *E. coli* was higher than that by *B. subtilis* at any time (Figure 3a). Coincidentally, the rate of P reduction was more in *E. coli* than that of *B. subtilis* in the first three hours (Figure 3b).

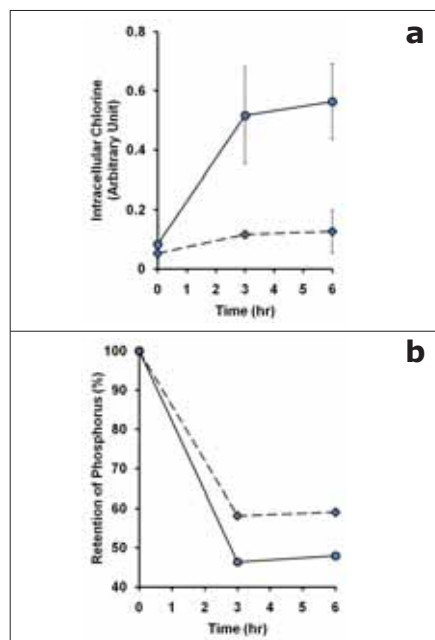


Figure 3. Uptake of chlorine and loss of phosphorus by cells treated with 0.75 mg/L chlorhexidine. The cellular contents of chlorine (a) and phosphorus (b) in *B. subtilis* (diamond) and *E. coli* (circle) at different time points were subjected to environmental scanning electron microscope (ESEM) and then determined using EDAX as described in Materials and Methods. Standard deviation is shown with 3 samples taken.

Topological changes of bacteria after CHX treatment

Figure 4a and 4b are the morphology of control cells of *B. subtilis* and *E. coli*, respectively. The cells were intact and typically rod shaped before the CHX treatment but significant changes in morphology were observed after treatment. Many dented spots were found over the cell surface of *E. coli* including the tips and the trunk of a rod cell (Figure 4d) while the affected region of *B. subtilis* was mainly retained to the tips of a rod cell (Figure 4c). The number of these dented spots on cell surface was increased when the concentration of applied CHX increased (Figure 5a). Longer exposure to CHX progressively caused more dented spots on the cell (Figure 5b). The number of dented spots at the tips and at the trunk, however, was differently distributed in *E. coli* that the dented spots were mainly observed at the cylindrical zone (Figure 6b and 7b). In contrast, the dented spots were found mainly at the tips in *B. subtilis* (Figure 6a and 7a). The morphological changes

of both *B. subtilis* and *E. coli* exposed to CHX were found similar to that of cells treated with cerulenin (Figure 8) which is an antibiotic that inhibits the biosynthesis of sterol and fatty acids in cells.⁽³⁰⁾ It has also been well documented that cerulenin affects lipid synthesis and perturbs the integrity of cytoplasmic membrane in cells.⁽³¹⁾

Although SEM pictures provide useful information about the effect of CHX on bacteria, the exact affected sites on both cells of *B. subtilis* and *E. coli* could not be determined. TEM provides a useful tool for revealing changes in the internal structures of cells. Significant cytological changes were observed in the CHX-treated cells of *B. subtilis* and *E. coli* in comparison to those of the

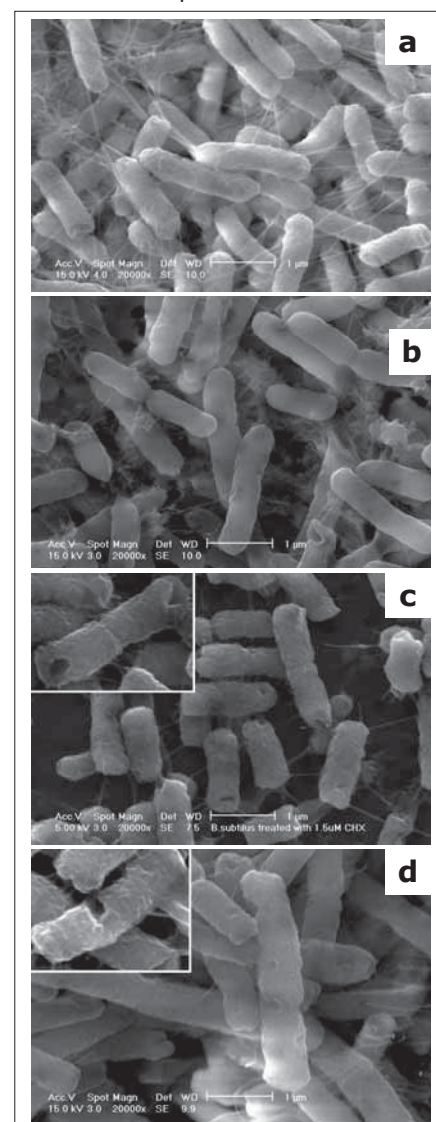


Figure 4. Morphological change of *B. subtilis* and *E. coli* before and after exposure to chlorhexidine. Bacterial cell samples were prepared as described in Materials and Methods and examined under environmental scanning electron microscope. Control of *B. subtilis* cells (a), Control of *E. coli* cells (b), *B. subtilis* cells treated with 0.75 mg/L chlorhexidine for 4 h (c) and *E. coli* cells treated with 0.75 mg/L chlorhexidine for 4 h (d). Magnification in all cases x20,000. Bars represent 1 μm. Magnification in inserts of (c) and (d) x30,000.

control (Figures 9a and 10a). In both cases, the outer membrane in *E. coli* and the cytoplasmic membrane in *B. subtilis* cells were detached from their cell wall (see arrows). This implies that the dented spots found in CHX-treated cells were probably due to the disruptions of the phospholipid bilayer in the membrane. The observations of membrane

collapses in CHX-treated cells (Figures 9b and 10b) and bulging of cell envelope in some treated cells (Figures 9c and 10c) support this conclusion.^(26,32-34) The damaged membrane eventually lead to the formation of ghost cells in the culture of *B. subtilis* and *E. coli* (Figures 9d and 10d). The ghost cells, however, still possessed a cell wall but not an

intact cytoplasmic membrane. It has been reported that at high concentration, perfusion of CHX into the cells caused precipitation in the cytoplasm.^(35,36) The coagulated cytoplasmic materials, therefore, allowed leakage of cellular contents through the damaged sites on the membrane as evidenced in the TEM pictures (Figure 9c and 10c).

Relationship between CHX and cellular phospholipids

There are reports indicating that transmembrane disruptions could lead to reduction in cellular content of ions, ATP and other metabolites.⁽³⁴⁾ As suggested by

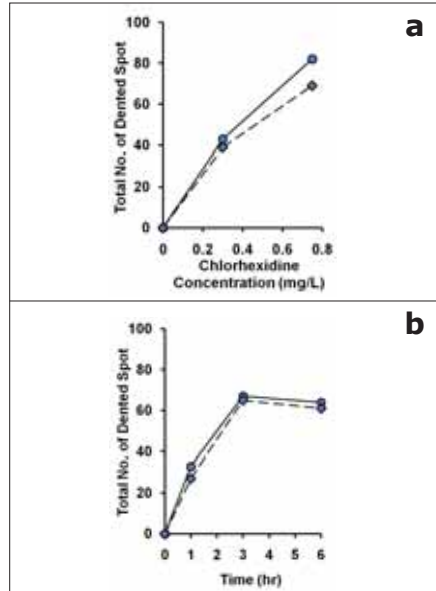


Figure 5. Total number of dented spot observed on the bacterial cell surface. Dented spots including trunk and tips were counted against different chlorhexidine concentrations (a) and against time (b) in 50 cells of *B. subtilis* (diamond) and *E. coli* (circle). Counting of dented spot was described in the Materials and Methods.

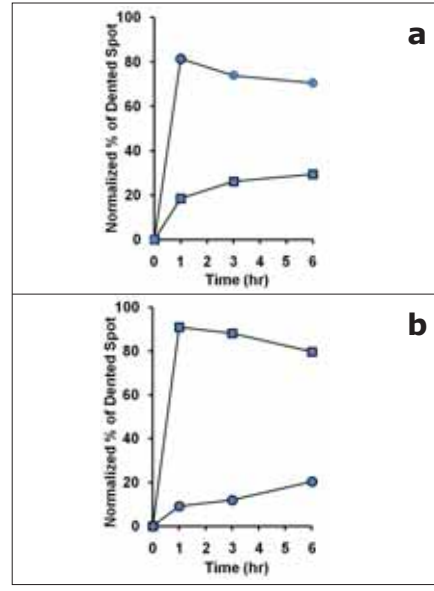


Figure 7. Distribution of dented spots at different sites of cells treated with chlorhexidine against time. Bacterial cells were incubated in media with 0.75 mg/L chlorhexidine over a 6-h period. Cells at particular time point were harvested and examined under environmental scanning electron microscope (ESEM) as described in Materials and Methods. With the aid of ESEM, the number of dented spot at trunk (rectangle) and tip (circle) was counted in *B. subtilis* (a) and *E. coli* (b). Total 50 cells were counted.

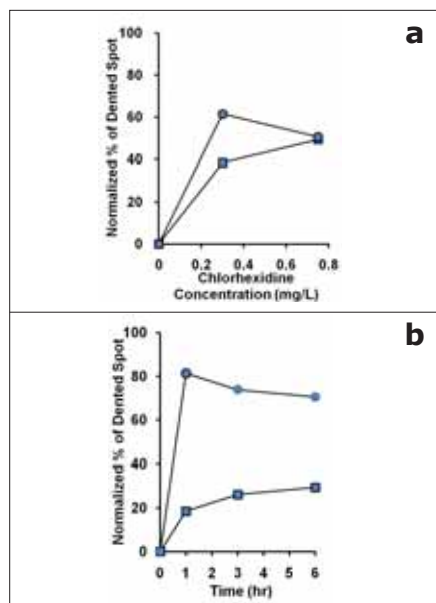


Figure 6. Distribution of dented spots at different sites of cells after chlorhexidine treatment. Bacterial cells were incubated in media in the presence of different concentrations of chlorhexidine. After 3 h incubation, bacterial cells were harvested and examined under environmental scanning electron microscope (ESEM) as described in Materials and Methods. With the aid of ESEM, the number of dented spot at trunk (rectangle) and tip (circle) was counted in *B. subtilis* (a) and *E. coli* (b). Total 50 cells were counted.

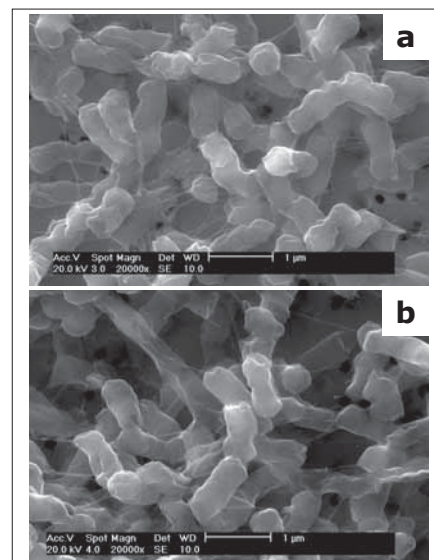


Figure 8. Scanning electron micrographs of *B. subtilis* and *E. coli* after exposure to cerulenin. Bacterial cell samples were prepared as described in Materials and Methods and examined under environmental scanning electron microscope. *B. subtilis* cells treated with 15 mg/L cerulenin for 4 h (a) and *E. coli* cells treated with 15 mg/L cerulenin for 4 h (b). Magnification in all cases x20,000. Bars represent 1 µm.

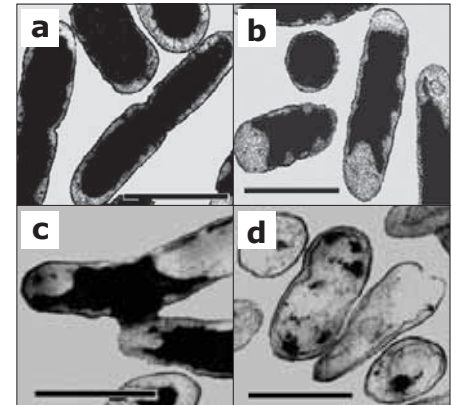


Figure 9. Cytological change of *B. subtilis* after treatment with chlorhexidine. The cells were prepared as described in Materials and Methods and examined under transmission electron microscope. The control cells, characterized by intact cell membrane with cell wall and complete cell content (a). After 4 h of incubation with 0.75 mg/L chlorhexidine, treated cells show detached cytoplasmic membrane from cell wall at the two poles of a rod cell (see arrows in b), leakage of cell content (see arrow in c) and the formation of ghost cells (d). Magnification in all cases 20,500. Bars represent 1 µm.

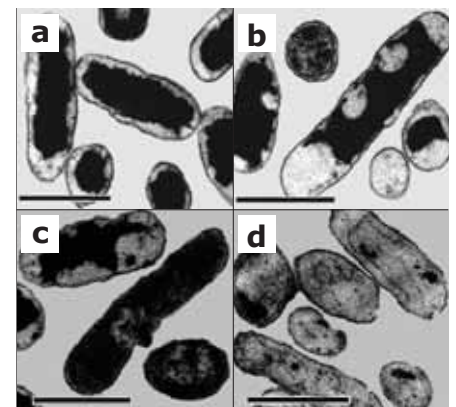


Figure 10. Cytological change of *E. coli* after treatment with chlorhexidine. The cells were prepared as described in Materials and Methods and examined under transmission electron microscope. The control cells, characterized by intact cell membrane with cell wall and complete cell content (a). After 4 h of incubation with 0.75 mg/L chlorhexidine, treated cells show detached cytoplasmic membrane from cell wall at both poles and cylindrical part of a cell (see arrows in b), leakage of cell content (see arrow in c) and the formation of ghost cells (d). Magnification in all cases 20,500. Bars represent 1 µm.

Tattawasart *et al.*,⁽²⁶⁾ chlorine (Cl) could be used as a marker representing the amount of CHX taken up by the cells. Phosphorus (P), which is a major component of the phospholipid bilayers, could also be used as an elemental marker reflecting the alternations within the cells. With the aid of an EDAX, content of Cl and P expressed as percentage under different conditions was estimated. Figure 11 shows the relationship between the uptake of CHX, represented by chlorine, and the changes of phospholipids, represented by phosphorus. As shown in the figure, the phosphorus content decreased in both *B. subtilis* and *E. coli* while chlorine concentration increased (Figure 11), indicating that the uptake of CHX was responsible for the collapse of phospholipid bilayers in the cell envelope. Figure 11 also reveals that the decrease of lipid content as reflected by the phosphorus content in *B. subtilis* was more severe than that in *E. coli* as there was a rapid drop of phosphorus even at very low concentration ranges of chlorine. The results from both growth study and elemental analysis explicate that *B. subtilis* was more sensitive to CHX than *E. coli*.

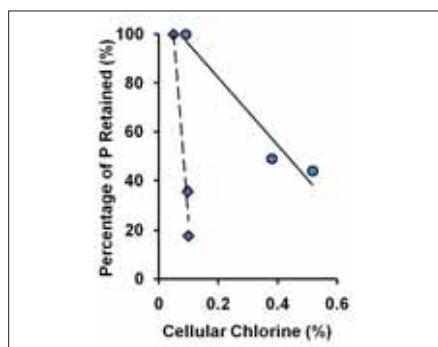


Figure 11. Effect of chlorhexidine exposure on phospholipids content in *B. subtilis* and *E. coli*. The uptake of chlorhexidine was reflected by cellular chlorine while phospholipid was reflected by cellular phosphorus as described in the Materials and Methods. The bacterial cells were treated with three different working concentrations of chlorhexidine for 3 h and then subjected to EDAX to determine their contents of chlorine and phosphorus. The loss of phosphorus and uptake of chlorine by cells were plotted in order to illustrate their relationship among the two different microorganisms, *B. subtilis* (diamond) and *E. coli* (circle).

DISCUSSION

The antimicrobial activity of CHX has been investigated for some times.⁽³⁷⁻³⁹⁾ Although the microbial inhibitory effect of CHX was strong, it lasted for only a short period of time. Once the effect of CHX demised with time, cells could regain their ability to grow. The results obtained in this study, hence, confirm that CHX indeed is bacteriostatic.⁽⁴⁰⁾ But contrary to previous reports, *E. coli*, a representative of Gram (-) bacteria, was found more

resistant than *B. subtilis*, a representative of Gram (+) bacteria to CHX.^(40,42)

The similar morphological changes of CHX-treated cells in comparison to the cerulenin-treated cells suggest that cytoplasmic membrane had been disrupted. As the outer membrane of Gram (-) bacteria, represent by *E. coli* is mainly comprised of liposaccharide (LPS) and phospholipids, CHX might interact with these subcellular materials when the drug diffuses into the cell. Supporting evidences come from the observation that the number of dented spots increased when the concentration of CHX in both culture of *E. coli* and *B. subtilis* increased. However, the different topological changes in *E. coli* and in *B. subtilis* were most likely attributed to different structure of the cell wall between Gram (+) and (-) bacteria. As CHX has a high affinity to lipophilic compounds, it tends to interact with substances or regions that composed of a higher content of lipophilic substances. Therefore, wherever there is a higher amount of phospholipids, there will be the target site of CHX. In most cases, Gram (+) bacteria, represented by *B. subtilis*, have no or very thin outer membrane along the trunk but lots more lipid at the tip region. Consequently, the primary site of attack is the tip regions as there are more lipids incorporated than that of the trunk in Gram (+) bacteria.⁽⁴³⁾ Besides, teichoic acids that composed of higher phosphodiester bonds are mainly located at the tips of these cells,⁽⁴⁴⁻⁴⁶⁾ they may play a role to interact with CHX. Hence, the damaged sites occurred mainly at the tips of *B. subtilis*. Since the lipid distribution of cell envelope was different in *E. coli*, the target site of CHX in these two bacteria would also be different, leading to different damaged area. CHX has been reported to cause alteration of outer membrane, resulting in rupture of cell wall, coagulation and cytoplasmic leakage.^(25,26,33,47,48) Consequently, more dented spots were found on the tips of the former while trunk part of the later after the cells were treated with CHX. Formation of new cytoplasmic membrane may also be inhibited as CHX precluded into the cell to affect the active uptake of small molecules.⁽⁴⁹⁾

From the EDAX study, the weight percentage of phosphorus (P) decreased with the increased concentration of CHX for both bacteria. However, the rate of reduction of P in *B. subtilis* was higher than that in *E. coli*, suggesting that *B. subtilis* was more susceptible to CHX. This conclusion receives further supporting evidences from the growth study as well as the susceptibility tests. Since *B. subtilis* do not have an outer membrane, the foremost attacked site would be the cell wall. Nadir and Gilbert

(1979) commented that cell wall fraction would uptake CHX for approximately 50% of that for the whole cell.⁽⁵⁰⁾ As a result, wall thickness was the prominent concern of cell defence. Furthermore the tips of *B. subtilis* contain more teichoic acid which belongs to phosphodiester, cell damaged by CHX at the tips was observed. From a recent study, it was found that CHX releases lipopolysaccharide (LPS) from outer membrane⁽⁵¹⁾ and the structural alteration by CHX would cause loss of lipid content.⁽³³⁾ All these discoveries confirm that CHX indeed interact with phospholipids-lipopolysaccharide complexes and cations in the envelope.⁽⁵²⁾

Structural elements of interest including P, which is an important structural element of cell membrane, and Cl, marker which is a marker for the presence of CHX^(26,53,54) were analysed by EDAX which is a useful tool for studying the distribution of elements within bacterial cells. The increase weight percentage of chlorine and phosphorus after treatment with CHX suggested an increase uptake of CHX and the loss of phosphorus with time, respectively. In this study, it was also found that the increase uptake of CHX caused loss of phosphorus in cells and that the effect of CHX on *B. subtilis* was more profound than that on *E. coli* although there was only very little chlorine uptake by the former as shown in Figure 3a.

To conclude, CHX affects both *E. coli* and *B. subtilis* with different extend. It is because of the differences in the cell wall components of these two types of bacteria. Gram (-) bacteria have outer membrane which contains phosphorus. Hence, it is the target site for CHX. On the other hand, the cell wall of Gram (+) bacteria has teichoic acids which contain phosphates while at the caps, it has lots more phospholipids. Hence, the caps of this cell are the target site for CHX.

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Author's background

Both Miss TANG Pui-Fung and Mr. WONG Kin-Kai did partial of this research as their final year project under the supervision of Dr CHEUNG. Miss CHEUNG Sau-Ha was initially a Research Assistant to Dr CHEUNG. She subsequently did her MPhil degree under Dr CHEUNG's supervision. Dr CHEUNG HY could be contacted through: Tel: +852-2788-7746; Fax: +852-2788-7406; or via E-mail: bhhyun@cityu.edu.hk

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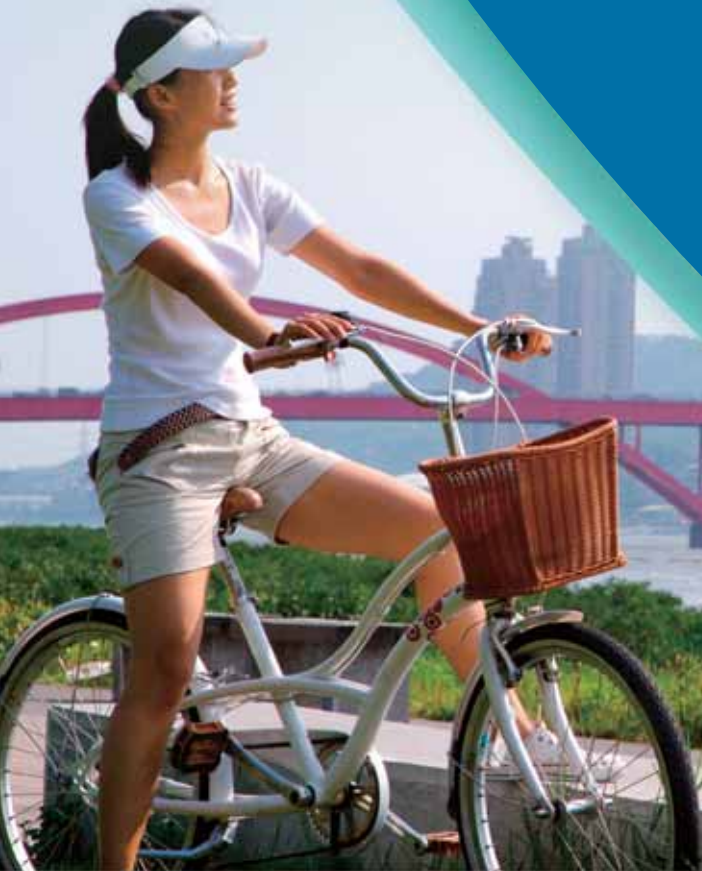
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Differences between *Peucedanum praeruptorum* Dunn and *Peucedanum decursivum* Maxim – the Two Commonly Mixed Species of Radix Peucedani (前胡)

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ABSTRACT

According to the Chinese Pharmacopoeia, Qianhu (前胡) is the root of *Peucedanum praeruptorum* Dunn (白花前胡) or *Peucedanum decursivum* Maxim (紫花前胡). It is commonly used for relieving lung heat and resolving phlegm-heat. The two species of genus *Peucedanum*, however, are different and could be distinguished by a variety of methods. In this brief review, differences between the two species are highlighted and compared in many aspects, namely, the morphological appearance, characteristic of pulverized powder, genomic profiles, major bioactive components, and pharmacological activities. It is concluded that these two species have their own unique features and functions. Hence, it is suggested that they should not be used interchangeable.

Keywords: *Peucedanum praeruptorum* Dunn; *Peucedanum decursivum* Maxim; Qianhu; Radix Peucedani

INTRODUCTION

Qianhu, also called Hogfennel Root, is the dried root of *Peucedanum praeruptorum* Dunn (PPD) or *Peucedanum decursivum* Maxim (PDM). It is a traditional Chinese medicine commonly used for removing lung heat, resolving phlegm-heat and dispelling "wind", which is an exogenous pathogenic factor characterized by upward and outgoing dispersion, rapid change, and constant movement.⁽¹⁻²⁾ The two species of genus *Peucedanum* are commonly mixed for use in China. With the advancement in authentication techniques and knowledge, it is now possible to distinguish between these two species by means of physical, chemical and biological analysis and instrumental studies.

The PPD plant (Figure 1) is a perennial herb found growing in semi-shaded or sunny areas of elevated hillsides, forests, roadside and hillside tussock at an altitude of 250-2000 m. The whole plant is about 60-1000 cm in height. The flowers are white in color. Flowering of the plant normally takes place during

July to September. The fruiting period is between October and November. The plant is mainly distributed in Gansu, Jiangsu, Anhui, Zhejiang, Jiangxi, Wuyishan (Fujian), Hunan, Hubei, Guangxi, Sichuan and Guizhou.

The PDM plant (Figure 2) is also a perennial herb, but with purple flowers. It is usually 1-2 m high and grows on hillsides, in forests, streamside and shaw. The plant is mainly distributed in Liaoning, Hebei, Shanxi, Jiangsu, Anhui, Zhejiang, Jiangxi, Taiwan, Hubei, Hunan, Guangdong, Guangxi and Sichuan.



Figure 1. *Peucedanum praeruptorum* Dunn

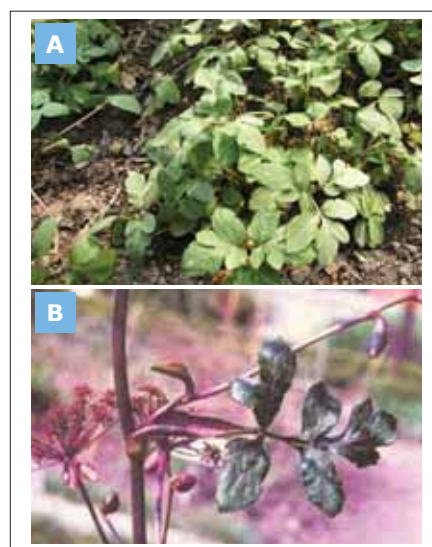


Figure 2. *Peucedanum decursivum* Maxim. Plate A = whole plant; B = flowering part

Both PPD and PDM are drought enduring, cold resistant and highly adaptable. The plants grow well in cool and moist areas, especially in places with fertile humus. However, heavy clay soil with low moisture is not an ideal growth condition.⁽³⁾

After for a growth period of 2 to 3 years, the root is collected in winter and next spring when the stems and leaves wither or before the floral stems begin growing. Basic treatments on the raw plant collected include removal of foreign matter, washing, softening, and cutting into thin slices for drying either in the sun or at a low temperature.⁽⁴⁾

MORPHOLOGICAL DIFFERENCES IN APPEARANCE

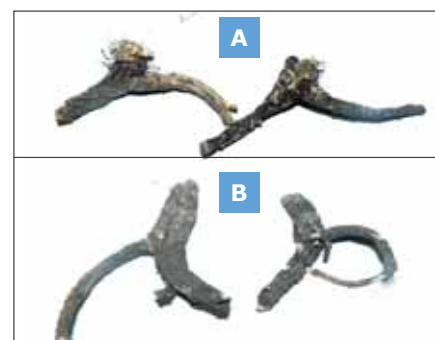


Figure 3. Morphologies of Radix Peucedani. Plate A: Dried root of *Peucedanum praeruptorum* Dunn; Plate B: Dried root of *Peucedanum decursivum* Maxim

The dry root of PPD is irregular, cylindrical, conical, or fusiform in shape with a slightly twisted appearance. The low part of the root has a branch with length of 3-15 cm and diameter of 1-2 cm, and is usually removed. The root looks blackish brown to grayish yellow with scars of a stem and fibrous remains of periclaste at the root stock. The upper part of the herb has concentrated crabwise annular, while the lower part have longitudinal groove, with ruled and crabwise lenticels. The herb is hard and brittle; the cross-section after braking is irregular, pale yellowish white in colour, and with a brown cambium ring and ray texture. The cortex occupies three fifth of the root; it is pale yellow with dispersed brownish yellow oil droplet. The xylem is yellowish brown. The odor is

aromatic while the taste is sweet, followed by bitter and pungent.

The major difference between PPD and PDM is that PDM does not have any fibrous remains of periclaste at the root stock but possesses leaf sheath residues around the stock (Figure 3). The broken cross section area of the PDM is white with narrow cortex and less oil droplet. The ray texture is not clear, and the xylem occupies more than half of the area of the root cross-section. The odors and taste are similar to PPD, but the taste is much blander.⁽⁵⁾

Differences in the transverse section between *Peucedanum praeruptorum* Dunn and *Peucedanum decursivum* Maxim

The transverse section of the dried root of PPD has 8-20 rows of cells in the cork region. The narrow cortex beneath consists of 2-3 rows of exodermises with tangentially elongated cells. The phloem occupies three fifth of the radius of the root. The outer part of phloem has curved rays, contains abundant cleaves and scattered cells. The cambium is in a ring form. The xylem vessels are arranged radially with some oil cavities. Sometimes fibers are found in a group of xylem vessels. There are 2-6 rows of xylem cells which have distinct rays. Parenchymatous cells contain numerous starch granules.

PDM has the major difference with PPD in the xylem. The xylems of PDM occupy half of the radius of the root. Vessels are arranged irregularly, and the centre of the root is surrounded by scattered fiber bundles. It lacks oil cavities and has indistinct rays.^(3, 5-6)

CHARACTERISTIC DIFFERENCES IN POWDER



Figure 4. Microscopic characteristics of the pulverized powder of *Radix Peucedanum*. Plate A: *Peucedanum praeruptorum* Dunn dried root powder; Plate B: *Peucedanum decursivum* Maxim dried root powder A-1: stone cell; A-2: cork cell; A-3: fragment of oil canal; A-4: Xylem fibers; A-5: starch granules; A-6: vessel. B-1: sclerenchyma cell; B-2: fragment of oil canal; B-3: xylem ray cell; B-4: xylem fibre; B-5: cork cell; B-6: vessel; B-7: starch granules^(6,7)

The powder of dried root of PPD is pale yellowish brown. Stone cells are square, ovate or triangular with diameter of 22-29 μm and length of 66-103 μm ; striations are distinct. There are abundant oil canal fragments containing yellow oil droplets. Xylem fibers are present in singly scattered form or in bundles. Fusiform, usually a few rows of overlapping cork cell, appear on the surface in rectangular or triangular shape. Vessels are mainly bordered and pitted (Figure 4A).

PDM dried root powder is pale reddish brown (Figure 4B). Similar to PPD, there are abundant oil canal fragments containing strip shaped yellow secretions. Xylem fibers are slender and present in singly scattered form or in bundles. Few rows of cork cell are overlapped, observed as polygonal or irregular shape on the surface view. The vessels are mainly reticulated and scalariform.⁽⁵⁻⁶⁾

GENOMIC DIFFERENCES

Choo et al recently reported that the genomic sequences between PPD and PDM are significantly difference, which could be exemplified by the internal transcribed spacer (ITS) sequence and random amplified polymorphic DNA (RDNA). According to his results, PDM should be considered a part of *Angelica*, and not *Peucedanum*.⁽⁷⁻⁹⁾

DIFFERENCES IN CHEMICAL COMPONENTS

The genus *Peucedanum* is well known for its rich source for pyranocoumarins. The root of PPD contains a number of pyranocoumarin substances, namely praeruptorin A, B and C. (Figure 5)⁽¹⁰⁻¹²⁾ Pyranocoumarin glycosides, such as praeroside II, III, IV and V (Figure 6) are also present in the herb. It was reported that furanocoumarin glycosides such as praeroside I, isorutarin, rutarin and marmesinin (Figure 7), as well as coumarin glycoside, namely scopione and skimmion were also isolated from the herb.⁽¹³⁻¹⁴⁾

Other components found in this herb include Pteryxin, peucedanocoumarin I, II, III, qianhuocoumarin A, 9-angeloyloxy-10-

oxo-dihydroseselin (Figure 8), psoralen, 5-methoxy, psoralen, 8-methoxy psoralen, peucedanol, nodakenin, decuroside, apterin, D-mannitol, galactitol, Pd-saponin V, 3-O- α -L-arabinopyranosyl hederagenin-28-O- β -gentiobioside,⁽¹⁵⁾ acetylactylodiol, tanshinone IIA, tanshinone I, cis-3',4'-diisovalerylhellactone, cis-3',4'-diseneciolykhellactone,⁽¹⁶⁾ sclerodin, palmitic acid, bergapten, imperatorin, 2-6-dimethylquinoline, daucosterol,⁽¹⁰⁾ D-glucopyranose-1-hexadecanoate, D-mannitol monohexadecanoate, elutheroside B¹, apiosylskimmion and mannitol.⁽¹⁷⁾

A series of furanocoumarins were found in the root of PDM, namely decuroside I, II, III, IV and V,⁽¹⁸⁾ bergapten and nodakenin.⁽¹⁹⁻²⁰⁾ Besides, nodakenin⁽²⁰⁾ had been reported in this herb. Pyranocoumarins such as xanthyletin, decursin and decursidin have also been found.⁽¹³⁾ (Figure 9-12)

Other components found in this herb include 3'(S)-acetoxy-4'(R)-angeloyloxy-3, 4'-dihydroxanthyletin, Pd-C-V, Pd-C-II, (+)-3' S-Decursinol, (+)-Trans-Decursidinol,⁽²¹⁾ and isopeucenidin.⁽²⁰⁾

DIFFERENCES IN PHARMACOLOGICAL ACTIVITIES

Inhibitory effects on cell proliferation of aortic smooth muscle

Praeruptorin C (Pra-C) was reported to show inhibitory effects on aortic smooth muscle cells of cattle. The inhibitory effect is directly proportional to Pra-C concentration between 0.001 $\mu\text{mol/L}$ and 10 $\mu\text{mol/L}$. This effect is due to the inhibitory ability of Pra-C towards cell mitosis.⁽²²⁾

Inhibitory effects on hypertension and vascular hypertrophy; reduction in collagen content and abnormal vascular responses

Pra-C inhibits the thickening of the intermediary of blood vessels and initiates the maintenance of calcium ion (Ca^{2+}) concentration in cell homeostasis. Pra-C can reduce collagen formation, increase SMC and release NO. Formation of high state vascular ring was inhibited.⁽²³⁻²⁴⁾

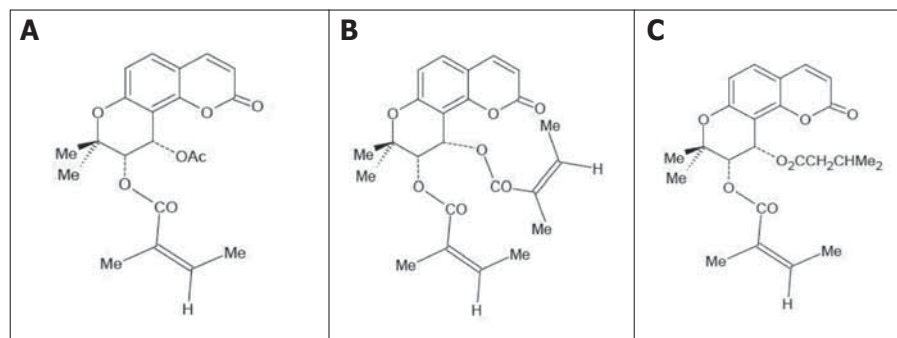


Figure 5. Chemical structures of some pyranocoumarins compounds isolated from PPD. Frame A: praeruptorin A; B: praeruptorin B; C: praeruptorin C

Anti-heart failure

A study showed that the extract of PPD can significantly reduce the IL-6 levels in rats, which is one of the factors that causes heart failure when combined with cardiac fibroblast cells, as the receptor produces high concentrations of nitric oxide to promote cardiomyocyte apoptosis.⁽²⁵⁾

Anti-Cough and Anti-inflammatory

In the concentrated ammonia spraying method it was found that the extract of PPD showed an anti-cough effect, while a significant anti-inflammatory effect was proved in the Xylene-induced Auricle

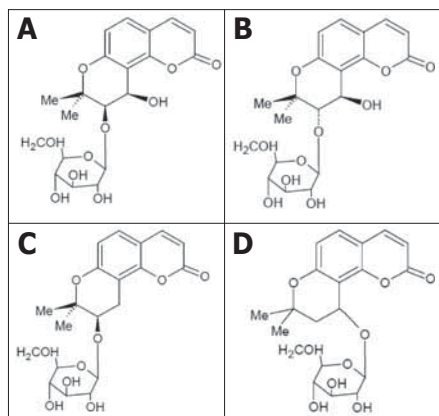


Figure 6. Chemical structures of some pyranocoumarin glycosides compounds isolated from PPD. Frame A: praeroside II; B: praeroside III; C: praeroside IV; D: praeroside V

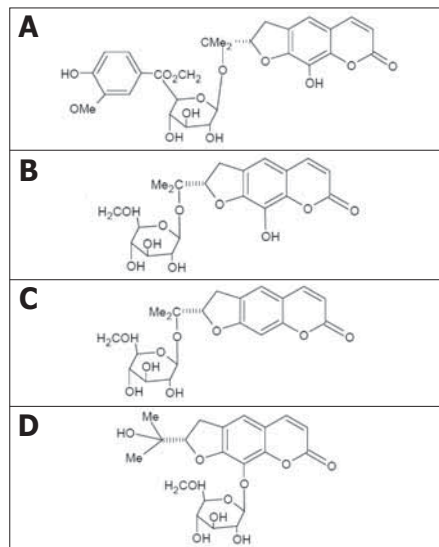


Figure 7. Chemical structures of some furanocoumarin glycosides compounds isolated from PPM. Frame A: praeroside I; B: isorutarin; C: marmesinin D: rutarin

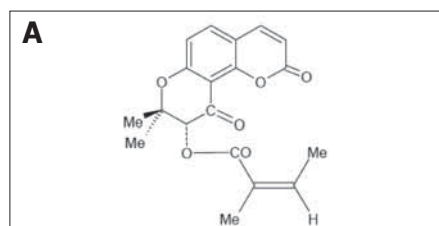


Figure 8. Chemical structure of 9-angeloyloxy-10-oxo-dihydroseselin.

inflammation test.⁽²⁶⁾ PDM has similar pharmacological effects, except the anti-cough function.⁽²⁷⁾ The major chemical in the herbs, nodakenin, can enhance the cholinergic nervous system by improving or ameliorating memory dysfunction.⁽²⁸⁾

Antimicrobial activities

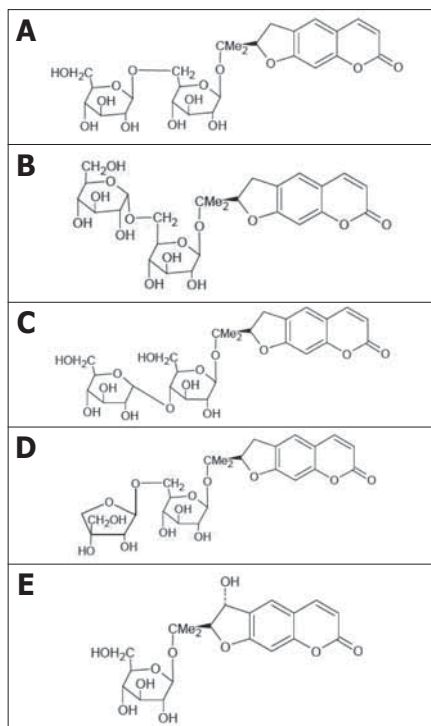


Figure 9. Chemical structure of furocoumarin glycosides isolated from PDM. Frame A: Decuroside I; B: Decuroside II; C: Decuroside III; D: Decuroside IV; E: Decuroside V

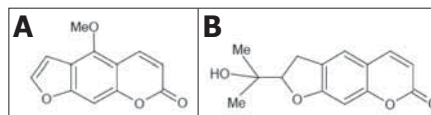


Figure 10. Chemical structure of furocoumarins isolated from PDM. Frame A: Bergapten; B: Nodakenin

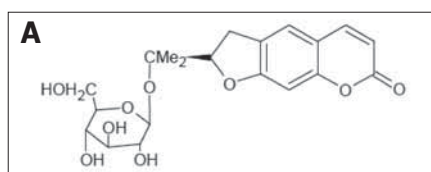


Figure 11. Chemical structure of Nodkenin.

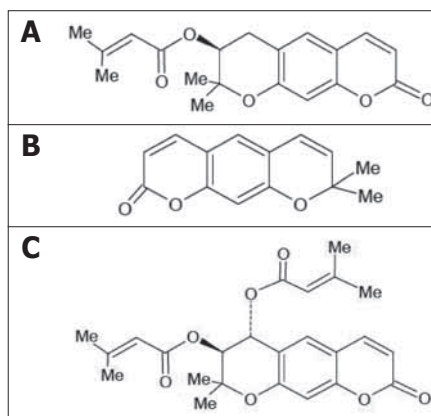


Figure 12. Chemical structure of pyranocoumarins. Frame A: Decursin; B: xanthyletin; C: Decursidin

The root extract of PPD was analyzed and tested for gross behavioral effects and acute toxicity in mice. It was observed that no behavioral effects were evoked while one of the chemical components, praeruptorin A, showed antimicrobial activity on *Streptococcus agalactiae* after oral administration.⁽²⁹⁾

DISCUSSION AND FUTURE DEVELOPMENT

Herbs with regional differences have unique chemical composition and diverse concentration of the effective components. Therefore, the chemical profiles of herbs in different regions have to be identified in order to enhance a suitable application of the herb in future. Morphological study is a simple and low cost identification method. However this method is not accurate as subjective observation by humans is involved. Hence fingerprint identification technology should be developed. High Performance Liquid Chromatography (HPLC) can establish stable and highly reproducible chromatographic fingerprint identification. Gas Chromatography (GC) can also be used in the fingerprint identification, especially for low boiling point components like terpenes.

Nowadays green chemistry is one of the emerging areas, which encourages environmentally friendly practice in science, giving rise to the growing use of Capillary Electrophoresis (CE), Fourier Transform Infrared Spectroscopy (FTIR) and High Performance Thin Layer Chromatography (HPTLC). Fingerprint identification using these three instruments has developed rapidly. Similar to HPLC, CE can demonstrate stable and highly reproducible chromatographic fingerprint identification for both qualitative and quantitative analysis. The analytical time and solvents required for CE are much less than that for HPLC, thus saving up a lot of materials. FTIR fingerprint identification is established based on the special functional groups of the chemical components in the herbs. It can prove rapid identification in less than two minutes with little solvent consumption. HPTLC fingerprint identification also operates with small amount of solvent, enabling quick and low cost qualitative analysis.⁽³⁰⁻³¹⁾

CONCLUSION

The two species, *Peucedanum praeruptorum* Dunn and *Peucedanum decursivum* Maxim differ from each other in many aspects, such as morphological appearances, characteristics of pulverized powder, genomic sequences of ITS, chemical components, and even pharmacological effects. These differences are compared and summarized in Table 1. The data suggest that these two species should not be used interchangeably or mixed.

Table 1. The differences between *Peucedanum praeruptorum* Dunn (PPD) and *Peucedanum decursivum* Maxim (PDM)

Difference	PPD	PDM
Origin	<i>Peucedanum praeruptorum</i> Dunn	<i>Angelica decursiva</i> (Miq.) Franch. <i>Peucedanum decursivum</i> (Miq.) Maxim
Macroscopic Characteristics	root shorter cortex wider (3/5) oil spots more	longer relatively narrow relatively less
Transaction Identification	xylem relatively narrow Oil cavities in xylem a few rays radiated	occupy half of the radius of the root lack indistinct
Power	Cork cell 8~20 rows Vessels bordered pit	few rows reticulated and scalpriform
Genomic Grouping	Peucedanum	Angelica
Major Chemical Components	Praeruptorin A, B, C, D and E.; praeroside II, III, IV and V; Praeroside I; Isorutarin, Rutarin; Marmesinin; Scopoine and Skimming	Decurosides I, II, III, IV and V; Ergapten and Nodakenetin; Nodakenin; Xanthyletin, Decursin and Decursidin
Pharmacological Effects	Inhibit cellular mitosis; Hypertension, Abnormal vascular responses; Anti-heart failure; Anti-cough and anti-inflammatory; Antimicrobial activities	Anti-inflammatory; Enhance cholinergic nervous system

Author's background

Both **YIP, Chong Kit** and **LAU, E Jane** are currently doing their undergraduate final year project on herbal qualitative analysis of qianhu species under **Dr. CHEUNG Hon-Yeung's** supervision in the City University of Hong Kong. **Dr. CHEUNG** is the Associate Professor of Pharmaceutical Microbiology & Biotechnology. His email address: bhhonyun@cityu.edu.hk

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Dual 5 α -Reductase Inhibitor for a Potent & More Comprehensive BPH Management



- The first & the only available dual 5ARI provides rapid, potent and consistent suppression of DHT, which is maintained at 4 years.^{1,2,3}
- Provides rapid improvement as early as 1 month in various measures, including prostatic volume and urinary flow.²
- Provides a sustained reduction in prostate volume and symptom improvement over 4 years.^{3,4}
- Reduces the risk of AUR and BPH-related surgery by 57% and 48%, respectively, at 2 years.² The reduction was durable over 4-year treatment.¹
- Avodart™ is well tolerated^{1,2,3}

Avodart™
dutasteride

References:

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AVODART™ (Dutasteride) abridged prescribing information

Indications Treatment of moderate to severe symptoms of benign prostatic hyperplasia (BPH). Reduction in the risk of acute urinary retention (AUR) and surgery in patients with moderate to severe symptoms of BPH. **Dosage and Administration Adults (including elderly):** The recommended dose of AVODART is one capsule (0.5 mg) taken orally once a day. The capsules should be swallowed whole and may be taken with or without food. Although an improvement may be observed at an early stage, it can take up to 6 months before a response to the treatment can be achieved. No dose adjustment is necessary in the elderly. **Renal impairment:** The effect of renal impairment on dutasteride pharmacokinetics has not been studied. No adjustment in dosage is anticipated for patients with renal impairment. **Hepatic impairment:** The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied. **Contraindications** Patients with known hypersensitivity to dutasteride, other 5 α reductase inhibitors, or any component of the preparation; women and children. **Warnings and Precautions** Dutasteride is absorbed through the skin, therefore women and children must avoid contact with leaking capsules. If contact is made with leaking capsules the contact area should be washed immediately with soap and water. The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied. Because dutasteride is extensively metabolized and has a half-life of three to five weeks, caution should be used in the administration of dutasteride to patients with liver disease. Digital rectal examination, as well as other evaluations for prostate cancer, should be performed on patients with BPH prior to initiating therapy with dutasteride and periodically thereafter. Serum prostate-specific antigen (PSA) concentration is an important component of the screening process to detect prostate cancer. Generally, a serum PSA concentration greater than 4 ng/mL (Hybritech) requires further evaluation and consideration of prostate biopsy. Physicians should be aware that a baseline PSA less than 4 ng/mL in patients taking dutasteride does not exclude a diagnosis of prostate cancer. Dutasteride causes a decrease in serum PSA levels by approximately 50% after six months in patients with BPH, even in the presence of prostate cancer. Although there may be individual variation, the reduction in PSA by approximately 50% is predictable as it was observed over the entire range of baseline PSA values (1.5 to 10 ng/mL). Therefore, to interpret an isolated PSA value in a man treated with dutasteride for six months or longer, PSA values should be doubled for comparison with normal ranges in untreated men. This adjustment preserves the sensitivity and specificity of the PSA assay and maintains its ability to detect prostate cancer. Any sustained increases in PSA levels while on

dutasteride should be carefully evaluated, including consideration of non compliance to therapy with dutasteride. Total serum PSA levels return to baseline within 6 months of discontinuing treatment. The ratio of free to total PSA remains constant even under the influence of dutasteride. If clinicians elect to use percent free PSA as an aid in the detection of prostate cancer in men undergoing dutasteride therapy, no adjustment to its value is necessary. **Pregnancy and Lactation** The effects of dutasteride 0.5 mg/day on semen characteristics were evaluated in normal volunteers aged 18 to 52 (n=27 dutasteride, n=23 placebo) throughout 52 weeks of treatment and 24 weeks of post treatment follow-up. At 52 weeks, the mean percent reduction from baseline in total sperm count, semen volume, and sperm motility were 23%, 26%, and 18%, respectively, in the dutasteride group when adjusted for changes from baseline in the placebo group. Sperm concentration and sperm morphology were unaffected. After 24 weeks of follow-up, the mean percent change in total sperm count in the dutasteride group remained 23% lower than baseline. While mean values for all semen parameters at all time points remained within the normal ranges and did not meet predefined criteria for a clinically significant change (30%), two subjects in the dutasteride group had decreases in sperm count of greater than 90% from baseline at 52 weeks, with partial recovery at the 24-week follow-up. The clinical significance of dutasteride's effect on semen characteristics for an individual patient's fertility is not known. Dutasteride is contraindicated for use by women. Dutasteride has not been studied in women because pre clinical data suggests that the suppression of circulating levels of dihydrotestosterone may inhibit the development of the external genital organs in a male foetus carried by a woman exposed to dutasteride. It is not known whether dutasteride is excreted in breast milk. **Adverse Reactions Clinical Trial Data:** The following investigator-judged drug-related adverse events (with incidence more than or equal to 1%) have been reported more commonly in the three phase III placebo controlled studies on dutasteride treatment compared to placebo:

Adverse event	Incidence during year 1 of treatment		Incidence during year 2 of treatment	
	Placebo (n= 2158)	Dutasteride (n= 2167)	Placebo (n= 1736)	Dutasteride (n= 1744)
Impotence	3%	6%	1%	2%
Altered (decreased) libido	2%	4%	<1%	<1%
Ejaculation disorders	<1%	2%	<1%	<1%
Breast disorders*	<1%	1%	<1%	1%

* includes breast tenderness and breast enlargement

No change to the adverse event profile was apparent over a further 2 years in open label extension studies.

Postmarketing Data: Allergic reactions, including rash, pruritus, urticaria, localised oedema and angioedema. **Overdose** There is no specific antidote for dutasteride, therefore in cases of suspected overdose, symptomatic and supportive treatment should be given as appropriate.

Please refer to the AVODART full prescribing information for warnings, precautions, interactions, pregnancy, lactation, adverse reactions and overdose.

Full prescribing information is available upon request. Please read the full prescribing information.

™Avodart is a trademark of the GlaxoSmithKline group of companies.

Hong Kong Pharmacy Conference 2010 (23 – 24 January 2010)

Pharmacist in the New Decade – Building Our Healthy Land

Day 1 (23 Jan 2010)

1:30pm	Registration
2:30pm – 2:40pm	Opening Ceremony
2:40pm – 2:50pm	Welcome Speech by Conference Chairperson
2:50pm – 3:00pm	Opening Remarks: Dr. PY Lam
3:00pm – 3:40pm	Theme 1: A record for all citizens - building the HK-wide eHR by Dr. NT Cheung
3:40pm – 4:10pm	Break, Poster and Exhibition
4:10pm – 4:50pm	Theme 2: Current Development of Pharmaceutical Care Services in public hospitals of China by Mr. Zhao Zhigang
4:50pm – 5:30pm	Theme 3: The Detective in the Drug Saga by Dr. Yuen Kwok Yung
6:30pm – 10:00pm	Conference Dinner

All lectures will be presented in English.

Pharmacist in the NEW DECADE
Building Our Healthy Land

HONG KONG
PHARMACY
CONFERENCE
23-24 JAN, 2010

- **Conference Details**
 - **Date:** 23rd – 24th January, 2010
 - **Venue:** Hong Kong Convention and Exhibition Centre
- **Enquiry and Registration**
 - Contact Person :
 - Ms. Judy Kwok (852)96334533
 - Ms. Amy Chu (852)95099070
 - Mr. Ng Man Keung (852)61556652
 - Email : hkpharmacyconference@gmail.com
 - Website : <http://www.pharmacyconference.org>

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Day 2 (24 Jan 2010)

8:00 am	Registration		
Concurrent session	I	II	III
Topics	Medication Reconciliation & Informatics	Quality Assurance	Integrative Medicine
8:30am – 9:10am	Ia. Medication Reconciliation – Patient Safety Solution by Dr. Adam Bursua and Dr. Vicki Groo	Ila. Emerging new roles of Certified Specialist Pharmacists in Pharmacovigilance in the Hong Kong Setting by Iris Chang, President, Practising Pharmacist Association of Hong Kong	IIla. Multidisciplinary Approach to Herbs-induced Liver Injury Network by Dr. Chau Tai Nin, Associate Consultant, Division of Gastroenterology and Hepatology, Department of Medicine and Geriatrics, United Christian Hospital
9:10am – 9:50am	Ib. Clinical Pharmacy Service - Medication Reconciliation: What have we done and our way forward? By Ritchie Kwok, Pharmacist, Department of Pharmacy, Queen Mary Hospital	IIlb. Microbial Quality Assurance of Pharmaceutical Products by Dr Cheung Hon Yeung	IIlb. TCM in Childhood Eczema by Prof. Ellis Hon, Professor, Department of Medicine and Therapeutics, Division of Pediatrics, CUHK
9:50am – 10:30am	Ic How Informatics impact on medication reconciliation? (TBC)	IIlc. Quality Medicines and GMP by Mr. Steve Williams, Director / Senior GMP Consultant/Training Director, SeerPharma Pty Ltd, (Australia)	IIlc. Interactions of Herbal Medicines with Anticancer Agents by Prof. George Leung, Assistant Professor, Department of Pharmacology and Pharmacy, HKU
10:30am – 11:00am	Break, Poster and Exhibition		
11:00am – 11:40am	Id. What is IT doing for us in patient care ? by Ms. Chiang, Senior Pharmacist, Chief Pharmacy Office, Hospital Authority	IIld. The Review Committee of Regulation of Pharmaceutical Products in Hong Kong – Recommendations & Way Forward by Dr. Gloria Tam and panelists from the Review Committee	IIId. Community Pharmacy Initiatives: Quality Assurance Programme by Mr. Philip Chiu, Senior Pharmacist, Manning
11:40am – 12:20pm	Ie. Pharmacy Automation - reducing medication errors and improving efficiency – Singapore Experience by Mr Wu Tuck Seng, National University Hospital of Singapore		IIIE. Meeting the challenges of Chinese medicine development by Dr. Edmund Lee Executive Director, HK Jockey Club Institute of Chinese Medicine
12:20pm – 2:15pm	Lunch + Symposium + Multimedia Show		
2:15pm – 2:45pm	If. Six Sigma in a Flash: How will Six Sigma affect you as a pharmacist? By Dannie Yung	IIId. "One country, two systems" in the pharmacy profession: experience sharing by a HK pharmacist practising in Shanghai by Kitty Law	IIIf. Supportive Cancer Care with Chinese Medicine –Could it be a safe and effective alternative? by Dr. William Cho, Scientific Officer, Department of Oncology, Hospital Authority
2:45pm – 3:15pm		IIe. Student Debate: "Should Pharmacist be on duty for ALL opening hours of Pharmacy?"	IIIf. Clinical update on Breast Cancer by Prof. Janice Tsang, Assistant Professor, Department of Clinical Oncology, HKU
3:15pm – 3:45pm			IIIf. Clinical update on Colon Cancer by Prof. Daniel Chua, Associate Professor, Department of Clinical Oncology, HKU
3:45pm – 4:15pm	Ig. Safer OTC drug use, safer community by Lai Sze Man Jeannie and So Man Chun, Kelvin		IIIf. The role of clinical pharmacist in clinical oncology unit by Mr. Elton YT Yip, Princess Margaret Hospital, Hong Kong
4:15pm – 4:45pm	Ih. Pharmaceutical Care for the Elderly by by Mr. Billy Chung, Chief Operating Officer, The Hong Kong Pharmaceutical Care Foundation, Mr. So Yiu Wah, President, The Society of Hospital Pharmacists, Dr. Anna Yung PhD, Senior Visiting Pharmacist Officer, The Hong Kong Pharmaceutical Care Foundation		

All lectures will be presented in English.



Active Ingredient:
Pramipexole

Presentation:
Tablets: 0.25 mg x 30's and 1 mg x 30's.

Indications:
Indicated in the treatment of signs and symptoms of idiopathic Parkinson's disease. It may be used as monotherapy or in combination with levodopa.

Mirapex is indicated for the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome.

Pharmacological Properties:
Pramipexole, the active ingredient of MIRAPEX®, is a dopamine agonist and binds with high selectivity and specificity to the dopamine D2 subfamily receptors and has a preferential affinity to D3 receptors; it has full intrinsic activity.

MIRAPEX® alleviates parkinsonian motor deficits by stimulation of dopamine receptors in the striatum. Animal studies have shown that pramipexole inhibits dopamine synthesis, release, and turnover.

The precise mechanism of action of MIRAPEX® as a treatment for Restless Legs Syndrome is not known. Although the pathophysiology of Restless Legs Syndrome is largely unknown, neuropharmacological evidence suggests primary dopaminergic system involvement.

Dosage and Administration:

Parkinson's disease
The tablets should be taken orally, swallowed with water, and can be taken either with or without food.

The daily dosage is administered in equally divided doses 3 times per day.

Initial treatment:

As shown below dosages should be increased gradually from a starting dose of 0.375 mg per day and then increased every 5 - 7 days. Providing patients do not experience intolerable side effects, the dosage should be titrated to achieve a maximal therapeutic effect. If a further dose increase is necessary the daily dose should be increased by 0.75 mg at weekly intervals up to a maximum dose of 4.5 mg per day.

Maintenance treatment:
The individual dose should be in the range of 0.375 mg to a maximum of 4.5 mg per day. During dose escalation in three pivotal studies both in early and advanced disease efficacy was observed starting at a daily dose of 1.5 mg. This does not preclude that in individual patients doses higher than 1.5 mg per day can result in additional therapeutic benefit. This applies particularly to patients with advanced disease where a reduction of the levodopa therapy is intended.

Treatment discontinuation:
MIRAPEX® should be tapered off over several days.

Restless Legs Syndrome
The tablets should be taken orally, swallowed with water, and can be taken either with or without food.

The recommended starting dose of MIRAPEX® is 0.125 mg taken once daily 2 - 3 hours before bedtime. For patients requiring additional symptomatic relief, the dose may be increased every 4 - 7 days to a maximum of 0.75 mg per day

As long term efficacy of Mirapex in the treatment of Restless Leg Syndrome has not been sufficiently tested, patients' response should be evaluated after 3 months treatment and the need for treatment continuation should be reconsidered.

Treatment discontinuation:
MIRAPEX® can be discontinued without tapered dose reduction.

Contraindications:
Hypersensitivity to pramipexole or to any of the excipients

Precautions:
When prescribing MIRAPEX® tablets in a patient with renal impairment a reduced dose is suggested.

Hallucinations and confusion are known side effects of treatment with dopamine agonists and levodopa in Parkinson's disease patients. Hallucinations were more frequent when MIRAPEX® was given in combination with levodopa in Parkinson's disease patients with advanced disease than in monotherapy in Parkinson's disease patients with early disease.

Patients and caregivers should be aware of the fact that behavioural changes can occur (e.g. pathological gambling, hypersexuality, increased libido, binge eating). Dose reduction/taper discontinuation should be considered.

Patients should be alerted to the potential sedating effects associated with MIRAPEX®, including somnolence and the possibility of falling asleep while engaged in activities of daily living. Since somnolence is a frequent adverse event with potentially serious consequences, patients should neither drive a car nor operate other complex machinery until they have gained sufficient experience with MIRAPEX® to gauge whether or not it affects their mental and/or motor performance adversely. Patients should be advised that if increased somnolence or episodes of falling asleep during activities of daily living (e.g., conversations, eating, etc.) are experienced at any time during treatment, they should not drive or participate in potentially dangerous activities and should contact their physician.

Effects on ability to drive and use machines
Patients should be aware of the fact that hallucinations can occur and may adversely affect their ability to drive.

Drug Interactions:
Medication that inhibit the active renal tubular secretion of basic (cationic) drugs, such as cimetidine, or are themselves

eliminated by active renal tubular secretion, may interact with MIRAPEX® resulting in reduced clearance of either or both medication. In case of concomitant treatment with these kinds of drugs (incl. amantadine) attention should be paid to signs of dopamine over stimulation, such as dyskinesias, agitation or hallucinations. In such cases a dose reduction is necessary.

While increasing the dose of MIRAPEX® in Parkinson's disease patients it is recommended that the dosage of levodopa is reduced and the dosage of other antiparkinsonian medication kept constant.

Side Effects:
The following side effects are listed under the use of MIRAPEX®: abnormal dreams, confusion, constipation, delusion, dizziness, dyskinesia, fatigue, hallucinations, headache, hyperkinesia, hypotension, increased eating (binge eating, hyperphagia), insomnia, libido disorders, nausea, peripheral oedema, paranoia; pathological gambling, hypersexuality and other abnormal behaviour; somnolence, weight increase, sudden onset of sleep; pruritus, rash and other hypersensitivity.

Patients treated with pramipexole tablets have reported falling asleep during activities of daily living, including the operation of motor vehicles, which sometimes resulted in accidents. Some of them did not report a warning sign such as somnolence, which is a common occurrence in patients receiving pramipexole tablets at doses above 1.5 mg/day, and which, according to the current knowledge of sleep physiology, always proceeds falling asleep. There was no clear relation to the duration of treatment. Some patients were taking other medication with potentially sedative properties. In most cases where information was available, there were no further episodes following reduction of dosage or termination of therapy.

Patients treated with dopamine agonists for Parkinson's

disease, including MIRAPEX®, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation.

Forensic Classification:

P1S1S3

XARELTO®
Bayer Healthcare
Bayer Schering Pharma

Active Ingredient:

Rivaroxaban

Presentation:

Rivaroxaban 10mg Film-coated tablet

Pharmacological Properties:

Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of Factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated Factor II) and no effects on platelets have been demonstrated.

Indications:

Prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery.

Dosage and Administration:

The recommended dose is 10 mg Rivaroxaban taken orally once daily. The initial dose should be taken 6 to 10 hours after surgery, provided that haemostasis has been established. The duration of treatment depends on the individual risk of the patient for venous thromboembolism which is determined by the type of orthopaedic surgery.

- For patients undergoing major hip surgery, a treatment duration of 5 weeks is recommended.
- For patients undergoing major knee surgery, a treatment duration of 2 weeks is recommended.

If a dose is missed the patient should take Rivaroxaban immediately and then continue the following day with once daily intake as before. Can be taken with or without food.

Contraindications:

Hypersensitivity to the active substance or to any of the excipients; Clinically significant active bleeding; Hepatic disease associated with coagulopathy and clinically relevant bleeding risk; Pregnancy and lactation.

Precautions:

Haemorrhagic risk

Several sub-groups of patients, as detailed below, are at increased risk of bleeding. These patients are to be carefully monitored for signs of bleeding complications after initiation of treatment. This may be done by regular physical examination of the patients, close observation of the surgical wound drainage and periodic measurements of haemoglobin. Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

Renal impairment

In patients with severe renal impairment (creatinine clearance <30 ml/min) Rivaroxaban plasma levels may be significantly increased which may lead to an increased bleeding risk. Use is not recommended in patients with creatinine clearance < 15 ml/min. Rivaroxaban is to be used with caution in patients with creatinine clearance 15 - 29 ml/min.

Rivaroxaban is to be used with caution in patients with moderate renal impairment (creatinine clearance 30 - 49 ml/min) concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations.

Hepatic impairment

In cirrhotic patients with moderate hepatic impairment (classified as Child Pugh B), Rivaroxaban plasma levels may be significantly increased which may lead to an increased bleeding risk. Rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Rivaroxaban may be used with caution in cirrhotic patients with moderate hepatic impairment (Child Pugh B) if it is not associated with coagulopathy.

Other haemorrhagic risk factors

Rivaroxaban, like other antithrombotic agents, is to be used with caution in patients with an increased bleeding risk such as:

- congenital or acquired bleeding disorders
- uncontrolled severe arterial hypertension
- active ulcerative gastrointestinal disease
- recent gastrointestinal ulcerations
- vascular retinopathy
- recent intracranial or intracerebral haemorrhage
- intraspinal or intracerebral vascular abnormalities
- recent brain, spinal or ophthalmological surgery.

Hip fracture surgery

Rivaroxaban has not been studied in clinical trials in patients undergoing hip fracture surgery to evaluate efficacy and safety in these patients. Therefore, Rivaroxaban is not recommended in these patients.

Spinal/epidural anaesthesia or puncture

When neuraxial anaesthesia (spinal/epidural anaesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis. The risk of these events may be increased by the post-operative use of indwelling epidural catheters or the concomitant use of medicinal products affecting haemostasis. The risk may also be increased by traumatic or repeated epidural or spinal puncture. Patients are to be frequently monitored for signs and symptoms of neurological impairment (e.g. numbness or weakness of the legs, bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis. An epidural catheter is not to be removed earlier than 18 hours after the last administration of Rivaroxaban. The next Rivaroxaban dose is to be

administered not earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs the administration of Rivaroxaban is to be delayed for 24 hours.

Information about excipients

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

Interactions:

The use of Rivaroxaban is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir). These active substances are strong inhibitors of both CYP3A4 and P-gp and therefore may increase Rivaroxaban plasma concentrations to a clinically relevant degree which may lead to an increased bleeding risk. Fluconazole is expected to have less effect on Rivaroxaban exposure and can be co-administered with caution. Care is to be taken if patients are treated concomitantly with medicinal products affecting haemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid, platelet aggregation inhibitors or other antithrombotic agents. The concomitant use of Rivaroxaban with strong CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort) may lead to reduced Rivaroxaban plasma concentrations. Strong CYP3A4 inducers should be co-administered with caution.

Side Effects:

Bleedings or anaemia, nausea, increased GGT and an increase in transaminases, tachycardia, thrombocythaemia, syncope, dizziness, headache, nausea, constipation, diarrhoea, abdominal and gastrointestinal pain, dyspepsia, dry mouth, vomiting, blood creatinine increased, blood urea increased, pruritus, rash, urticaria, confusion, pain in extremity.

Forensic Classification:

P1S1S3

每月一粒 輕鬆護骨

對抗骨質疏鬆，無需經常服藥，由「邦維亞」開始！

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- 如有任何爭議，羅氏大藥廠將保留最終之決策權

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