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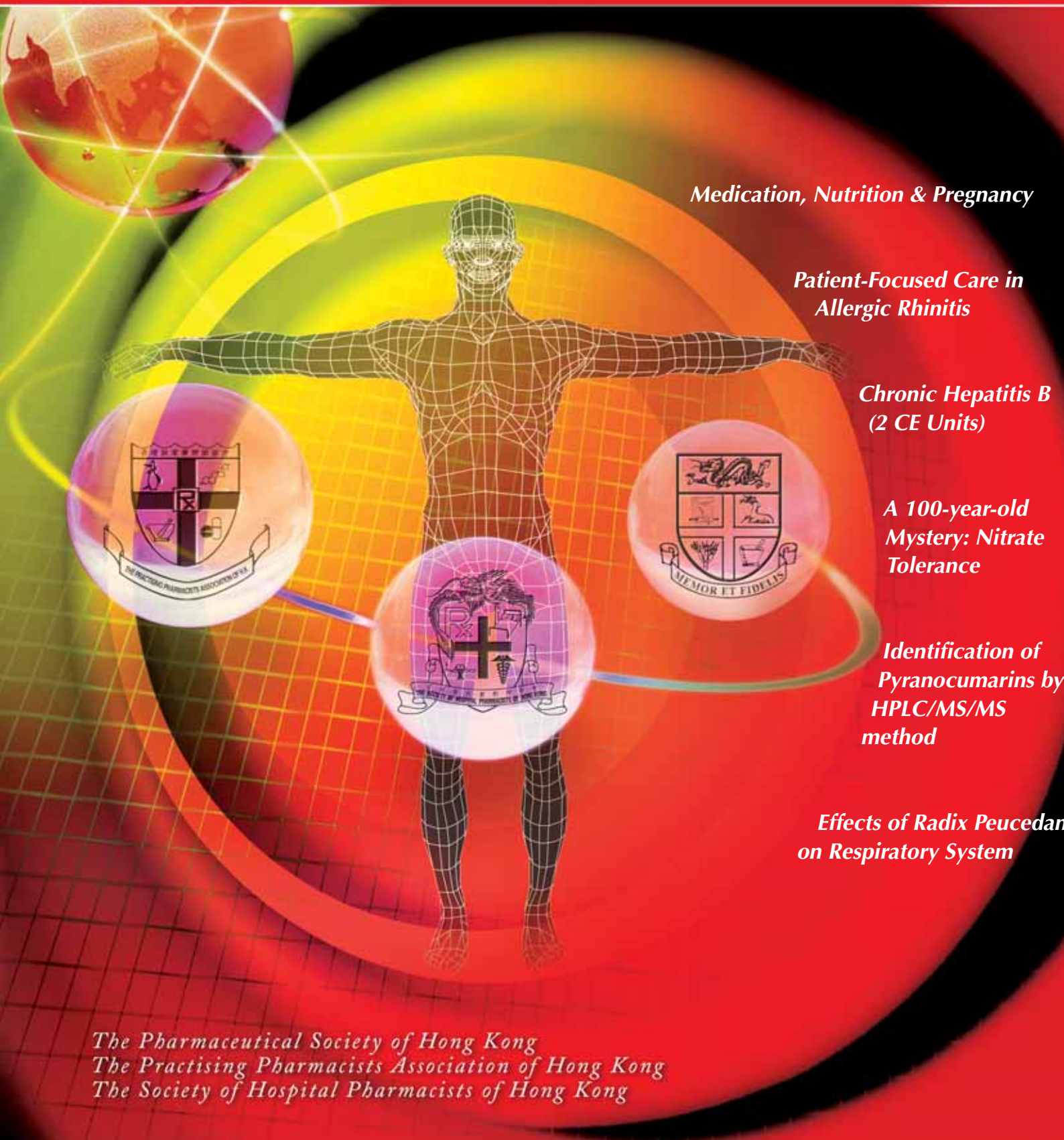

Medication, Nutrition & Pregnancy

Patient-Focused Care in Allergic Rhinitis

Chronic Hepatitis B (2 CE Units)

A 100-year-old Mystery: Nitrate Tolerance

Identification of Pyranocumarins by HPLC/MS/MS method

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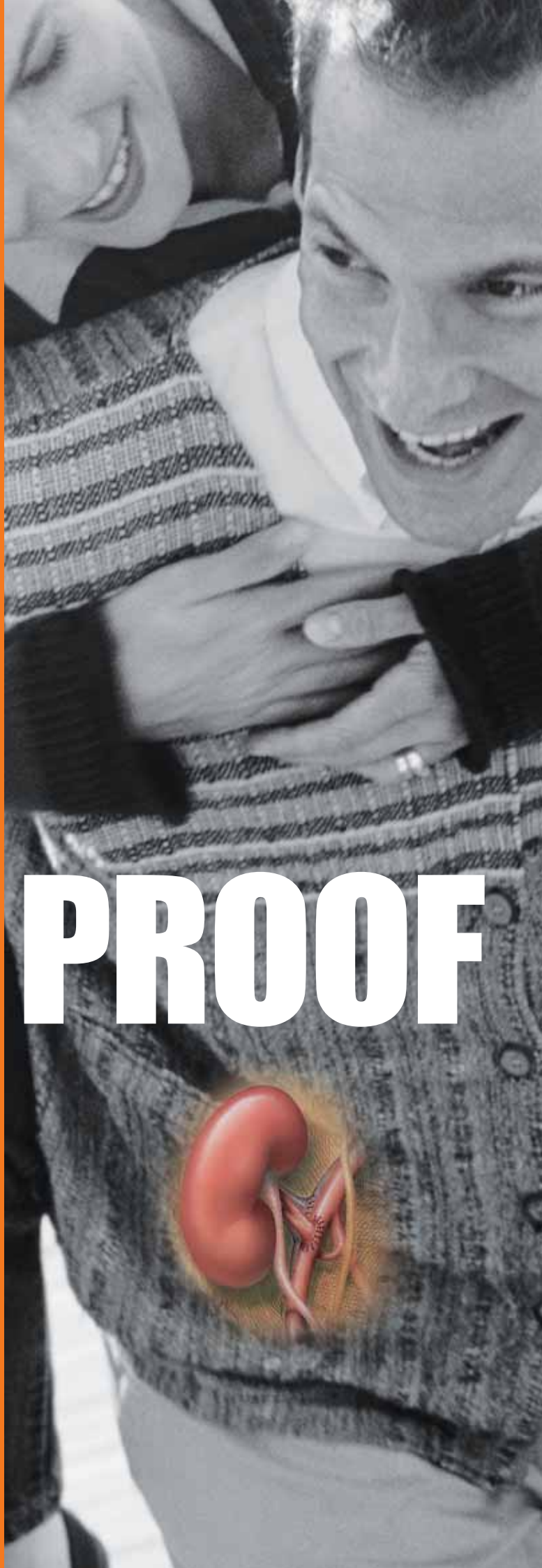

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INSTRUCTIONS FOR AUTHORS

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

Pharmacy Practice	Drug & Therapeutics
OTC & Health	Pharmaceutical Technology
Medication Safety	Herbal Medicines & Nutraceuticals
Society Activities	New Products

Comments on any aspects of the profession are also welcome as Letters to the Editor.
There is no restriction on the length of the articles to be submitted. They can be written in English or Chinese. The Editorial Committee may make editorial changes to the articles but major amendments will be communicated with the authors prior to publishing.
It is preferable to have original articles submitted as an electronic file, in Microsoft Word, typed in Arial 9pt. Files can be sent to the following address:

e-mail: ***pharmjhk@yahoo.com***

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For any queries on submission, please feel free to contact the Editorial Committee through mail or by the e-mail address.

In early September, Customs officers have seized a record breaking worth of suspected counterfeit Chinese and Western medicine in a territory-wide operation. A total of 38 drug stores and one supplier throughout the territory were raided. One should be aware of that selling counterfeit medicine is a criminal offence. Furthermore, under the Trade Descriptions Ordinance, the maximum penalty for selling any goods bearing false trade marks, is a fine of $500,000 and imprisonment for five years. Unlike garment or VCD, medicine has impact on an individual's life and, thus, the issue draws a lot more attention from the general public. Furthermore, a more vigorous Customs enforcing action is expected. In fact, selling counterfeit from a pharmacy goes beyond a criminal offence issue, because our behavior reflects professionalism, ethical standard and integrity. Pharmacists have been working hard to build our profession image and to gain confidence both from the patients and the policy makers. How much more does it cost if we loss our credibility as a member of healthcare provider? Actually, there is much we can do by picking up the hat of a gate keeper so as to prevent the circulation of counterfeit on the market.

After the SARS period, there are hot discussions in the community on who should shoulder the responsibility and how. The government's approach is "to work harder and to improve the healthcare system". On one hand, the Secretary for Health, Welfare & Food, Dr E K Yeoh offered his apologies during the past few weeks. On the other hand, many of the constructive actions have been taken. For example, the enhancement of infection-control facilities in public hospitals; an emergency fund being under planning to assist families affected by SARS. Besides, a special working group has been set up to follow up the Expert Committee's 46 recommendations to enhance Hong Kong's defences against the illness. Having said that, one will not disagree that there is much room for improvement on the ways that the government communicates with the citizens and the SARS victims. While the call for resignation is increasing outside, we need to consider if it is the most effective way to show accountability... whether the healthcare service will be compromised as a result or there will be a light of improvement. Do we urgently need a better system, a better crisis management, and better communication? Or we need to find someone to be blamed? Listening to the comment from the Expert Committee, I get the impression that our health care system is outdated and needs a total revamp. I'm not sure I agree totally. There certainly are some things wrong, and some improvements are needed. Maintaining good public health is a shared responsibility; it is believed that the government, healthcare staff and the public can all actively contribute. One of the Expert Committee recommendations is to engage the community and to fully utilize various healthcare professionals. Pharmacists play an important role in maintaining medication supply for the chronically ill during the SARS epidemic. Besides, as one of the front line workers, pharmacists must embrace to ensure that patients participate in their own healthcare as decision makers and managers of health risk.

There is a gap between technical knowledge possessed by a pharmacist and a quality pharmaceutical care being delivered. Communication skill is the key to fill this gap. In the pharmacy practice section, we have an easy to read article from Mr. YW So who helps us to check whether we are aware of the basics of patient counseling technique. Ongoing self-awareness on communication skill is crucial to improve our service so as to enhance our professional image and relationship with the patients. Conversation between the patient and pharmacist promotes trust, and pharmacists need to encourage and assure understanding. As patients and as consumers, they have the right to a higher level of effective communication and a provider who encourages active participation. Also try never to forget that patients deserve our empathy and respect. Elvina Poon shares her experience on helping patients with allergic rhinitis. In her article titled "Improving Outcomes in allergic Rhinitis Through Patient-Focused Care", there is a very thorough discussion on how we anticipate allergic rhinitis patients' needs. Pharmacist is a drug expert, but s/he is also capable to contribute in total disease management. Once a while, it has been challenged that a pharmacist can be replaced by a medicine dispensing machine. A thoughtful patient counseling and a professional counter prescribing is, therefore, so important for us to differentiate ourselves, or we shall lose our value.

In the OTC section, we also have 2 articles discussing about the use of nutrition supplements. Windy Chan covers the topic generally, while Gloria Yung puts the focus on pregnant women in her article. Gloria also touches on some common ailments that a pregnant woman would face and she provides some very good advices that you should not miss.

That chronic hepatitis is a public health problem of global significance is not in dispute. Hepatitis B and hepatitis C viruses are major causes of chronic hepatitis. In this issue of the HKPJ, we have the first article of the series to discuss about chronic hepatitis B. The article is informative and covers topics from virology and diagnosis to latest treatment options and preventive measures. This is also the PCCC article for this quarter. In the same section, Marcus Law briefly walks through the hypotheses regarding the genesis of nitrate tolerance and the controversies of nitrate-free period in anti-anginal therapy.

Both myself the Editorial Committee wish you would enjoy reading this issue of HKPJ because there is a lot of hard work behind the papers. As a member in the Editorial Committee, I am proud of the good work and I am enjoying working with a group colleagues from different sectors of the pharmacy profession. The HKPJ has been established for 12 years. To sustain the success of it, we need your contribution. We need medical writers, we need people to help in administration, we need photographers and we need your comments on the Journal. If you are interested to join our team and to spend your energy for the profession in a different way, please contact us today (e-mail: pharmjhk@yahoo.com).

Michael Leung
Managing Editor

Patient Counselling by Pharmacist

Yiu-Wah So

I INTRODUCTION

The importance of good communication when dealing with patients is sometimes overlooked because communication is a familiar part of our daily life. Some people might equate communication with talking. However, knowing how to talk does not mean knowing how to communicate well. People can improve their communication skills through learning.

As a pharmacist communication skills are very important during patient counselling. By using effective communication skills pharmacists can ensure the safe and effective use of medicines by patients. There are four stages in communication:

1. Questioning
2. Listening
3. Explaining
4. Reflection

II FOUR STAGES IN COMMUMICATION

i) Questioning

There are two types of question: open and closed questions. Most of the questions asked by pharmacists are close-ended. It is mainly for practical reasons because these questions may be constructed easily to enable a faster information flow from the patient. However, we have to remember that open questions often allow us to find out more information. Perhaps the best approach is to combine open with closed questions as this seems to allow the most efficient collection of information. There is an example in panel 1.

It often pays to hone your skills when questioning. For example, if you asked whether a patient has any drug left, he might deny because he might think that you are checking on his compliance and will not give him the drug this time. On the other hand, if you ask him whether he has enough medication, this could make him feel you are on his side and might be willing to tell you even more (Panel 2).

ii) Listening

Listening is important. It is a process to understand the patient's emotions and feelings during his speech. Active listening means respect for the patient. Simply nod the head; smile and direct eye contact are good non-verbal means to communicate with the patient. Without paying attention when the patient speaks, he will feel he is being ignored and will not be eager to tell you much. Sometimes a complaint will also be raised against you.

iii) Explaining

Counselling is to empower and support a patient to find his own solution. To provide advice on health, minor illness and drug usage, explaining is the core skill. An explanation can be subdivided into simple and complex. Simple explanations just simply reveal the facts. For instance, telling the patient the indication of the drug and how to administer the medication. Complex explanations include more detailed information like how the drug works and the expected side effects. Avoid overloading the patient with too much information.

iv) Reflection

Reflection is using the interviewer's own word to re-express what you had listened. This process involves reflection of feeling to let the patient know we understand what he said. Figure 1 shows a checklist to help a pharmacist to evaluate the structure of interview.

III CONCLUSION

The appropriate use of non-verbal communication, empathy with patients and assertiveness should always be remembered. Also emotional barriers such as perceptions and prejudice should be avoided.

So Yiu Wah is a pharmacist graduated from the U.K.. He currently works for the Queen Mary Hospital (QMH). This is an article extracted from the Pharmacy Bulletin of QMH published in May/June (Issue 5, 2003)

Panel 1. A combination use of open and closed questions

Case example:	
Pharmacist:	"Do you know how to take TNG sublingual tablet?" (closed question)
Patient:	"Yes."
Pharmacist:	"Tell me how then?" (open question)
Patient:	"Put it in the mouth and do not swallow..."

Panel 2. To obtain information from patient with honed questioning skill

Case example:	
Pharmacist:	"Do you find there is any shortage of medication?"
Patient:	"Oh, yes, the lipid-reducing drug (in fact it is Zocor 20mg) I have to buy it by myself!"
Pharmacist:	"Apart from this, any others?"
Patient:	"Just that one, the red one (in fact it is Adalat Retard) I got plenty."

The shortage of Zocor is due to the patient not cutting tablets in halves. While the surplus Adalat Retard were in excess due to self-adjustment of dosage from twice daily to once daily because of the side effects from the drug.

Checklist for the evaluation of the structure during patient interview

During the interview, did the pharmacist perform the following:			
1. Identify the patient	YES	NO	N/A
2. Introduce yourself	YES	NO	N/A
3. Explain purpose of the interview	YES	NO	N/A
4. Explain how patient will benefit from the interview	YES	NO	N/A
5. Obtain a complete and accurate history of			
a. present medical problems	YES	NO	N/A
b. past medical problems	YES	NO	N/A
c. present prescription drug use incl. OTC	YES	NO	N/A
d. past prescription drug use	YES	NO	N/A
e. patient compliance with drug regimens	YES	NO	N/A
f. drug allergies or sensitivities	YES	NO	N/A
6. Assess, through open-ended questions, the patient's understanding:			
a. of medication dosage	YES	NO	N/A
b. of dosage frequency	YES	NO	N/A
c. of method of administration	YES	NO	N/A
7. Assess patient's actual use of medication	YES	NO	N/A
8. Obtain from patient information regarding factors that may affect compliance:			
a. lifestyle	YES	NO	N/A
b. attitudes toward disease and medication	YES	NO	N/A
c. physical and/or mental impairments	YES	NO	N/A
d. patient's perception of the severity of disease	YES	NO	N/A
e. patient's perception of the importance of the prescribed drugs	YES	NO	N/A
9. Gather complete drug history before providing new information	YES	NO	N/A
10. Determine appropriate dosage regimen based on prescription directions, drug characteristics and patients compliance factors	YES	NO	N/A
11. Explain new prescription to patient			
a. Provide the indications	YES	NO	N/A
b. Explain dosage regimens	YES	NO	N/A
c. Suggest time of administration	YES	NO	N/A
d. Explain or demonstrate method of administration	YES	NO	N/A
e. Explain potential side effects	YES	NO	N/A
f. Explain methods to minimize side effects	YES	NO	N/A
12. Provide written and/or pictorial information to enhance understanding	YES	NO	N/A
13. Arrange for follow-up with patient if necessary	YES	NO	N/A

This checklist is an aid to develop one's own interview structure. The whole list may be covered at the first time. At the following interviews some material may be excluded.

Figure 1. Checklist for the evaluation of the structure during patient interview

Announcement...

Pharmacy Central CE Committee (PCCC) 2003-2004

Please be introduced to the members for Pharmacy Central CE Committee (PCCC) 2003-2004:

Chairman:	Warren Tsang (PSHK)
Vice-Chairman:	Rowdget Young (HKP(PS)A)
Secretary:	Mary Au-Yeung (CUHK)
Treasurer:	Jammie Yuen (SHP)
CE article coordinators:	So Ho Chung (HKP(PS)A), Joan Zuo (CUHK)
CE seminar coordinators:	Benjamin Lee (SHP), Phyllis Kwong (PPA), Cindy Ho (PSHK), Tracy Ho (PPA)
Membership coordinator:	Jaime Chu

Due to the special circumstances with SARS, many planned activities related to continuing education were affected. PCCC understands this impact and re-adjusted the CEU requirement for 2003. A CE certificate will be issued to members upon completion of 12 CEU in 2003. In addition, effective immediately, a maximum of 10 CEU obtained from approved non-PCCC organized seminars/conferences can be counted towards earning the CE certificate. We hope all of you will take advantage of these changes and earn your CE certificate for the year.

HKPJ Editor's comment: PCCC indicated a letter will be sent to each CE subscriber annually to inquire which PCCC and approved non-PCCC events he/she has attended.

Over-the-counter Supplements and Medications Use in Pregnancy

Gloria Yung

Being pregnant is a miraculous moment for most women. In general, women who are planning to be pregnant and those throughout the pregnancy have regular body check up with their family doctors or obstetricians. In order to prepare for the new life, pregnant women have a different nutritional demand. Moreover, they may experience some ailments, usually minor, owing to their physiological changes. In community pharmacies, both non-pharmacological and pharmacological measures can be recommended to patients to help relieving their discomfort.

I SPECIAL NUTRITIONAL REQUIREMENT BEFORE AND THROUGHOUT PREGNANCY

The nutritional requirements during pregnancy increase to meet the needs of the growing fetus, as well as the maternal physiological needs. To meet the overall increasing energy demands, the average woman must consume an additional 300 kcal per day beyond her baseline needs. [1] Some supplements are recommended during pregnancy as the increased requirement in particular minerals and vitamins may not be met even by a balanced diet.

i) Folic acid

Folic acid is a vitamin B which reduces the risk of neural tube defects, including spina bifida and anencephaly, by up to 70% when taken regularly by women of child bearing age. [2] It must be taken before and during the first trimester of pregnancy in order to be effective. Folic acid can be found naturally in leafy vegetables, beans (legumes), citrus fruits, and whole grains. In 1992, the U.S. Public Health Service (PHS) recommended that all women of childbearing age consume folic acid 400 mcg daily to reduce their risk of having a pregnancy affected with spina bifida or other neural tube defects (Table 1).

ii) Calcium

For proper bone and teeth development, the Recommended Daily Intake (RDI) for pregnant women is 1300mg. Therefore, for women who do not take dairy food regularly, calcium supplementation becomes essential. Owing to the different amount of elemental calcium content among calcium salts, we should perform the conversion before recommending the proper dose (Table 2). Although

Table 1. Natural sources for varying amounts of folate which were obtained from the FDA (FDA Consumer, May 1994)

Food source of folate	
Food Type	Micrograms (per 100 grams of food, or 3.5 oz)
Dark-green leafy vegetables	120-160
Fruits (particularly citrus)	50-100
Beans (legumes)	50-300
Whole grains	60-120
Breakfast cereals	100 or 400

calcium carbonate, which contains the highest calcium content, is more frequently associated with gastrointestinal discomfort, calcium salts with low calcium content may hinder patient compliance.

iii) Iron

The daily requirement of iron steadily increases throughout pregnancy. Although iron absorption efficiency increases during pregnancy, prophylactic dose of iron supplementation is still recommended for those at risk of deficiency e.g. with poor diet. In general, daily supplementation of 30-60 mg of elemental iron daily in non-anaemic women is sufficient. Enteric coated tablets or liquid suspension can improve the tolerance of iron supplements. However, the constipation problem of pregnant women may be worsened with higher doses of iron supplement. (Table 3)

Table 2. Percentage of calcium in various salts

Salt	% Calcium	Approximate equiv. to elemental calcium 1300mg
Calcium carbonate	40	3250mg
Calcium phosphate, tribasic	39	3333mg
Calcium chloride	27	4815mg
Dibasic calcium phosphate dihydrate	23	5652mg
Calcium citrate	21	6190mg
Calcium lactate	13	10000mg
Calcium gluconate	9	14444mg

Table 3. Iron preparations and dosages

Preparations	Elemental iron content (%)	Dose containing 60mg elemental iron (mg)
Iron fumarate	30	200
Iron gluconate	11	550
Iron sulphate	20	300

II COMMON MINOR AILMENTS DURING PREGNANCY

i) Nausea and vomiting

Recurrent morning nausea and vomiting occurs in about one-half of pregnancies during the first three months. However, the symptoms can occur any time throughout the day or night. The contributing factors of morning sickness include hormonal changes or emotional fluctuations. Even though these symptoms are not very severe in most of women and may subside with time, they are troublesome and may lead to malnutrition and dehydration. Non-pharmacological methods are generally recommended first to relieve the symptoms such as "small but frequent meals", avoiding fatty or spicy foods, and wearing motion sickness bands ("sea-band") on the wrists and psychological support. Checking the diet and any new food supplement taken is also important because some vitamin preparations may exacerbate the nausea and vomiting. In addition, complementary medicine may work in some women. When all the above failed, some old generation antihistamines and prokinetics can be recommended in the community pharmacy (Table 4).

ii) Headache

Generalized headaches are more frequent during the first trimester of pregnancy due to the hormonal changes. Paracetamol is the drug of choice in such situation. However, headaches occurring during second and third trimesters can be a sign of pre-eclampsia (other co-exist signs include blurred vision or sensitivity to light, and abdominal pain) and should be referred.

iii) Varicose veins

Varicose veins are common in pregnant women. [7] These are caused by the reduced venous tone which is induced by estrogen and progesterone - mediated relaxation of the vascular smooth muscle that usually begin from the early trimester of pregnancy. In the later trimester, intra-abdominal pressure increase and direct pressure on the iliac veins by the gravid uterus increases back pressure on the distal venous system and ruptures venous valves. [6] Consequently, the veins of the lower extremities and the vulva are commonly affected. Venous dilation results in characteristic distension and often tortuous varices, a feeling of heaviness, and often edema. Leg edema can generally be relieved by taking more rest and by elevating the legs. During pregnancy, supportive therapy may be initiated in symptomatic patients. Elastic stockings are usually recommended to keep the veins compressed [5] and to increase interstitial pressure in the surrounding tissue. Nilsson L. *et al*., [4] found that a significant improvement of venous emptying, combined with a subjective decrease of leg problems such as swelling, tiredness and pain after short term treatment with graduated compression hosiery. Furthermore, most women with varicose veins in pregnancy can, however, be reassured that the veins will probably resolve. [6] Treatment other than wearing compression sockings should be deferred.

iv) Heartburn

Heartburn is common in later stages of pregnancy. It affects 30% to 50% of pregnant women and occurs primarily in the second and third trimesters. The occurrence of heartburn is related to pressure from the growing fetus and hormonal changes which decrease pressure in the lower oesophageal sphincter and slow peristaltic waves in the lower oesophagus. Lifestyle changes and dietary modification are recommended as initial measures for relief of symptoms. Simple nonpharmacologic solutions such as

Table 4. Anti-emetics for morning sickness [17]

Drug	Dose	Comment
Meclizine	25-50mg QD PO	Considered drug of choice because of low teratogenic risk
Dimenhydrinate	50-100mg Q4H PO	Low teratogenic risk
Pyridoxine	50mg QD	Ineffective
Phenothiazines		
Promethazine	12.5-25mg TID PO	Teratogenic potential is inconclusive

Table 5. Pregnancy categories for gastrointestinal medications	
Drug	**Pregnancy category**
Cimetidine	B
Dimenhydrinate	B
Famotidine	B
Meclizine	B
Metoclopramide	B
Nizatidine	C
Omeprazole	C
Promethazine	C
Ranitidine	B
Sucralfate	B

frequent small meals, remaining upright after eating, and elevating the head of the bed will often suffice. [8]

Ingesting antacids after meals and at bedtime is safe during pregnancy. If symptoms persist, histamine -2 blockers or proton pump inhibitors may be used (Table 5). [9] Large studies of proton pump inhibitors use in pregnancy are lacking, however, although they have been used safely throughout pregnancy in women with Zollinger-Ellison syndrome. [10]

v) Constipation and haemorrhoids

Constipation is a common problem in late pregnancy. The contributing factors of constipation include the increased circulating progesterone in the mid and late pregnancy that may slow the gastrointestinal movement [11], compression of the enlarging uterus on the bowel, and the increased absorption of water in the colon. In addition, many pregnant women take prenatal vitamins that are high in iron content which may lead to constipation. [12] Haemorroid in pregnancy, apart from constipation, can be caused by peripheral vasodilation and pressure from the gravid uterus on the pelvic veins, resulting in more blood in the venous bed. Therefore, relieving constipation is important to retard the development of haemorroids. A study, by Buckshee K. *at el*., found that a flavonoid combination, a micronized diosmin 90% and hesperidin 10% is safe, acceptable, and effective in the treatment of hemorrhoids of pregnancy in short term with caution. [13]

Dietary supplements of fibre in the form of bran or wheat fibre are likely to help women experiencing constipation in pregnancy. If the problem fails to resolve, stimulant laxatives are likely to be more effective. [11]

vi) Cramp

Many pregnant women experience leg cramps. They become more common as pregnancy progresses and mostly at night. In a prospective, double-blind, randomized trial, oral magnesium supplementation was found to be useful in the treatment of pregnancy-related leg cramps. [15] If a woman finds cramp troublesome in pregnancy, the best evidence goes to magnesium lactate or citrate, to be taken as 5mmol in the morning and 10mmol in the evening. [16] Reduced serum levels of pyridoxine and thiamine during pregnancy may also play a role in muscle cramp. [14] The evidence that calcium reduces cramp is weak and seems to be a placebo effect. [16] Massage and placing the affected muscle(s) on stretch are the only methods which relieve cramps when they occur.

III SOURCES OF PATIENT INFORMATION

Nowadays, families who plan to have baby become more concern about prenatal care. Pharmacists can provide reliable sources of information about the health issues and safe drug uses during pregnancy. Apart from prenatal courses and books, more up-to-date information is available in some user-friendly internet resources. Some examples are as below:

MedlinePlus Health Information
http://www.nlm.nih.gov/medlineplus/pregnancy.html

4woman.gov The National Women's Health Information Center
http://www.4woman.gov/Pregnancy/index.htm

BBCi Parenting - Pregnancy
http://www.bbc.co.uk/parenting/baby/index_pregnancy.shtml

IV CONCLUSION

In the market, there are many pre- and maternal - formulated nutritional supplements e.g. in milk powder, tablets form available. When used in combination, we should check the total daily intake of individual ingredients for efficacy and safety ground. Even though most medicines given in pregnancy are for the benefit of the mothers, the fetus is an unintended recipient. Drugs taken by a pregnant woman may be passed to the fetus via the placenta and many can have pharmacological effects on the fetus. Therefore, as a rule, non-pharmacological methods are the first option in the management of minor ailments in pregnancy.

Gloria Yung graduated from CUHK and is now working in the Kowloon Central Cluster of Hospital Authority.

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Nutritional Supplements: Who Needs Them?

Windy Chan

Nutrient deficiencies are uncommon in Hong Kong. Nonetheless, you can find shelves of pharmacies and supermarkets abound with vitamin and mineral supplements. Many are heavily advertised on the basis that if a little do you good then more will do you better.

News and information about dietary supplements become more popular in the mass media, creating increased curiosity and public awareness. The explosion of the dietary supplement market is compelling pharmacists not only becoming aware of but also being well knowledgeable in nutrition.

I VITAMINS AND MINERALS

Vitamins are organic nutrients necessary in small amounts for normal growth and good health. Only two vitamins - D and K - can be synthesized by the body from non-dietary sources; others have to be obtained from the diet or by supplementation. Inadequate intake of vitamins would have adverse effects on body's vital processes. Classic vitamin deficiency syndromes include night blindness, scurvy, beriberi and pellagra. Minerals function as constituents of enzymes, hormones, and vitamins. Calcium and iron are the two elements drawing particular dietary attention from normal individuals.

A set of well-recognized dietary standards for optimum nutrition - the Recommended Daily Allowances (RDAs) - has been served as the benchmark of nutritional adequacy world widely. The RDAs are levels of daily intake of essential nutrients adequate to maintain health. Their traditional goal was to prevent diseases caused by nutrient deficiencies.[1]

In decades, the roles of nutrients have evolved from the prevention of classical deficiency diseases, to the reduction of risk of chronic diseases like osteoporosis, cardiovascular diseases and cancer. This evolution led to a reform in the nutrient reference values. In the early 1990s, the U.S. Food and Nutrition Board undertook the task of revising the RDAs and a new family of nutrient reference values was born - the Dietary Reference Intakes (DRIs). The DRI was actually a set of four reference values: Estimated Average Requirements (EAR), Recommended Dietary Allowances (RDA), Adequate Intakes (AI), and Tolerable Upper Intake Levels (UL). Definitions of these terms are summarized in Panel 1. The primary goal of having new dietary reference values was to not only prevent nutrient deficiencies, but also reduce the risk of chronic diseases.[1] The DRI project has been divided into seven nutrient groups ranging from vitamins, electrolytes, and trace elements to macronutrients and food components. The corresponding reports have been released in stages. Values for some micronutrients are listed in Table 1.

Many people take vitamin pills in the belief that more must be better, or as insurance against insufficiencies from diet. The public demands for supplements are further fuelled by the health claims and promotions in the mass media. Scientists and nutritionists have long been fascinated in the risk reductions in chronic diseases by the use of high doses of certain micronutrients, such as calcium, folic acid, vitamin E, selenium and chromium.[2] Although a few trials investigating this issue have been conducted, the science of vitamin supplementation for chronic disease prevention is not well developed, and much of the evidence comes from observational studies.[3] For most people, the necessary daily amounts of nutrients can be obtained from a well balanced diet. The primary functions and major food sources of some micronutrients are presented in Table 1.

Graphic extracted from http://www.fh21.com.cn/y1/tebie/weishengsu/

II WHO NEEDS SUPPLEMENTS?

When an adequate intake of nutrients cannot be achieved from the diet alone, either because of the eating habits or elevated physiological needs for particular micronutrients, supplements may act as useful complement to the diet. In general, an inexpensive supplemental preparation supplying close to 100% of the RDA for each nutrients will meet the needs of most patients requiring or desiring supplements. Some population groups are more vulnerable to particular nutrient deficiencies and more attention should be paid.

a) Women

Panel 1. Dietary Reference Intakes Definitions

Recommended Dietary Allowance (RDA): the average daily dietary intake level that is sufficient to meet the nutrient requirement of nearly all (97 to 98 percent) healthy individuals in a particular life stage and gender group.

Adequate Intake (AI): a recommended intake value based on observed or experimentally determined approximations or estimates of nutrient intake by a group (or groups) of healthy people, that are assumed to be adequate-used when an RDA cannot be determined.

Tolerable Upper Intake Level (UL): the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals in the general population. As intake increase above the UL, the potential risk of adverse effects increases.

Estimated Average Requirement (EAR): a daily nutrient intake value that is estimated to meet the requirement of half of the healthy individuals in a life stage and gender group-used to assess dietary adequacy and as the basis for the RDA.

Table 1. Daily reference intakes, food sources and functions of nutrients

Nutrients	RDA*	UL*	Food sources	Function
Vitamin A (Retinol)	Male:900mcg Female:700mcg	3,000mcg	Liver, fish, eggs, whole milk, green leafy vegetables	Required for normal vision, gene expression, reproduction, embryonic development and immune function
Vitamin B1 (thiamine)	Male:1.2mg Female:1.1mg	Not determinable	Yeast, peas, beans, grain products, wheat germ	Coenzymes in the metabolism of carbohydrate and branched-chain amino acids
Vitamin B2 (riboflavin)	Male:1.3mg Female:1.2mg	Not determinable	Dairy products, meat, fish, grains, cereals and green vegetables	Coenzymes in numerous redox reactions
Vitamin B3 (niacin)	Male:16mg Female:14mg	35mg	Meat, fish, cereals, grains and nuts	Coenzymes or cosubstrate in many biological reduction and oxidation reactions - thus required for energy metabolism
Vitamin B6 (pyridoxine)	1.3mg	100mg	Chicken, fish, kidney, pork, eggs, soya beans, whole wheat products and nuts	Coenzyme in the metabolism of amino acids, glycogen and sphingoid bases
Vitamin B12 (cyanocobalamin)	2.4mg	Not determinable	Meat, fish, milk, dairy products and eggs	Coenzyme in nucleic acid metabolism; prevents megaloblastic anemia
Vitamin C (ascorbic acid)	Male:90mg Female:75mg	2,000mg	citrus fruits oranges, greens, broccoli, tomatoes, potatoes	Cofactor for reactions requiring reduced copper or iron metalloenzymes and as a protective antioxidant
Vitamin D (calciferol)	5mcg	50mcg	Sunlight, fortified milk and margarine, eggs and butter	Maintain serum calcium and phosphorus concentrations
Vitamin E (alpha-tocopherol)	15mg	1,000mg	Vegetable oils, margarine, nuts, wheat germ and green leafy vegetable	A metabolic function has not yet been identified. Vitamin E's major function appears to be as a non-specific chain-breaking antioxidant
Calcium	1,000mg	2,500mg	Milk, cheese, yogurt, tofu, broccoli	Essential role in blood clotting, muscle contraction, nerve transmission, and bone and tooth formation
Folate	0.4mg	1mg	Liver, yeast, and leafy green vegetables. Easily destroyed during cooking, food processing and storage.	Coenzyme in the metabolism of nucleic and amino acids; prevents megaloblastic anemia
Iodine	0.15mg	1.10mg	Seaweeds, seafood	Component of the thyroid hormones; and prevents goitre and cretinism
Iron	Male:8mg Female:18mg	45mg	Vegetables, cereal, meat, poultry	Component of hemoglobin and numerous enzymes; prevents microcytic hypochromic anemia
Phosphorus	700mg	4,000mg	Milk, yogurt, cheese, peas, meat, eggs,	Maintenance of pH, storage and transfer of energy and nucleotide synthesis
Zinc	Male:11mg Female:8mg	40mg	Fortified cereals, red meats, seafood	Component of multiple enzymes and proteins; involved in the regulation of gene expression

Note:
RDA = Recommended dietary allowances; UL = Tolerable Upper Intake Levels.
** Unless otherwise stated, the values for adults age between 19 and 50 are presented.*
Sources: Dietary Reference Intakes reports which can be accessed via www.nap.edu.

Iron-deficiency anemia is a significant problem suffered by many women of childbearing age, particularly if they have heavy periods and a poor dietary intake of iron.

Women who are trying to conceive can benefit from supplementation. A mother's diet can influence the health of baby, and vitamin or mineral deficiencies would have serious adverse effects. During pregnancy, red-cell mass increases by about 25% and requirements of iron and folic acid increase in line. Higher intake of folic acid prior to pregnancy has been shown to reduce the subsequent risk of fetus neural tube defects. The required level is so high that it is difficult to attain through dietary manipulation. Therefore, a daily supplement of folic acid at a dose of 400mcg was recommended. The regimen should be continued for the first 12 weeks of pregnancy by which time the neural tube should have been closed.[4]

During pregnancy, iron supplements are not necessary unless iron-deficiency anemia is diagnosed. In this case, supplements are required, because anemia increases the risk of low birth weight and iron-deficiency anemia in the baby during the first year or two of its life.

Demands for other micronutrients are also increasing during pregnancy, but these can usually be satisfied by a balanced diet. Multivitamins and minerals supplements may be useful if the woman suffer from morning sickness or poor appetite in which loss or reduced intake of nutrients arise.

b) Older adults

Older adults are easier to be inadequately nourished. There is a concern about the nutritional status of people without teeth, those living in institutions, older age groups and those in low socio-economic groups. Due to inadequate exposure to sunlight, the housebound elderly may benefit from supplementation with calcium and vitamin D.[5] The absorption and the status of micronutrients, especially vitamin B_{12}, may be impaired with aging. It is advisable for the elderly to take more foods fortified with vitamin B_{12} or a supplement.[4]

c) Vegetarians

Vegetarians exclude meat, fish, or even dairy products and eggs in their diets, limiting the consumption of some micronutrients. Calcium, iodine, vitamin B_{12} and vitamin D are of particular importance. Even though grain products and cereals are good sources of iron, they mainly contain the non-heme iron which is with lower absorption than the heme iron from animal sources like meat and poultry.[1] Therefore, it has been suggested that the iron requirement is approximately two-fold greater for those consuming non-vegetarian diet. Supplements or fortified food are recommended if deficiency occurs.

d) Alcoholics

Alcoholics are at higher risk of malnutrition due to reduced oral intake and poor absorption. They often suffer from multiple deficiencies, predominantly of the water-soluble vitamins (e.g., vitamin B_1, B_2 and B_6, C and folic acid) and minerals (e.g., magnesium, zinc, copper, potassium and phosphorus). Supplementation with vitamin B complex and vitamin C is justified, however, it should be noted that this would not protect against the

Table 2. Adverse effects and drug interactions of nutrients

Nutrients	Adverse effects of excessive intake	Drug interactions
Calcium	Anorexia, nausea, vomiting, constipation, polyuria, hypercalcemia, hypercalciuria, renal stones	◆ Corticosteroids inhibit calcium absorption from the gut ◆ Calcitonin, furosemide, magnesium, cholestyramine, estrogen and some anticonvulsants lower calcium serum levels ◆ Thiazide diuretics increase serum calcium levels
Folic acid	Limited data May mask symptoms of vitamin B12 deficiency	◆ Folic acid deficiency may be induced by long term use of sulfasalazine, trimethoprim, and combined oral contraceptives ◆ Phenytoin may inhibit folic acid absorption; folic acid may decrease serum phenytoin levels
Iron	Gastrointestinal irritation, abdominal pain, constipation, diarrhea	◆ Antacids reduce absorption of iron ◆ Iron chelates with tetracycline, resulting in decreased absorption of both ◆ Iron reduces absorption of levodopa
Vitamin A (retinol)	Headache, diplopia, fatigue, hair loss, nausea, vomiting, hepatotoxicity, hypercalcemia, teratogenic risk (note: from preformed vitamin A only)	◆ Large doses increase hypoprothrombinemic effect of warfarin ◆ Oral contraceptives increase vitamin A plasma levels
Vitamin B2 (riboflavin)	A harmless yellow-orange fluorescence or discoloration of the urine	◆ Nothing reported
Vitamin B3 (niacin)	Adverse effects from consuming supplements include nausea, vomiting, diarrhea, flushing or burning sensations, hepatotoxicity, arrhythmias, hyperuricemia (no evidence of these effects in consumption of naturally occurring niacin in foods)	◆ Nothing reported
Vitamin B6 (pyridoxine)	Peripheral sensory neuropathy from high intakes of supplemental forms; prolactin inhibition	◆ Pyridoxine deficiency may be caused by: isoniazid, hydralazine, penicillamine, oral contraceptives ◆ Pyridoxine may reduce serum levels of phenobarbital and phenytoin, or antagonize effect of levodopa (but not co-carbdopa or co-beneldopa)
Vitamin C	Gastrointestinal disturbances, renal stones, excess iron absorption	◆ Anticoagulation effect of warfarin may be reduced ◆ Megadoses may cause crystalluria with acidic drugs or more rapid excretion of basic drugs
Vitamin D	Anorexia, nausea, weakness, polyuria, constipation, vague aches, stiffness, hypercalcemia, kidney stones, renal failure, hypertension	◆ Phenytoin or barbiturates may decrease the half-life of vitamin D, leading to osteomalacia in susceptible individuals
Vitamin E	Relatively nontoxic Hazards of long-term, high dose therapy unclear; adverse effects from supplements may include hemorrhagic toxicity	◆ Anticoagulation effect of warfarin may be enhanced

Key resources:
1. Thomas JA. Drug-nutrient interactions. Nut Rev. 1995;53:271-282
2. Thomas JA, Burns RA. Important drug-nutrient interactions in the elderly. Drugs Aging. 1998;13:199-209.

damaging effects of alcohol abuse.[4, 5]

e) Smokers

Smoking interferes with the absorption of a number of vitamins, particularly that of vitamin C which undergoes increased turnover in regular smokers. As their diets are usual less healthy and less balanced, any deficiency is best remedied by encouraging consumption of more fresh fruit and vegetables, rather than by taking vitamin supplements.[4]

f) Other at risk

Slimmers, and people on restricted diets or having poor appetites for long are at risk of deficiencies. Many weight-reducing products can induce diarrhea and thus loss of nutrients and electrolytes. The importance of a healthy diet and ways to achieve should be emphasized.[5]

III ADVERSE EFFECTS/ DRUG INTERACTIONS OF VITAMINS

The total upper intake level of vitamins and minerals is defined as the maximum dose likely to be safe in nearly all individuals. Exceeding this dose can result in adverse effects, which are listed in Table 2. Excessive intakes of the fat-soluble vitamins lead to accumulation in the body, upsetting the normal functioning or even imposing toxicities. Individuals with high alcohol intake, preexisting liver disease, hyperlipidemia or severe protein malnutrition may be distinctly susceptible to the adverse effects of excess preformed vitamin A intake. While excessive doses of the water-soluble counterparts are excreted through the kidneys, creating fewer problems. It is of note that evidence of adverse effects often comes from the consumption of supplements; little comes from that of naturally occurring nutrients in food.

Just as one drug may interact with another, drugs may also interact with nutrients. Vitamin and mineral deficiencies can result from a drug affecting the absorption, metabolism or excretion of nutrients. On the other hand, dietary supplements can alter drug absorption and metabolism. Some examples are listed in Table 2.

IV CONCLUSION

Nutrition is the foundation to health. There is good evidence of the benefits of some supplements in some populations. However, for most people, supplementing the diet with vitamins and minerals is not necessary and could potentially be harmful. Pharmacists should advise people to concentrate on eating a healthy, well balanced diet with adequate intake of fruit and vegetables, and to await further official advice before resorting to dietary supplementation. Primary attention should be directed toward improving the diet; under some circumstances, a supplement is appropriate.

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Improving Outcomes in Allergic Rhinitis Through Patient-Focused Care

Elvina Poon

The high prevalence of allergic rhinitis and its effect on patients' quality of life has caused it to be classified as a major chronic respiratory disease. It is reported to affect 10% to 40% of the global population and its prevalence increases in both children and adults. Pharmacists are in a good position to give a positive impact on patient outcomes by using effective communication strategies, addressing environmental controls and targeting treatment therapy to patient-specific symptoms.

I COMMUNICATION STRATEGY

The pharmacist, as the first-line healthcare provider to interface with patients seeking a nonprescription allergy medication, has a unique opportunity to intervene in the management of allergic rhinitis.[1]

In panel 1 and 2 are two scenarios that the patient is first handled inappropriately by a pharmacist, but then handled effectively by another pharmacist.

From the two scenarios, we know that a caring attitude and empathic listening are the keys to start an effective pharmacist-patient communication, and most importantly, to understand the patient's condition and needs. In the second scenario, the pharmacist takes a sensitive and caring approach. Through patient caring, it gives a trust for patient to truly express her feeling and suffering. The pharmacist makes no attempt to minimize the impact of illness to the patient.

Through listening, a pharmacist can understand how the patient interprets allergic rhinitis and its treatment. For

Panel 1. Scenario 1 - The patient is inappropriately handled by a pharmacist

LW, a 21-year old office lady, suffers from allergic rhinitis. She came to the pharmacy with swollen and bloodshot eyes. She looked so upset and frustrated. She complained that the allergy medication was not working well, and asked for the pharmacist's advice.

Pharmacist: *Well, that is what the allergy is. It's not a big deal. Be thankful you don't have diabetes or something serious.*

LW was so upset and left the pharmacy.

Panel 2. Scenario 2 - The Patient is effectively handled by a pharmacist

LW went to another pharmacy and asked for the pharmacist's advice.

Pharmacist: *How do you feel today?*

LW: *I feel so frustrated because the allergy is really brothering me. My nose keeps running and my eyes are swelling.*

Pharmacist: *I understand that. It is exhausting. Are you taking any medication for allergy?*

LW: *I have been taking an antihistamine pill and a decongestant nasal spray for a month already. I also use some corticosteroid nasal sprays when the symptoms are getting severe. However, the medication seems not working well. My nose is still blocked and I feel so sleepy every time when I take the antihistamine pill. I cannot perform my daily work.*

Pharmacist: *I see. You know the decongestant nasal spray can only be used for a short period of time, not more than a week. Otherwise, it will block your nose more. Also, corticosteroid nasal spray is used to prevent symptoms not to treat symptoms. It is better to take a week before the allergy starts and to use it on a day-to-day basis. Antihistamine is used to treat allergic symptoms. There are some non-drowsy antihistamine pills that won't affect your daily activities.*

LW: *No wonder my medications are not working because I have not used them not in the correct way.*

Pharmacist: *Do you clean your house often? The most effective way to control allergy is to avoid allergen exposure.*

LW: *No, I seldom clean my house.*

Pharmacist: *You should clean your house more frequently. The mattress and pillows should be washed at least every 2 weeks at a temperature higher than 103°F.*

LW: *Okay. I am going to clean my house everyday and take my medication in the correct way. Thank you so much for your advice. You are very helpful.*

After 1 month, LW's allergy symptoms are improving.

example, does the patient understand what allergic rhinitis is? Does the patient understand the treatment therapy and how the medicines work? Are there any perceived problems in carrying out the treatment therapy? How do the symptoms of allergic rhinitis affect the patient's functioning on a daily basis? How does it affect on the life of the patient? This kind of information also needs to be gathered, understood and responded to in a way that expresses care.[2]

It is especially imperative that patients with allergic rhinitis understand the condition. This includes actions they may take to reduce the level of allergens that may cause symptoms to flare up. This also includes environmental control.

II ENVIRONMENT MODIFICATION[3]

The most effective method for controlling allergic rhinitis is to avoid allergen exposure; therefore, environmental control measures should be the first-line therapy aimed at reducing concentrations of pollen, dust mites, mold and animal dander. During high pollen season, reducing pollen exposure by closing windows and doors, and utilizing air conditioners and limiting outdoor activities are important. Thorough cleaning and maintaining humidity below 50% by the use of a dehumidifier can reduce dust mites and their feces. The following measures will also minimize exposure to allergens:

- Carpets should be removed from the bedroom. Comforters and bedspreads should be vacuumed with a machine that has a high efficiency particulate air (HEPA) filter.
- Mattress and pillows should be encased with plastic backings, frequently cleansed to prevent the accumulation of dust and dust mites.
- Bedding should be washed in hot water (>130^{o}F) at least every two weeks to kill the ova and remove mites and pollen.
- Periodic airing for 10 minutes and sun exposure will kill dust mites in bedding, drapes and rugs.
- Foam instead of feather pillows should be used.
- Windows should be covered with washable curtains or shades instead of Venetian blinds that are excellent dust catchers. All blinds should be frequently washed.
- A HEPA filter in the bedroom can help keep the air clean, and the use of a dehumidifier can help reduce humidity during humid months, to reduce the growth of dust mites and indoor molds.
- Cold outside walls promote mold growth and should be avoided by mold-sensitive individuals. Cooling systems should also be checked periodically for mold growth.
- Household plants should be eliminated from the bedrooms as their soil may be a rich source of mold.
- A face mask should be used during indoor and outdoor activities to avoid increased exposure to dust, mold and pollen (vacuuming, mowing, threshing).
- If a pet at home is the cause of the allergic symptoms, the pet should be kept out of the bedroom, and, if possible, away from carpeted areas. (Removing carpets altogether is the best.) Applying special sprays can help control antigens from pets.

III DRUG TREATMENT THERAPY

It is also very important that the patient understands the difference between medicines that treat symptoms (antihistamine) and those that prevent symptoms (corticosteroid nasal sprays, for example). Patients often use sprays inappropriately because they believe they will relieve symptoms if used on an "as-needed" basis. When their symptoms are not relieved, they think the product is ineffective. This is unfortunate, since patient education could have prevented this misconception.[2]

Patient education when dispensing medication is very important. Information includes the following:

- Name of the medication
- Strength and dosing information
- How long should the medication be used
- The benefits of using the medicine
- Major side effects
- Precaution
- Beneficial activities
- Drug interactions
- Storage recommendations
- What to do if a dose is missed
- How long will it take to become effective?

Important Allergic Rhinitis Medication Counseling Issues[2]

1. First Generation Anithistamine

This medication will help control sneezing, running nose, watery and itchy eyes, nose and throat. It will not improve nasal congestion and eye redness.

For control of seasonal allergic rhinitis, initiate therapy 2 weeks before the allergy season for maximum effectiveness and continue throughout the season.

It may cause drowsiness, sedation, dizziness, confusion and slow reaction time.

Do not operate automobile or other machinery until the response to this medication are aware of by the patient.

Avoid alcohol beverage as the sedative side effect may exacerbate.

It may cause dry mouth, urine retention, constipation and blurred vision.

Avoid in patients with narrow angle glaucoma or prostatic hypertrophy.

Always inform your doctors and pharmacist that you are taking this medication. This will allow your pharmacist to screen for any drug interactions.

It is a class of first line agent for children and pregnant women. Chlorpheniramine and tripelennamine are the preferred antihistamines.

2. Second generation Antihistamine

It will help control sneezing, runny nose, watery and itchy eyes, nose, ears, and throat.

It will not improve nasal congestion or eye redness. It should be taken as directed: Do not exceed the maximum recommended dose.

For control of seasonal allergic rhinitis, initiate therapy 2 weeks before allergy season for maximum effectiveness. Continue throughout the season.

It associates with less sedation and anticholinergic side effect.

If any unexplained dizziness, syncope, or blackouts are experienced, notify a physician immediately.

3. Intranasal antihistamine

In contrast to oral antihistamine, it can reduce nasal congestion.

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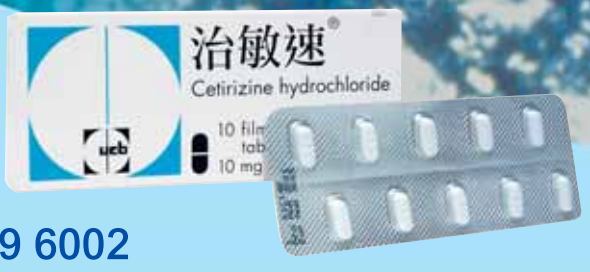

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It can be used as either first line treatment for the symptoms of allergic rhinitis or in conjunction with oral antihistamine or nasal corticosteroidal therapy.

Patient should be warned of the potential for drowsiness (11%) and bitter taste.

If a dose is missed, the dose should be taken as soon as remembering, unless it is almost time for next dose. Do not double-dose.

4. Topical Decongestants

It will improve nasal congestion and help breathe better. (For ophthalmic products: This medication will improve eye redness.)

Pharmacists can demonstrate appropriate medication delivery technique to the patients.

Use as directed: Do not exceed the maximum recommended dose.

Do not use for more than 3 to 5 consecutive days due to risk of rebound congestion.

5. Systemic Decongestants

It will improve nasal congestion and help breathe better.

It should be taken as directed: Do not exceed the maximum recommended dose.

Last dose of a day can be taken 3 to 5 hours before bedtime to avoid trouble sleeping.

If a patient has high blood pressure, heart disease or diabetes, do not use this product without consulting a physician. Monitor blood pressure and report any irregular heart beats or chest pain to healthcare providers.

Avoid during the first trimester of pregnancy due to reports of abdominal wall defects to the fetus.

Hypertensive crisis can result from combining decongestant with monoamine oxidase inhibitors or tricyclic antidepressants

6. Intranasal Corticosteroids

It will improve sneezing, runny nose, itchy nose and throat, and nasal congestion. It will not improve itchy, watery, or red eyes.

It can be given to patients who should not receive antihistamines/ decongestant (e.g. patients with glaucoma, hypertension, prostatic hypertrophy) and the lowest effective doses should be used.

It can be used to prevent symptoms. It may take up to 2 weeks for maximum effectiveness. Even though you may not detect an effect, the medication is working.

If a dose is missed, it should be taken as soon as remembering, unless it is almost time for next dose. Do not double-dose.

An appropriate medication delivery technique is required for maximum effectiveness (with Pharmacist demonstration).

For control of seasonal allergic rhinitis, initiate therapy 2 weeks before the allergy season for maximum effectiveness. If acute rhinitis symptoms are experienced during this period, alternatives for symptom control should be considered by doctor or pharmacist while the patients are waiting for the medication to take effect.

Possible adverse effects are minimal, including nasal irritation, nasal burning and dryness. Instructing patients to direct the spray away from the nasal spectum can prevent these side effects. Nasal dryness can be minimized with the use of nasal saline prior to administration. For patients with "drier" noses and predominant nasal congestion, aqueous nasal corticosteroid is preferred.

For patients with rhinorrhea or "wet" noses, the nonaqueous preparation is preferred.

Discontinue if patients have nasal bleeding and ulceration.

7. Mast cell Stabilizers

It will improve the following symptoms when used as directed: sneezing, runny nose, and itchy nose and throat and nasal congestion. It will not improve itchy, watery, or red eyes.

They are the first line agents for children and pregnant women.

It can be used to prevent symptoms. The therapy may start 1-2 weeks prior to allergen exposure. It may take 2 to 4 weeks for maximum effectiveness. Even before an effect can be detected, the medication begins working (when used as directed). If acute rhinitis symptoms are experienced during this period, alternatives for symptom control should be considered by doctors or pharmacists while the patients are waiting for the medication to take effect.

Patients should be reminded for not to share their nasal spray with others because this may spread bacteria and viruses.

For optimal absorption, blow the nose or clean the nose with normal saline drop prior to spray the medication.

Possible adverse effects are minimal because the medication is being delivered directly to the site of action. However, you may experience some nasal irritation and unpleasant taste.

8. Intranasal Anticholinergics

It will improve runny nose, but can not relieve sneezing; itchy nose, ears, throat, or eyes; watery or red eyes; or nasal congestion.

Adverse effects are minimal because the medication is being delivered directly to the site of action. The most common side effects are headaches, nosebleeds and nasal dryness which can be reduced with use of saline nasal spray.

IV CONCLUSION

Effective pharmacist-patient communication can be achieved by effective listening strategies, caring and empathic understanding for the allergy patients. Incorporate those communicating techniques can improve patients' understanding of correct drug usage and the importance of environmental control. This will lead to a better patient outcome and a more satisfying practice.

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Chronic Hepatitis B

Shirley Chih; Sharon Lam

2 CE Units

I INTRODUCTION

Chronic hepatitis B (CHB) is a chronic necroinflammatory disease of the liver caused by persistent infection with the Hepatitis B Virus (HBV). It is defined as the presence of positive Hepatitis surface antigen (HBsAg) for more than 6 months. There are 2 types of CHB, depending on the HBeAg or anti-HBe status: HBeAg positive and HBeAg negative CHB. Table 1 shows the serologic difference between the HBeAg positive and HBeAg negative CHB. Some patients have a viral mutation in the precore region that prevents expression of HBeAg; these patients have active liver disease and HBV DNA in the serum but are HBeAg negative.[1] HBeAg negative CHB is more common in Mediterranean countries and Asia. There are also clinical differences between these 2 types of CHB: Patients with HBeAg negative CHB have lower plasma HBV DNA level and are more likely to have a variable course of disease progression. Often, patients present with fluctuating levels of serum aminotransferases and HBV DNA. The liver disease may be compensated or decompensated; the former refers to the state when the liver is still capable of carrying out normal functions, whereas the latter refers to the failure of liver to perform properly at which state ascites, jaundice and/or varical bleeding may occur.

CHB is the leading cause of death worldwide, affecting 360 million of population globally.[2] CHB causes a serious health burden since it is the primary cause of cirrhosis and hepatocellular carcinoma (HCC) that are associated with high morbidity and mortality.

Table 1. Serologic Differences between HBeAg positive and HBeAg negative hepatitis B

	HBeAg positive CHB	HBeAg negative CHB
HBeAg	+	-
Anti-HBe	-	+
HBV DNA	+	+

II EPIDEMIOLOGY OF HEPATITIS B

The prevalence and patterns of transmission of the disease vary globally. Figure 1 shows the geographic distribution of chronic HBV infection. For highly endemic regions, such as China, Southeast Asia and Africa, the prevalence of chronic infection is more than 8%. The main routes of transmission in these regions are perinatal and person-to-person contact. In North America, Northwestern Europe and Australia, CHB is relatively uncommon with a prevalence rate of less than 1%. Infection is mainly through sexual contact or needle-sharing among drug users.

The likelihood of developing CHB is greatly affected by the age when HBV infection occurs. If the infection is acquired perinatally, the chance of it becoming chronic can be as high as 90%. However, only about 5% of the infected adults will develop chronic infection. Among HBeAg positive and HBeAg negative CHB patients, the risks of development of cirrhosis per annum are 2-5.5% and 8-10%, respectively.[2] For chronic carriers without cirrhosis, the incidence of HCC ranges from <0.2% per year in Western countries to 0.6% per year in Asia. For cirrhotic patients, the overall risk is over 2% per year.[2] The 5-year mortality rate differs for various stages: 0-2% for patients without cirrhosis, 14-20% for patients with compensated cirrhosis and 70-86% following decompensation.[2]

How Common is Hepatitis B in Hong Kong?

In the last 20 years, the carrier rate in Hong Kong has gradually fallen from 10% to 8%. This was due to the implementation of newborn and preschool children vaccination programme. Since 1983, the Medical and Health Department has been testing pregnant women for hepatitis B, and giving free vaccination to susceptible newborn babies. This programme was extended to cover all newborn infants in 1988. All babies born in Hong Kong now routinely receive the hepatitis B vaccine for free. If the mother is a carrier, the baby will receive additional immunoglobulin to make sure that

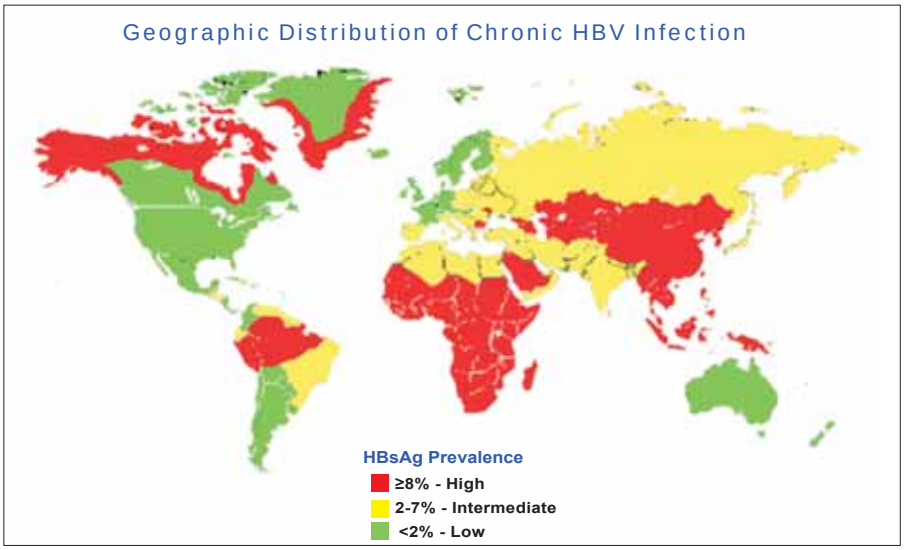

Figure 1. Geographic Distribution of Chronic HBV Infection. (Adapted from the website of Centers of Disease Control and Prevention www.cdc.gov)

he/she will not be infected. The success rate exceeds 90%. Furthermore, a campaign was launched to cover preschool children born in the period from 1985 to 1988. In other words, all children in Hong Kong should have been vaccinated against hepatitis B before they enter school.

III HEPATITIS B VIRUS (HBV)

HBV is a small partially double-stranded DNA virus (Figure 2). It is the only hepatotropic virus with a DNA genome. The HBV virion or Dane particle has a diameter of about 42 nm. Hepatitis B surface antigen (HBsAg) is present on the envelope. The core contains HBV DNA, DNA polymerase and core protein (HBcAg). Hepatitis e antigen (HBeAg) is produced from HBcAg and found in blood as free protein. HBsAg is also released into circulation although its function remains unclear.

After entry into a hepatocyte, the virus is uncoated. The partially double-stranded DNA is released and transported into the nucleus where it is converted into a covalently closed circular DNA (cccDNA). The cccDNA is used as a template for the production of pregenomic RNA. By the action of polymerase protein, a new DNA is transcribed from pregenomic RNA that is subsequently destroyed by polymerase-associated RNAase. The new DNA is converted into the partially double stranded DNA form and then packaged with proteins into new virions before release. Some of the cccDNA remains in the nucleus, acting as non-replicating viral repository that is unaffected by most of the antiviral drugs. This explains why there is a rapid reappearance of serum HBV DNA after cessation of antiviral therapy.

HBV is not cytotoxic by itself; however, the immunological responses that are elicited for eliminating the infected hepatocytes are responsible for the liver damage. This is mediated mainly by the action of cytotoxic T cells and T helper cells, causing apoptosis of the infected hepatocytes and release of cytokines that inhibits viral gene expression and replication. Humoral response is involved as antibodies are released to neutralize the free circulating viral particles. (Details of immunogenesis of HBV are beyond the scope of this article.) The immune system simultaneously results in the clearance of the HBV-infected hepatocytes (i.e. protection) and cell damage (i.e. liver injury). However, for unknown reasons, the immune response against HBV is often inadequate to allow eradication. On the other hand, the necroinflammatory response of hepatocytes is sustained.

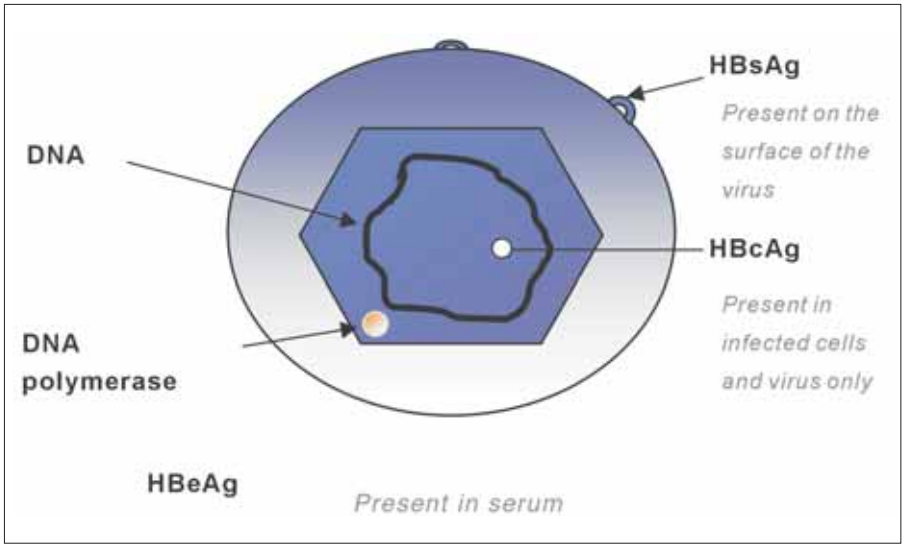

Figure 2. Hepatitis B Virus.

IV SEROLOGY AND NATURAL HISTORY OF CHB INFECTION

a) Serology of CHB infection

There are three main types of antigen found in chronic hepatitis B infection, the corresponding antibodies and their clinical significance are summarized in table 2.

b) Serum HBV DNA

The presence of serum HBV DNA is sensitive and specific for viral replication. Hybridization or signal amplification (branched DNA) assays detect 10^5 to 10^6 viral equivalents/mL, while the more sensitive polymerase chain reaction (PCR)-based assays detect 10^2 to 10^3 viral equivalents/mL. Recovery from acute HBV and HBeAg seroconversion in chronic HBV is associated with the disappearance of HBV DNA by non-PCR-based assays. Using the PCR-based assays, patients may remain HBV DNA positive for many years, which indicates the persistence of a small number of virions that are contained by the host immune system. The main use of HBV DNA assays is to assess chronic active HBV patients for treatment and to evaluate their response.[1]

c) Natural course of CHB infection

The natural course of chronic HBV infection can be described by phases, as shown in Figure 3. During the initial immunotolerant phase, HBV DNA is high and HBeAg is positive. This is followed by an immunoactive phase when patients have high ALT and decreased HBV DNA levels. This is then followed by the non-replicative or minimally replicative phase in which seroconversion to antibody to HBeAg (anti-HBe) and remission of liver disease occurs. Reactivation of HBV and of liver disease activity may occur after seroconversion. The loss of hepatitis B surface antigen (HBsAg) and seroconversion to HBsAg (anti-HBs) indicates resolution of the infection.

V DIAGNOSIS OF CHB

A combination of biochemical and virological tests and histological examinations are employed to diagnose and classify HBV infection:

Table 2. Serology of chronic hepatitis B

Antigen	Antibody	Significance
HBsAg	Anti-HBs	HBsAg is used for the diagnosis of HBV infection in blood screening. Anti-HBs persists for years after HBV infection, conferring suppression of HBV.
HBeAg	Anti-HBe	HBeAg is a marker of active viral replication and its presence correlates with high titers of HBV DNA in serum, active liver disease and high rates of infectivity. The appearance of Anti-HBe, the antibody against HbeAg, suggests a resolution of HBV infection.
HBcAg	Anti-HBc	HBcAg is a marker of infectious viral materials and it is the most accurate index of viral infection. However, it is not frequently measured as it does not freely circulate in the bloodstream. Anti-HBc can be used to identify all patients who have been infected.

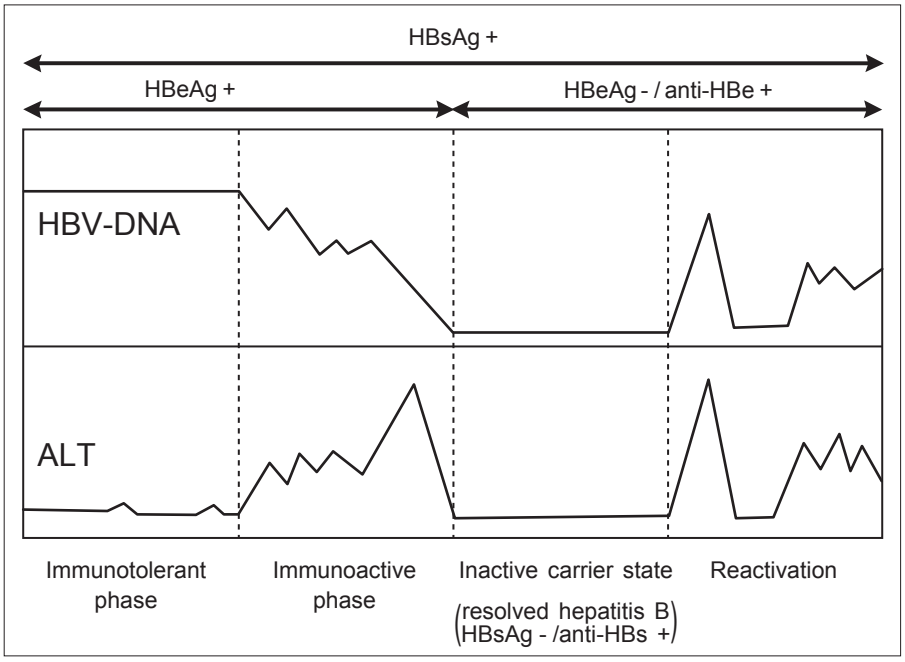

Figure 3. Natural History of Hepatitis B infection (Adapted from Fattovich G. Natural History of Hepatitis B; EASL International Consensus Conference on Hepatitis B[3])

Biochemical: Persistent or intermittent elevation in ALT/AST levels.
Virological: Presence of HBsAg in serum for at least 6 months and/or serum HBV DNA more than 10^5 copies/mL.
Histological: Evidence of necroinflammation unexplained by other causes.

During active viral replication, HBeAg and HBV DNA (by non-PCR-based assay) are positive, and ALT levels are usually elevated. These tests are necessary to decide if therapy is warranted. A carrier state is characterized by positive HBsAg and anti-HBs, negative HBeAg, normal ALT levels and undetectable HBV DNA (by non-PCR-based assays).

Liver biopsy is helpful in assessing the severity of liver damage, predicting prognosis, determining treatment and monitoring response. Liver biopsy is generally indicated if any of the parameters for active CHB are present - HBsAg along with either elevated ALT levels, HBeAg or HBV DNA, or all 3 of them. In most cases, all 3 parameters are present but in some the ALT levels may be normal or HBeAg may be negative.

VI TREATMENT

There are many therapies for chronic hepatitis B, but only interferon alpha, lamivudine and adefovir dipivoxil are licensed for this indication. Hepatitis B vaccine is introduced as the most effective mean to prevent HBV infection and its consequences. Many novel treatment options are still under investigation. These include thymosin, tenofovir and DNA vaccine, etc.

The goals of therapy are to eliminate or permanently suppress HBV, stop or reduce hepatic inflammation, prevent the development of hepatic fibrosis and/or decompensation, maintain sustained loss of HBV DNA and aminotransferases, and prevent progression to cirrhosis and HCC. The ultimate goal is to prolong survival.

The endpoints of treatment include biochemical, virological and histological responses:

Biochemical: Normalization of serum aminotransferases.
Virological: Decrease in HBV DNA level to below 10^5 copies/mL, loss of HBeAg (for patients who are HBeAg positive initially).
Histological: Decrease in histology activity index by at least 2 points compared with pretreatment liver biopsy.

A complete response is defined as HBsAg seroconversion, i.e. loss of HBsAg and emergence of Anti-HBs.

(i) Interferons (IFNs)

IFNs have antiviral, antiproliferative, and immunomodulatory effects. They can be divided into several subtypes: alpha (produced by B lymphocytes and monocytes), beta (produced by fibroblasts) and gamma (produced by helper T cells and natural killer cells). Only the alpha type is effective against HBV. Both interferon alpha 2a and 2b can be used for treatment of CHB.

a) Interferon alpha (INF-α)

Mechanism of Action
INF-α can induce T helper cells activity and HLA type 1 expression, cause maturation of B lymphocytes, and inhibit T cell suppressors.

Efficacy
INF-α is the first agent approved for treatment of CHB. It has been shown to be effective in suppressing HBV replication and inducing remission of liver disease. However, its efficacy is limited to a subset of patients[4], such as those with HBeAg positive CHB with high level of pretreatment ALT and low serum HBV DNA level. In patients with HBeAg negative CHB, HIV infection, compromised immune system or decompensated liver disease, its efficacy is limited.

Dosage
INF-α is administered subcutaneously. The recommended dosage for HBeAg positive CHB is 5 MU daily or 10 MU thrice weekly for 16-24 weeks. For children, the recommended dosage is 6 MU/m^2 thrice weekly up to a maximum dosage of 10 MU weekly. In HBeAg negative CHB, INF-α given in dosage of 5-6 MU thrice weekly for 12-24 months is recommended.

Prednisone Priming
The rationale for administering a tapering course of steroids prior to antiviral therapy (prednisone priming) is that recovery of immune function following steroid withdrawal may be beneficial particularly if this is timed with the initiation of INF-α therapy. Although a small subset of patients may benefit from prednisone priming, there is a risk of fatal exacerbations in patients with underlying cirrhosis. Therefore, prednisone priming is not recommended as a primary treatment of CHB.[5]

Adverse Effects
Adverse effects of INF-α are common. Flu-like symptoms, such as fever, chills, anorexia, nausea, fatigue, myalgia and headache, may appear a few hours after injection and have been reported.[6] The events tend to resolve after repeated exposure. Paracetamol can be prescribed for flu-like symptoms; however, the dose should not exceed 2g per day due to hepatotoxicity.

Other adverse effects may require dosage reduction or even premature discontinuation of INF-α. These include the worsening of flu-like symptoms, alopecia, bone marrow suppression (leucopenia and thrombocytopenia), psychiatric disturbance (depression, anxiety, delirium), thyroid dysfunction (both hypothyroidism and hyperthyroidism) and bacterial infections.[6]

It should be cautioned that in patients with cirrhosis, INF-α may result in transient ALT flare-up and subsequently hepatic decompensation. Therefore, INF-α should not be used in patients with very high ALT level (>5 ULN).

(ii) Nucleoside/Nucleoside Analogues

Nucleoside/Nucleoside analogues are chemically synthesized drugs that are able to mimic the natural nucleosides. They can be incorporated into newly synthesized HBV-DNA, thus causing chain termination and inhibiting viral replication. Some of the nucleoside analogues may even competitively inhibit the DNA-dependent and reverse transcriptase activity of the viral polymerase.

a) Lamivudine

Mechanism of Action

Lamivudine acts by terminating viral DNA synthesis and competitively inhibiting the viral polymerase/reverse transcriptase (HBV DNA polymerase). It is equally effective in patients of any race for infections caused by both the wild-type virus and precore/core promoter variants. In addition, there is evidence to suggest that lamivudine treatment may overcome cytotoxic T cell hyporesponsiveness seen in chronically infected patients.[7]

Efficacy

Lamivudine has been shown to be effective in terms of HBV-DNA suppression, normalization of ALT level and improvement in histology in both HBeAg positive and HBeAg negative/HBV DNA positive patients.[8, 9, 10] In HBeAg positive patients, one year of therapy with lamivudine (100 mg daily) significantly increased the rate of HBeAg seroconversion, the extent of which was related to the pretreatment ALT level. In patients with ALT >5xULN, lamivudine produced HBeAg seroconversion in 64% of patients vs 14% for placebo recipients. In patients with ALT in the range of 2-5xULN, the percentages were 26% vs 5%; in those with ALT <2xULN, the figures were 5% vs 2%.[11] Such findings indicated that patients with a more vigorous immune response to HBV respond better to the direct antiviral effect of lamivudine therapy. Children treated for one year with lamivudine in dosage adjusted for body weight (3 mg/kg) showed a similar response.[12] Hepatitis flares, sometimes severe, may occur if lamivudine is stopped before HBeAg seroconversion.[13]

Dosage

Lamivudine is administered orally and the recommended dose for adults is 100 mg per day, whereas that for children is 1 mg/kg per day to a maximum of 100 mg/day. The recommended duration of treatment is 1 year in HBeAg-positive patients, and can be longer than a year in HBeAg-negative patients.[7] However, in practice, the duration of treatment is determined by the development of seroconversion.

Adverse Effects

Lamivudine is remarkably free of side effects and discontinuation of therapy due to side effects is rarely necessary.[1] The common side effects reported are headache, fatigue, nausea, and abdominal discomfort. Other less common side effects include transient rise in amylase, lipase and creatinine kinase.[6]

Lamivudine Resistance

A major limitation of lamivudine therapy is drug resistance. HBV mutants that are resistant to lamivudine start to emerge after 6-9 months of lamivudine therapy. The emergence of resistance is commonly associated with a mutation in the YMDD (tyrosine-methionine-aspartate-aspartate) motif of the polymerase gene. The incidence increases with duration of therapy (approximately 70% among patients treated with lamivudine continuously for 5 years).[14, 15]

The YMDD mutation is associated with the reappearance of HBV-DNA (this must be distinguished from viral rebound due to non-compliance) and frequently ALT elevation. Although ALT values usually do not reach pretreatment levels, hepatitis flares may develop and this is sometimes associated with hepatic decompensation.[16] Therefore, the benefit of long-term lamivudine therapy is a balance between the concern about any possible harm or risk associated with YMDD mutations and the durability of treatment response.

Studies have shown that adefovir dipivoxil and entecarvir are effective for patients with YMDD mutants. Adefovir dipivoxil can be used to 'rescue' such patients. If these 'rescue' drugs are not available, stopping lamivudine therapy with close monitoring may be an option in patients who have developed YMDD mutants.[17, 18]

b) Adefovir dipivoxil

Adefovir dipivoxil is a diester prodrug of adefovir. The agent was approved for CHB in adults by the Food and Drug Administration (FDA) since September 2002.

Mechanism of Action

Adefovir acts as a nucleotide analog of adenosine monophosphate. After entry into cells, the active moiety, adefovir diphosphate, selectively inhibits HBV polymerase by direct binding in competition with the natural substrate and causes chain termination after it is incorporated into HBV DNA.

Efficacy

Adefovir dipivoxil 10 mg once daily has been associated with significant histological improvement ($p < 0.001$), reduction in serum HBV DNA levels ($p < 0.001$) and normalization of ALT ($p < 0.001$) in patients with CHB (both HBeAg positive and HBeAg negative) and compensated liver function.[19] Significantly more HBeAg positive patients who were treated with adefovir experienced HBeAg seroconversion compared to placebo recipients (12% vs 6%, $p<0.05$).[19] The clinical and antiviral effects of adefovir dipivoxil 10 mg were maintained in CHB patients who had clinical evidence of lamivudine-resistant hepatitis B virus following liver transplant.[19] Treatment results in a similar reduction in serum HBV DNA level regardless of the patterns of lamivudine-resistant mutations at baseline.[19]

Dosage

For patients with creatinine clearance ≥50mL/min, adefovir dipivoxil is administered in dosage of 10 mg once daily disregard of food intake. Dosage adjustment is required for patients with creatinine clearance < 50mL/min.

Adverse Events

Adefovir dipivoxil is well tolerated. In HBeAg positive and HBeAg negative CHB patients with compensated liver disease treated up for up to 92 weeks, nephrotoxicity is not evident and the most common adverse events in these groups are headache, pharyngitis, asthenia, abdominal pain and flu syndrome.[19]

Resistance

Due to close structural relationship with the natural substrate and flexibility of acyclic linker, adefovir subverts steric hindrance and thus hypothetically is linked to a low potential of resistance development.

(iii) Recommendations for the Treatment of Chronic Hepatitis B

Since the Asian-Pacific Consensus on the Management of Hepatitis was first published in 2000, the members of the Working Party continue to monitor the progress and review the relevant new data on treatment of CHB. An updated consensus statement was released early this year in the Journal of Gastroenterology and Hepatology.[5] The algorithm shown in Figure 4 is the summary of the Asian-Pacific consensus on the management of CHB.

The Asian-Pacific Consensus Working Party produced the following recommendations on the management of CHB:

Recommendation 1

Patients with persistently normal ALT should not be treated but they need adequate follow-up and HCC surveillance every 3-6 months.

Recommendation 2

Liver biopsy is recommended in viraemic patients with raised ALT prior to therapy.

Recommendation 3

HBV-DNA seropositive patients with ALT >2xULN should be considered for treatment.

For patients (both HBeAg positive and HBeAg negative adults and children) with an ALT level >5xULN, lamivudine is recommended if there is concern regarding the risk of hepatic decompensation with interferon.

For HBeAg positive patients with ALT level between 2 and 5xULN, the choice between interferon and lamivudine is less clear and either agent may be used.

For HBeAg negative patients with intermittent or persistent increase in ALT, moderate to severe inflammation and fibrosis on biopsy, and high serum HBV DNA levels (>10^5 copies/mL), a 12-month course of interferon induces a higher rate (24%) of sustained response than a similar course of lamivudine (13%).

Recommendation 4

Patients can be treated with either lamivudine or interferon. Lamivudine is recommended if there is a concern about hepatic decompensation.

Recommendation 5

During therapy, ALT, HBeAg and/or HBV-DNA (quantitative method) should be monitored at least every 3 months. During interferon therapy, the monitoring of adverse effects is mandatory.

Recommendation 6

At the end of therapy, ALT and HBV markers (including HBV DNA) should be monitored monthly for the first 3 months for early relapse and then every 3 months (for cirrhotic patients and those who remain HBeAg/HBV-DNA positive) to 6 months (for responders). For non-responders, further monitoring is required to recognize a delayed response and to plan re-treatment when indicated.

Recommendation 7

For interferon, the current recommended duration of therapy is 4-6 months.

Recommendation 8

For lamivudine in HBeAg positive patients, treatment can be stopped when HBV DNA loss with HBeAg

seroconversion is documented on two separate occasions 6 months apart.

Recommendation 9
Lamivudine is the agent of choice for patients with impending or obvious features of hepatic decompensation.

Recommendation 10
For immunosuppressed patients, lamivudine is the preferred treatment and interferon is usually ineffective or even contraindicated.

VII PROPHYLAXIS OF HEPATITIS B

a) Post-HBV exposure

Avoiding blood exposures is the primary way to prevent transmission of HBV. In addition to blood, body fluids containing visible blood, semen and vaginal secretions are also considered as potentially infectious. Table 3 shows the relative concentrations of HBV in various body fluids.

Apart from the above mentioned body fluids, the following fluids are also considered as potentially infectious for occupational transmission from patients to healthcare personnel: cerebrospinal fluid, synovial fluid, pleural fluid, peritoneal fluid, pericardial fluid and amniotic fluid. Due to the lack of epidemiologic studies in healthcare personnel, the potential risk is still unknown.

Table 4 lists out the recommendations from the Centers for Disease Control and Prevention (CDC) for post-exposure prophylaxis to HBV.[20,21,22]

b) Recommendations for Prevention of Transmission of Hepatitis B from Individuals with Chronic HBV Infection[4]

In order to minimize transmission of Hepatitis B, the following measures are recommended:

1. Carriers should be counseled regarding the prevention of HBV transmission. Counseling should include precautions to prevent sexual transmission, perinatal transmission, and risk of inadvertent transmission via environmental contamination from a blood spill.

2. Sexual and household contacts of carriers should be tested for HBV (HBsAg and anti-HBs) and should receive hepatitis B vaccination if tested negative.

3. Newborns of HBV-infected mothers should receive hepatitis B immune globulin (HBIG) and hepatitis B vaccine at delivery and complete the recommended vaccination schedule.

4. Carriers should be advised to cover open cuts and scratches and clean up blood spills with bleach, because HBV can survive on environmental surfaces for at least 1 week.

5. Persons who remain at risk for HBV infection such as infants of HBsAg-positive mothers, health

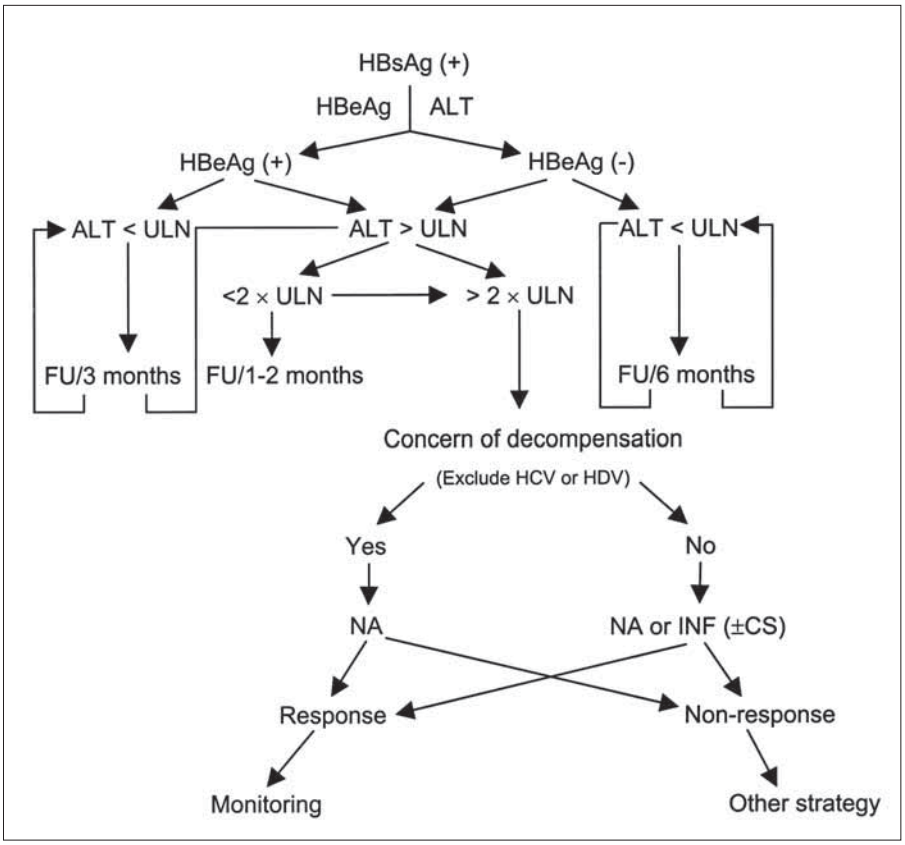

Figure 4. Summary of the Asian-Pacific Consensus on the Management of Chronic Hepatitis B. ALT, alanine aminotransferases; CS, corticosteroid; FU, follow-up; HCV, hepatitis C virus; HDV, hepatitis D virus; HBeAg, hepatitis B early antigen; HBsAg, hepatitis B surface antigen; IFN, interferon; NA, nucleoside or nucleotide analogs; ULN, upper limit of normal.

Table 3. Concentrations of HBV in Various Body Fluids

High	Moderate	Low / Not Detectable
Blood	Semen	Urine
Serum	Vaginal Fluid	Feces
Wound Exudates	Saliva	Sweat
		Tears
		Breast Milk

Table 4. Guide to Post-HBV exposure Immunoprophylaxis

Type of Exposure	Immunoprophylaxis
Perinatal	Vaccination + HBIG*
Sexual	Vaccination + HBIG
Household contact	
chronic carrier	Vaccination
acute case	None unless known exposure
acute case, known exposure	Vaccination ± HBIG
Inadvertent (percutaneous/permucosal)	Vaccination ± HBIG
Infant (<12 months) acute case in primary caregiver	Vaccination + HBIG

** HBIG = hepatitis B immune globulin*

care workers, and dialysis patients should be tested for response to vaccination. Infants of carrier mothers should be tested every 3 to 9 months, health care workers 1 to 6 months after vaccination, and dialysis patients annually.

6. Abstinence or only limited use of alcohol is recommended in hepatitis B carriers.

VIII PHARMACISTS' ADVICES

The followings are recommendations from the National Center for Infectious Diseases that can be used by pharmacists for general public education.

Hepatitis B vaccine is the best protection.

If you are having sex, but not with one steady partner, use latex condoms correctly and every time you have sex.

If you are pregnant, you should get a blood test for hepatitis B. Infants born to HBV-infected mothers should be given HBIG (hepatitis B immune globulin) and vaccine within 12 hours after birth.

Do not shoot drugs. If you shoot drugs, stop and get into a treatment program. If you cannot stop, never share drugs, needles, syringes, water, or "works", and get vaccinated against hepatitis A and B.

Do not share personal care items that might have blood on them (razors, toothbrushes).

Consider the risks if you are thinking about getting a tattoo or body piercing. You might get infected if the tools have someone else's blood on them or if the artist or piercer does not follow good health practices.

If you have or had hepatitis B, do not donate blood, organs, or tissue.

If you are a health care or public safety worker, get vaccinated against hepatitis B, and always follow routine barrier precautions and safely handle needles and other sharps.

Avoid drinking alcohol because alcohol can make your liver disease worse.

In addition, the Department of Health has a comprehensive website - Viral Hepatitis Preventive Service <http://www.info.gov.hk/hepatitis/english/index.htm>, which includes many useful educational materials on different types of viral hepatitis. Pharmacists can recommend their clients / patients to browse the website. There is also a Hepatitis Hotline providing 24-hour enquiry service on pre-recorded information for public.

IX CONCLUSION

CHB is the primary cause of cirrhosis and HCC. To date, there are 3 agents that have been approved for treatment of CHB and vaccines are available for prophylaxis. Nevertheless, the management of CHB will continue to evolve as the efficacy of new treatment strategies such as combination treatment (eg. INF + Nucleoside analogue), other immunomodulatory treatments (such as cytokines, interleukin, thymosin, GM-CSF) and vaccine therapy is being examined in ongoing trials. [23]

Ms Shirley Chih and ***Ms Sharon Lam*** graduated from the Chinese University of Hong Kong. They are currently working in field of clinical research in a pharmaceutical company.

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Questions for Pharmacy Central Continuing Education Committee Program

2 CE Units

Chronic Hepatitis B

1. Approximately how many people are affected by chronic hepatitis B globally?

(A) 3 million
(B) 30 million
(C) 80 million
(D) 300 million
(E) 3 billion

2. Chronic hepatitis B can be transmitted by:

(I) Sexual contact
(II) Blood transfusion
(III) Perinatal means
(IV) Person to person contact
(V) Contact of patients' urine and feces

(A) (II) and (III)
(B) (I) and (IV)
(C) (I), (II), (III), (IV)
(D) None of the above
(E) All of the above

3. Which of the following statement(s) is/are false?

(I) The prevalence rate of chronic hepatitis B varies globally, with higher rate in Southeast Asia, Africa and China.
(II) The carrier rate of hepatitis B in Hong Kong is decreasing from 10% to 8% over the past 20 years.
(III) Starting from 1988, all babies born in Hong Kong receive hepatitis B vaccine for free.
(IV) HBeAg negative chronic hepatitis B is more common in western countries.
(V) The likelihood of developing chronic hepatitis B is not affected by age when HBV infection occurs.

(A) (I) and (III)
(B) (IV) and (V)
(C) (I), (II), (IV), (V)
(D) None of the above
(E) All of the above

4. Which factors are employed for diagnosis of chronic hepatitis B?

(I) The presence of HBsAg for at least 6 months
(II) The presence of HBeAg for at least 6 months
(III) Alpha fetoprotein
(IV) Serum HBV DNA more than 10^5 copies/mL
(V) Persistent or intermittent elevation in aminotransferases level
(VI) Evidence of necroinflammation of liver biopsy
(VII) Total bilirubin

(A) (I), (IV), (V) (VI)
(B) (II), (IV), (V) (VI)
(C) (I), (III), (IV) (VII)
(D) None of the above
(E) All of the above

5. Which treatment regimens are licensed for the treatment of chronic hepatitis B?

(I) Interferon alpha 10MIU thrice weekly
(II) Interferon alpha 10MIU thrice weekly with prior prednisone priming
(III) Adefovir dipivoxil 10mg daily
(IV) Adefovir dipivoxil 30mg daily
(V) Lamivudine 150mg twice daily
(VI) Lamivudine 100mg daily

(A) (II), (III), (VI)
(B) (II), (IV), (V)
(C) (I), (IV), (VI)
(D) (I), (III), (V)
(E) (I), (III), (VI)

6. If the mother is a carrier of chronic hepatitis B, what medication(s) should be given to the baby at birth for prevention of infection?

(A) Interferon alpha
(B) Interferon alpha + Lamivudine
(C) Vaccination
(D) Vaccination + Hepatitis B immune globulin
(E) Nil medication

7. Which of the following statement(s) about interferon alpha is/are correct?

(A) The efficacy of Interferon alpha has been confirmed in many subtypes of CHB patients, including those with HBeAg negative chronic hepatitis B.
(B) Interferon alpha can be used for patients with very high ALT level (> 5ULN)
(C) The optimum treatment duration for HBeAg positive chronic hepatitis B is 16-24 weeks.
(D) Interferon alpha is administered intramuscularly.
(E) All of the above

8. Which of the following statement(s) about lamivudine is/are correct?

(A) Lamivudine is a nucleoside analogue
(B) A major limitation of lamivudine therapy is the emergence of YMDD mutant.
(C) The optimum treatment duration for HBeAg positive chronic hepatitis B depends on when seoconversion develops.
(D) A and C
(E) A, B and C

9. Which of the following statement(s) about adefovir dipivoxil is/are correct?

(A) Adefovir dipivoxil is a nucleoside analogue
(B) Adefovir dipivoxil is shown to be effective for HBeAg positive hepatitis B only.
(C) A major limitation of adefovir dipivoxil therapy is the emergence of resistant mutants.
(D) None of the above
(E) All of the above

10. Which of the following is/are not the recommendation(s) from the Asian-Pacific Consensus on the Management of Hepatitis?

(A) Patients with persistently normal ALT should not be treated but they need follow up and HCC surveillance every 3-6 months.
(B) During therapy, ALT, HBeAg and/or HBV DNA should be monitored at least every 6 months
(C) For immunosuppressed patients, lamivudine is preferred.
(D) For use of lamivudine in HBeAg positive patients, treatment can be stopped when HBV DNA loss with HBeAg seroconversion is documented on two separate occasions 6 months apart.
(E) Lamivudine is the agent of choice for patients with impending or obvious features of hepatic decompensation.

A 100-year-old Mystery: Nitrate Tolerance

Marcus Law

Organic nitrates (Table 1) are widely used for the treatment of ischemic heart disease and congestive heart failure. However, the clinical response is compromised by the development of nitrate tolerance. Though the problem has been recognized for over hundred years, its exact mechanism is not yet fully understood. Hence, nitrate tolerance has been described by people as a "100-year-old mystery". This article aims to review the controversies surrounding the issue and the approaches available nowadays in managing the problem.

I ACTIONS OF THE ORGANIC NITRATES

Nitrate is a prodrug that results in nitric oxide (NO) formation in vascular smooth muscle cell. NO is an endogenous modulator of vascular tone and can relax vascular smooth muscle throughout the body. It dilates systemic veins, hence reduces venous return and left-ventricular preload, resulting in a decreased myocardial oxygen demand. Peripheral arterial dilation induced by nitrates reduces systemic vascular resistance (afterload) and left ventricular systolic wall tension, leading to a reduction in myocardial oxygen consumption. On the other hand, the direct vasodilatory effect of nitrates on coronary circulation increases myocardial perfusion, thereby enhancing myocardial oxygen supply (Fig.1).

Table 1. Common preparations of organic nitrates

Organic nitrates	**Preparations**
Nitroglycerin	Sublingual, Spray
(TNG)	Transdermal Patches
	Injection
Isosorbide Dinitrate	Standard-Formulation
(ISDN)	Sustained-Release
	Injection
Isosorbide Mononitrate	Standard-Formulation
(ISMN)	Controlled-Release

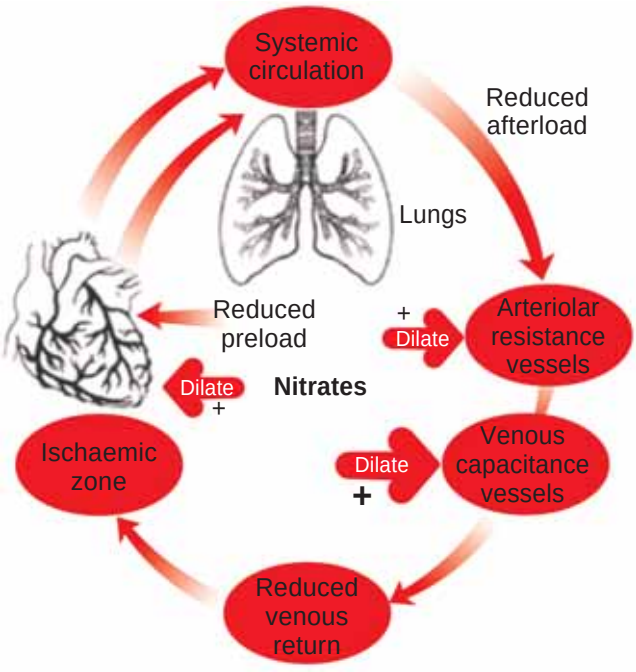

Figure 1. Action of the organic nitrates

II MECHANISMS OF NITRATE TOLERANCE

Nitrate tolerance is defined as the loss of hemodynamic and antianginal effects of nitrates during sustained therapy. Its mechanism is not yet fully understood. The four most important proposed hypotheses are summarized in table 2 [(1)].

Table 2. Current hypotheses regarding the genesis of nitrate tolerance

Hypothesis	**Description**
Sulfhydryl-Depletion Hypothesis	Inadequate generation of reduced -SH groups for organic nitrate biotransformation to nitric oxide
Neurohormonal Hypothesis	Nitrate-induced increases in vasoconstrictors (e.g. catecholamines, renin and angiotensin activity)
Plasma-Volume-Expansion Hypothesis	Increased intravascular blood volume related to decreased capillary pressure as a result of preferential venodilatation
Free-Radical Hypothesis	Increased production of superoxide anion, which enhances NO degradation

III PREVENTION OF NITRATE TOLERANCE

Although the mechanisms of nitrate tolerance remain unclear, several approaches to its prevention have been studied. They are as discussed as below.

a) Co-administration with counteracting drugs

Co-administration with drugs to counteract the underlying mechanisms proposed to be responsible for nitrate tolerance has been attempted. The approaches have included the use of diuretics (to limit plasma volume expansion), angiotensin-converting enzyme (ACE) inhibitors (to reduce

neurohormonal counter-regulation), vitamin E (as a free-radical scavenger) or N-acetylcysteine (as a thiol donor and free-radical scavenger). However, none have consistently proved effective [2].

b) Nitrate-free period

The only widely accepted method of preventing tolerance is the use of a dosing strategy that provides an interval of low-nitrate exposure during each 24-hour period. As mentioned by the British National Formulary (BNF) No.44, "many patients on long-acting or transdermal nitrates rapidly develop tolerance (with reduced therapeutic effects). Reduction of blood-nitrate concentrations to low levels for 4 to 8 hours each day usually maintains effectiveness in such patients." It has also stated several ways to minimize tolerance in different dosage forms:

i) First, for a nitrate patch --- "If tolerance is suspected during the use of transdermal patches, they should be left off for several consecutive hours in each 24 hours".

ii) Second, a short-acting nitrate preparation can be administrated by eccentric dosing where a larger dose is to be given in the early part of a day so that patients can have a low-nitrate period during the night. --- "In the case of modified-release tablets of isosorbide dinitrate (and conventional formulations of isosorbide mononitrate), the second of the two daily doses can be given after about 8 hours rather than after 12 hours. Conventional formulations of isosorbide mononitrate should not usually be given more than twice daily unless smaller doses are used".

iii) Third, long-acting nitrates can be given once daily in the morning. --- "Modified-release formulations of isosorbide mononitrate should only be given once daily, and used in this way do not produce tolerance".

IV CONTROVERSIES OF NITRATE-FREE PERIOD

Despite the clinical evidence for nitrate tolerance, the literature remains divided in the use of nitrate-free period. The arguments are summarized as follows:

a) Arguments against nitrate-free period

i) Physicians who do not use a nitrate-free period when prescribing nitrates for patients argue that continuous nitrate therapy provides substantial symptomatic and protective relief for many patients. Some pharmaceutical companies claim that the effectiveness of nitrates may be maintained when patients receive continuous therapy [3] and that means not all patients develop tolerance [4].

ii) Intermittent therapy has limitations that are twofold: (i) this regimen cannot provide continuous 24-hour protection; (ii) it may be associated with rebound myocardial ischemia during the nitrate-free period. Patients receiving intermittent nitroglycerin therapy may therefore experience an increase in frequency of angina at rest [1,5].

iii) Intermittent transdermal nitroglycerin therapy has adverse effects on exercise performance during the period of nitrate withdrawal. In a study of patients given nitroglycerin or placebo patches, the withdrawal of nitroglycerin caused a significant decrease in treadmill walking time as compared with placebo [1,5]. This finding was termed the "zero-hour effect". It may be attributed to the counter-regulatory effects on exercise performance after the rapid decline in plasma nitroglycerin levels following patch removal [5] (Fig.2).

iv) The fact that there is no clear explanation for tolerance development adds to the difficulties in evaluating the clinical importance of nitrate tolerance.

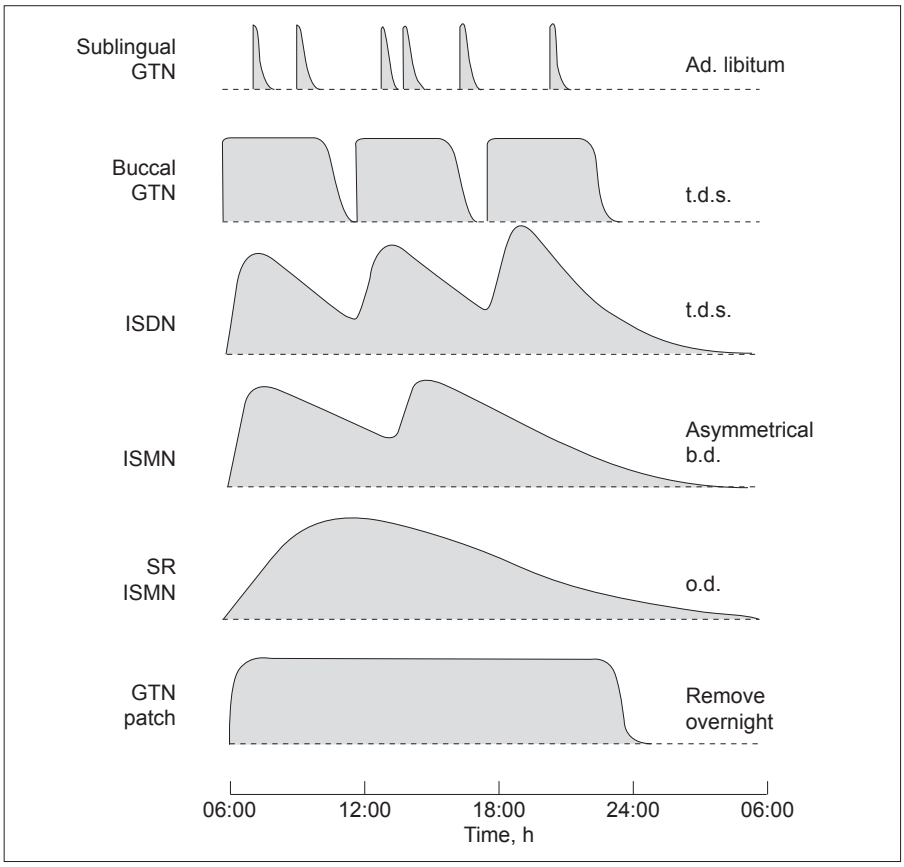

Figure 2. Decline of plasma nitrate concentrations in different preparations. Adapted from Thadani U et al.[7]

b) Arguments in support of nitrate-free period

i) Most studies have showed that nitrate administration designed to provide therapeutic effects 24 hours a day (e.g. continuous patch administration or oral ISDN given four times daily) is associated with tolerance and loss of hemodynamic and antianginal effects [6-12].

ii) The rationale for such dosing regimens is based on the observation that although tolerance to nitrates develops rapidly, it is rapidly reversed during the nitrate-free interval [9].

iii) There is considerable evidence that nitrate tolerance is a limiting factor in the treatment of stable angina pectoris and congestive heart failure [13]. A study showed that intravenous nitroglycerin produced immediate hemodynamic benefits in patients with severe heart failure, but the magnitude of this improvement was greatly diminished after 48 hours of continuous therapy with the drug [14].

iv) Patients who show rebound myocardial ischemia can be given beta-adrenergic blockers or calcium channel blocking agents for prevention of angina during the

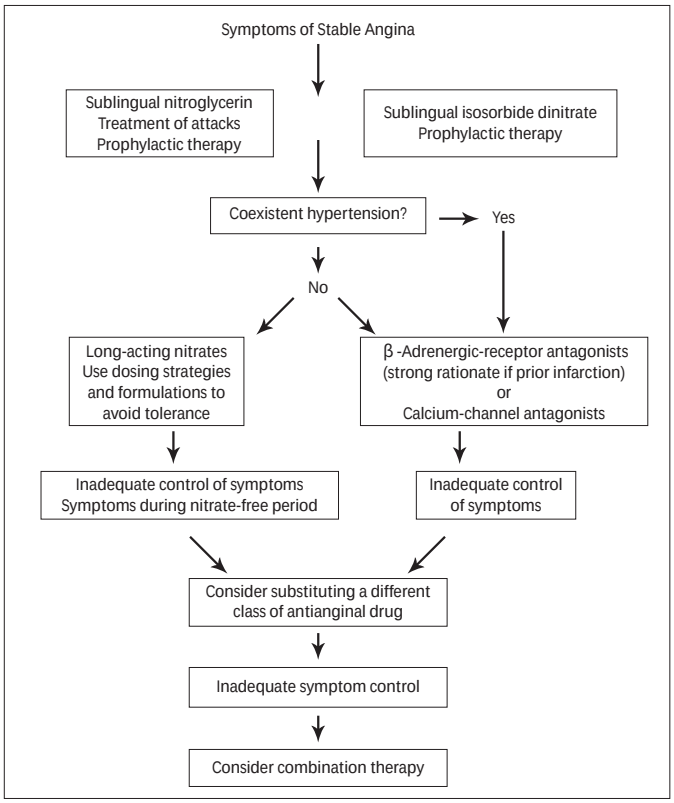

Figure 3. Treatment of Stable Angina with Antianginal Drugs. Adapted from Packer JD et al [1]

nitrate-unprotected period [15]. Nitrate-free interval should be arranged during the night since angina is more likely to occur during the working day. For patients with nocturnal angina, physicians may consider to arrange the nitrate-free interval during the day (Fig.3).

v) Adverse effects on exercise tolerance observed with nitrate patches have not been reported in studies of other long-acting nitrates given once daily or in eccentric dosing regimens [16], possibly because of the slower decline in plasma nitrate concentrations with these regimens (Fig.2).

V CONCLUSIONS

The mechanism of nitrate tolerance has remained unclear. Regimens which comprise a nitrate-free period have been developed in recent years. This approach of preventing nitrate tolerance remains the method which has been more extensively evaluated, although it has not yet been widely adopted by physicians.

Although the notion of nitrate tolerance remains controversial, existing evidence suggest that inclusion of a nitrate-free period would be a more prudent approach. In this respect, three points are worth consideration. Firstly, the majority of trials have shown the development of nitrate tolerance in patients receiving continuous therapy. Secondly, for those who need continuous, 24-hour protection from angina, nitrate-free period may be safely commenced by substitution or combination therapy with other drugs such as beta-adrenergic blockers or calcium channel blocking agents. Thirdly, as the majority of patients wear the patch during the day and remove it before sleep, exercise performance may not be of clinical importance. When nitrate-free period is arranged during the day, the use of once daily, long-acting nitrates; or short-acting nitrates given in eccentric dosing regimens may reduce the risk of deterioration in exercise performance compared to transdermal patches.

Ideally, for a patient newly diagnosed with angina, the use of long-acting nitrates with dosing strategies and formulations to avoid tolerance is the first-line therapy. Only when control of symptoms is inadequate or when symptoms appear during the nitrate-free period should substitution or combination therapy be considered [1]. However, since not all patients show nitrate tolerance, for those who respond favorably to an established regimen which does not include a nitrate-free period, such as continuous patch administration or oral ISDN given four times daily, it may not be necessary to change the dosing regimen. On the other hand, if tolerance is suspected, the regimen should be adjusted to provide a nitrate-free interval of several hours in each 24 hours. Pharmacists can play a more active role in working with physicians in formulating a more appropriate regimen for individual patients.

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Great News ....

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

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

Identification of Pyranocumarins in the Roots of *Peucedanum praeruptorum* Dunn by HPLC/MS/MS

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Bai-Hua Qian Hu, the dried roots of Peucedanum praeruptorum Dunn, is a rich source of pyranocoumarins. A new HPLC/MS/MS method was developed to identifying its pyranocumarins. Six compounds was identified by LC/MS/MS as pareruptorin A, pareruptorin B, peucedanumarin I,3', 4'-diisovaleryloxy dihydroseselin, qianhucoumarin H and pareruptorin E. The compound, 3', 4'-diisovaleryloxy dihydroseselin, was first found in P. praeruptorum. Some rules of LC-ESI-MS in positive ion mode of pyranocoumarins and a possible mechanism of fragmentation of it were discussed.

Keywords: Peucedanum praeruptorum Dunn; pyranocumarins; HPLC/MS/MS

I INTRODUCTION

Bai-Hua Qian Hu, the dried roots of *Peucedanum praeruptorum* Dunn, is an important Traditional Chinese Medicine used in alimentary and bronchial disorders and chest pains. Coumarins are widely distributed in plants. *P. praeruptorum* is known to be a rich source of pyranocoumarins. Beside the main pyranocoumarin, praeruptorin A, more than twenty angular-type dihydropyranocoumarins were isolated from the roots of *P. praeruptorum* Dunn(Table 1)[1,2,3,4,5,6,7,8,9,10,11,12]. The absolute stereostructure of (+)-praeruptorin A is 3'(S)-angeloyl-4'(S)-acetoxy-khellactone. X-ray crystallography of (±)-praeruptorin A showed that there are eight molecules (i.e. two each of four conformers) in each unit cell with their optical activities equally cancelled out. The four conformers are 3'(*R*)-angeloyl -4'(*R*)-acetoxy-khellactone in two conformational forms, and 3'(S)-angeloyl- 4'(S)-acetoxy -khellactone in two conformational forms[13]. Few reported methods for quantification and identification of Bai-Hua Qian-Hu are based on high-performnce liquid chromatography (HPLC)[14,15,17] and gas chromatography (GC)[16]. These methods are limited to the analysis of a limited number of known compounds.

LC-MS offers the possibility of taking advantage of both LC as a powerful separation technique and MS as a powerful and sensitive detection technique. It has been widely applied in the fields of environmental, pharmaceutical, biochemical and natural products analysis. Usually natural products contain complicated compounds. Detection and identification of compounds in natural products are important work to researchers. LC-MS has become an important method for rapid identification of compounds in plant extracts and other natural products. Literature is available on LC-MS of natural alkaloids, flavonoids, terpenoids, glycosides, etc. In this study an LC-MS method was developed for the separation and identification of pyranocoumarins in the roots of *P. praeruptorum* Dunn.

II MATERIALS AND METHODS

a) Materials

Plant material used for the present investigation was identified as Bai-Hua Qian-Hu, the root of *P. praeruptorum.* It was collected on a hill in Wu-Yi county in Zhejiang Province of China, in June 2003. The herbarium specimen was deposited at the BTC (Accession No. BHQH 0306A). Acetonitrile (MeCN) and methanol (MeOH) were HPLC-grade (Fisher, U.S.A.). Water was purified on a Reinstwasser system (St-Gallen, Switzerland).

b) Preparation of Sample Solutions

Dried and powdered Bai-Hua Qian-Hu (0.3 g) was extracted with 25 ml methanol by ultrasonic wave (59KHz, 30min). The mixture was filtered through Alltech 0.45µm membranes.

c) Chromatography

A liquid chromatographic system interfaced to an electrospray mass spectrometer (see below) was equipped with a quaternary pump, an autosampler, and a photo-diode array detector (PDA). The HPLC analysis was carried out on an Inertsil ODS-3 analytical column (2.1 x 150 mm, PSS 831923) packed with 5-µm C_{18} silica. The sample injection volume was 10 µL. The solvent system consisted of (A) methanol and (B) water containing 1.0% acetic acid, at a flow rate of 300 µL/min under gradient conditions: 0-5 min 60% A; 5-15 min linear increase to 78% A; 15-30 min hold on 78% A. The entire effluent from the column was introduced directly to the electrospray interface. The column temperature was maintained at 30°C.

d) Mass Spectrometry

A mass spectrometer (LCQ Advantage, Finngan) equipped with an electrospray source and HPLC system (see above) was used for LC-MS-MS. The electrospray source was operated in positive ion mode and spray voltage was 4.5 kv. Nitrogen was used as both sheath gas and Aux gas at flow rates of 60 and 20 arc, respectively. The capillary temp was 270°C and the capillary voltage was 37.0v. Collision energies at 30% were applied in MS/MS experiments.

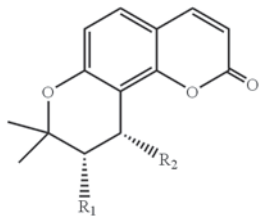
III RESULTS AND DISCUSSION

a) LC-MS analyses of the methanolic extract of the root of P. praeruptorum.

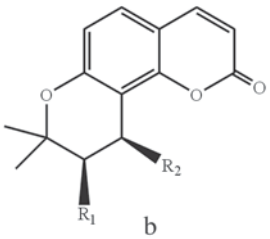
Under the above analytical conditions,

* Corresponding author. Tel:+852-27887746; Fax: +852-27887406; E-mail: bhhonyun@cityu.edu.hk

Table 1. Chemical structures of Pyranocoumarin



a



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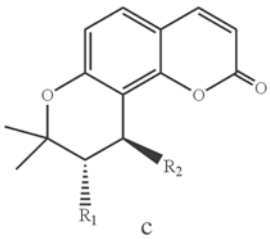
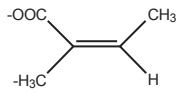
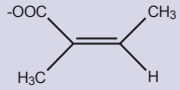
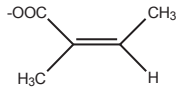
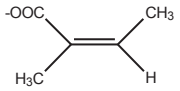
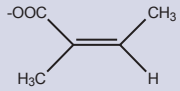
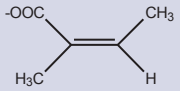
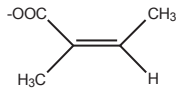
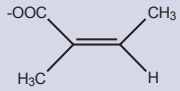
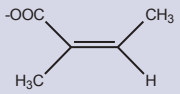
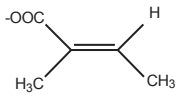
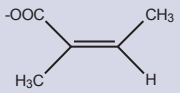
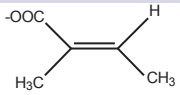
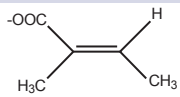
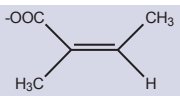
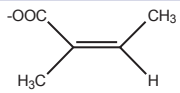
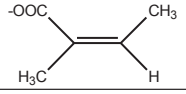


c

No	name	origin	R_1	R_2	Mp(°C)	$[\alpha]_D$	M
1	()-praeruptorin A	a, b		$-OOCCH_3$	156	0	386
2	(+)-praeruptorin A	a		$-OOCCH_3$	139.5~140.5	+53° (chf)	386
3	()-praeruptorin B	a, b			122	0	426
4	(+)-praeruptorin B	a			180	+10.7° (dioxane)	426
5	Pd-Ib	a		=O	209.5~212.5	+49.8° (dioxane)	344
6	Pd-III	a		$-OOCCH(CH_3)CH_2CH_3$	150.5~152.5	+25.9° (chf)	428
7	Peucedanumarin I	a	$-OOCCH(CH_3)CH_2CH_3$	$-OOCCH_3$	155.0~156.5	+24.2° (chf)	388
8	Peucedanumarin II	a	$-OOCCH_3$		134.5~136.0	+7.0° (chf)	386
9	Peucedanumarin III	a	$-OOCCH_3$		123.0~124.0	+28.6° (chf)	386
10	ptetyxin	b	$-OOCCH_3$		79.5~89.1	+14.3° (EtOH)	386
11	qianhucoumarin A	a	-OH		123.5~125.5	+209.6° (chf)	344
12	qianhucoumarin B	a	$-OOCCH_3$	-OH	159.0~161.0	+3.9° (chf)	304
13	qianhucoumarin C	a	-OH	$-OOCCH_3$	186.0~188.0	+7.6° (chf)	304
14	qianhucoumarin D	a	$-OOCCH_3$	$-OOCCH_3$	160.5~162.5	+4.0° (chf)	346
15	qianhucoumarin E	a		=O	103.5~105.5	+19.6° (chf)	342
16	qianhucoumarin H	a	$-OOCCH(CH_3)CH_2CH_3$				428
17	3'angeloyloxykhellactone	c		-OH	128.0~130.0	-7.2° (chf)	344
18	isobcconin	c	$-OOCCH_3$	$-OOCCH(CH_3)_2$	175~176.5		374
19	qianhucoumarin I	a	$OOCCH_3$				386

an HPLC chromatogram and an LC-MS chromatogram (total ion current, TIC) in positive mode, of the extract of the roots of *P. praeruptorum* are shown in Figure 1 and 2. In the HPLC chromatogram, five chromatographic peaks are shown distinctly and peak 1 is the biggest. The TIC chromatogram of the extract of the root of *P. praeruptorum* is similar to the HPLC chromatogram, indicating that the main ingredients of the roots of *P. praeruptorum* can be detected by UV detectors. The quasi-molecular mass of each peak was obtained at its retention time. From peak 1 to 5 they are the ions m/z 409.0,411.1,449.1,451.1 and 453.2.

b) LC-MS/MS analyses of the methanolic extract of the root of *P. praeruptorum.*

To get more structural information of the compounds and to elucidate the structure under each chromatographic peak, the LC-MS/MS experiment was carried out, during which the product ions of each component were at its retention time, providing a specific fragmentation profile of each component. All of the MS/MS spectrums of the above parent ions have the same product ions at m/z 245 and 227, indicating that these ingredients of the roots of *P. praeruptorum* have the same segment. UV spectrums (200 to 600nm) of those compounds detected by PDA also confirm it. The root of *P. praeruptorum* is known to be a rich source of angular-type pyranocoumarins. The product ion at m/z 227, the mass of seselin, gives good evidence that the chromatographic peaks are caused by dihydroseselin derivatives.

The MS/MS spectrum of chromatogram peak 1 (Figure 3) in positive ion type gives the quasi-molecular ion at m/z 408.9($M+Na^+$)and the product ions at m/z348.9 ($M-CH_3COOH+Na^+$), 326.9 (M^+-CH_3COOH, 308.9, 283.0, 245.0 ($M^+ - CH_3COOH - CH_3C=CCH_3CO$); 227.1 ($M^+ - CH_3COOH - CH_3C=CCH_3COOH$), 215.0, 201.1. This MS/MS data is consistent with those of pareruptorin A in references, thus the ion at m/z 408.9 (chromatogram peak 1) was identified as pareruptorin A. A possible mechanism of its fragmentation in positive ion mode is shown in Figure 7.

The MS/MS spectrum of chromatogram peak 2 (Figure 4) in positive ion type gives the quasi - molecular ion at m/z 411.0 ($M+Na^+$) and the product ions at m/z350.9 ($M-CH_3COOH+Na^+$), 328.9 (M^+-CH_3COOH), 308.9, 245.0 ($M^+ - CH_3COOH - CH_3CHCHCH_3CO$); 227.1 ($M^+ - CH_3COOH - CH_3CHCHCH_3COOH$). The ions at m/z411.0, 350.9 and 328.9 are 2 dalton more than those of pareruptorin A, suggesting that the structure may have 3'- isovaleryloxy other than 3'-angeloyloxy. Compared to references the ion at m/z 411.0 (chromatogram peak 2) was identified as peucedanumarin I.

Expect the quasi-molecular ion at m/z 448.8, the MS/MS spectrum of chromatogram peak 3 (Figure 5) in positive ion type is exactly same with those of pareruptorin A, indicating that the structure may have 4'-angeloyloxy other than 4'-acetyloxy. Compared to references, the ion at m/z 448.8 (chromatogram peak 3) was identified as pareruptorin B.

Expect the quasi-molecular ion at m/z 453.0, the MS/MS spectrum of chromatogram peak 5 (Figure 6) in positive ion type is exactly same with those of peucedanumarin I, indicating that the structure may have 4'-isovaleryloxy other than 4'-acetlyloxy. Compared to references, the ion at m/z 453.0 (chromatogram peak 5) was identified as 3', 4'-diisovaleryloxy dihydroseselin, a compound first found in the root of *P. praeruptorum*.

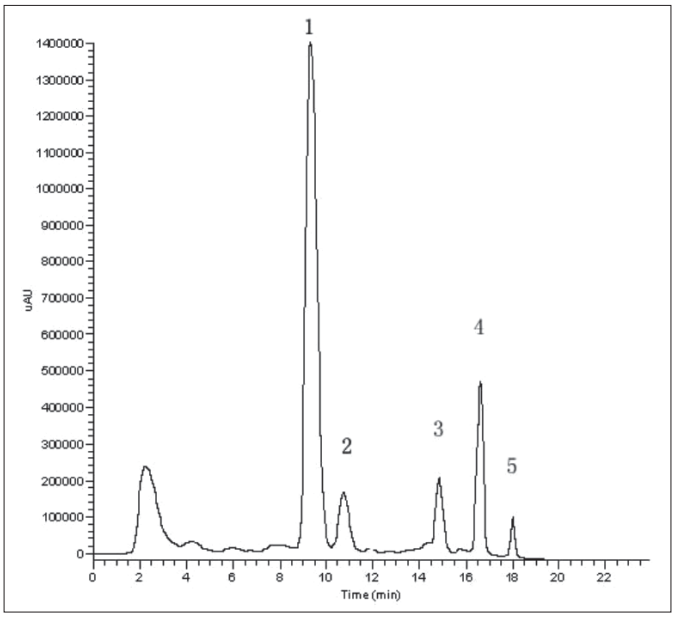


Figure 1. The HPLC chromatogram of P. praeruptorum

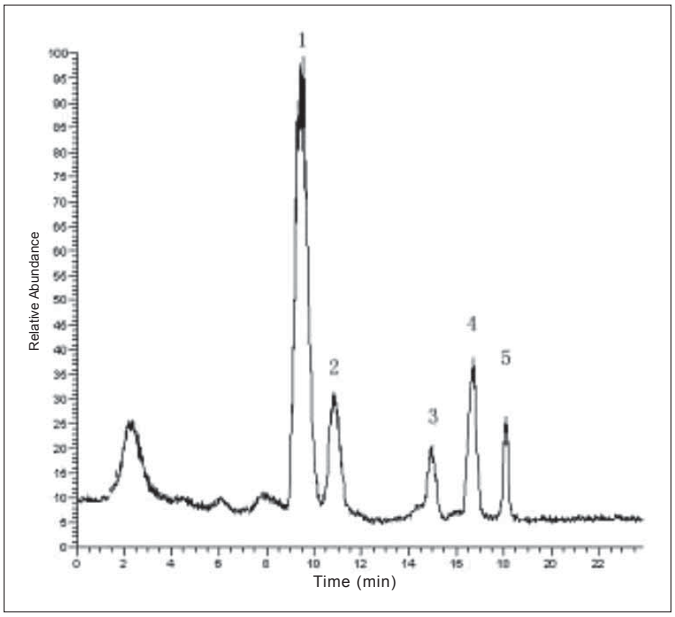


Figure 2. TIC of P. praeruptorum

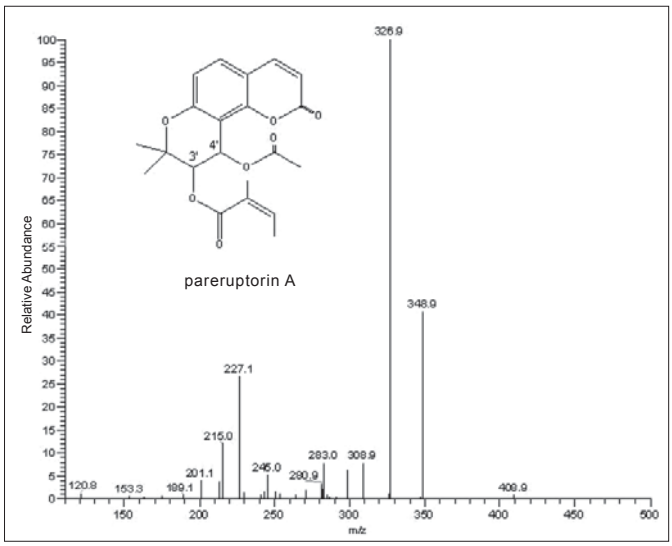


Figure 3. The MS^2 spectrum of chromatogram peak 1

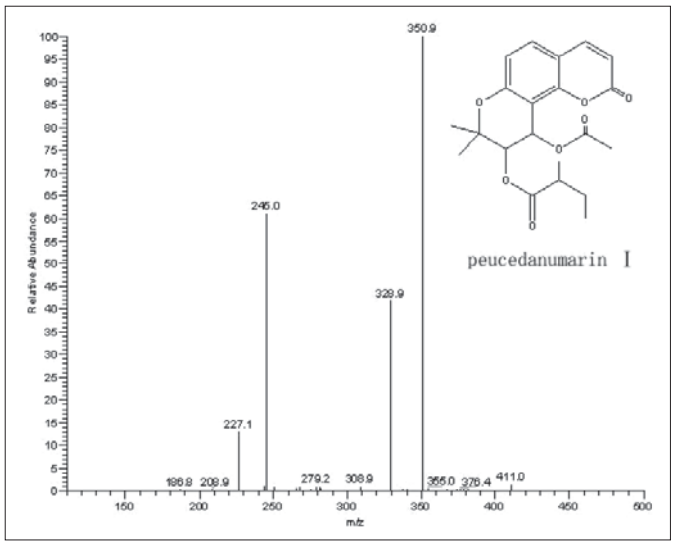


Figure 4. The MS^2 spectrum of chromatogram peak 2

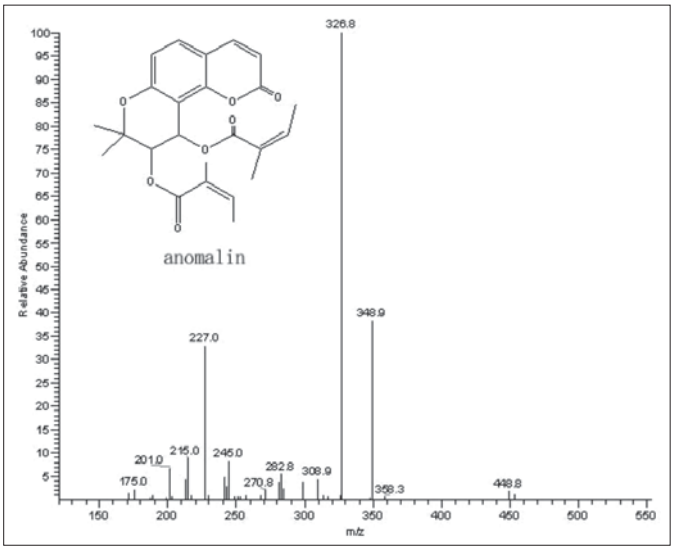


Figure 5. The MS^2 spectrum of chromatogram peak 3

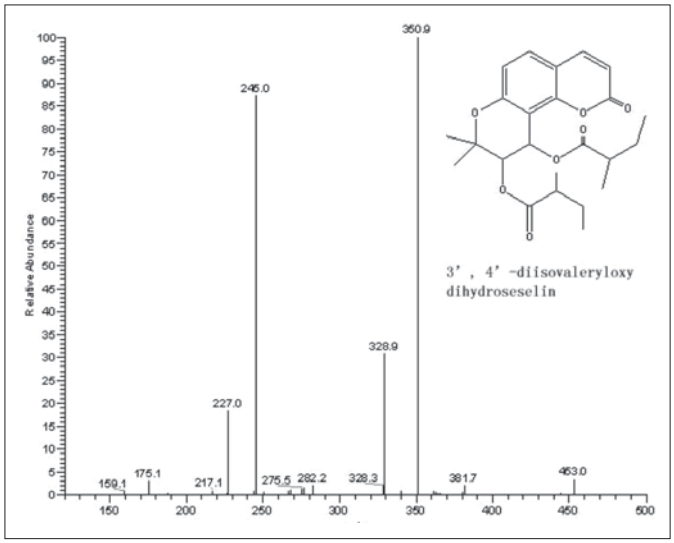


Figure 6. The MS^2 spectrum of chromatogram peak 5

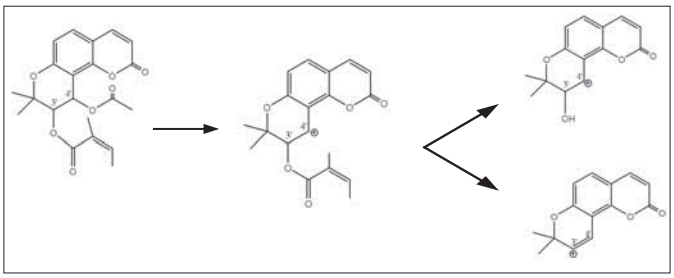


Figure 7. Possible mechanism of fragmentation of pareruptorin A

With the analysis of the mass spectra of these four compounds, some rules of LC-ESI-MS of pyranocoumarins in the root of *P. praeruptorum* could be drawn.

a. The quasi-molecular ion in positive ion mode of pyranocoumarins appeared as a $M+Na^+$ peak.
b. It is easier to lose the 4'group than 3'group in dihydroseselin derivatives.
c. There are two modes in 3'group loss, the segment ion at m/z 245 due to the loss of an acetyl group and m/z 227 due to the loss of acetyloxy group.
d. When it has a double bond in the 3'group, the product ion of segment lost 4'group is base peak and the relative abundance of the segment ion at m/z 245 greater than that of the segment ion at m/z 227. When there it is no double bond in the 3'group, the base peak is the adduct sodium ion of segment lost 4'group. and the relative abundance of the segment ion at m/z 245 is lower than that of the segment ion at m/z 227.

Interestingly, in the LC-MS experiment one quasi-molecular ion at m/z 451.1 is detected at chromatogram peak 4, but three different MS/MS spectra were obtained in LC-MS/MS experiment (Figure 8 to 10). The MS/MS spectrum at retention time 16.68 min (the middle of chromatogram peak 4) is combined by the MS/MS spectrum at retention time 16.40 min (the start part of chromatogram peak 4) and the MS/MS spectrum at retention time 16.90 min (the tail of chromatogram peak 4), indicating that the chromatogram peak 4 is not a pure peak and is made up by two of the same mass isomers. In the MS/MS spectrum at retention time 16.40 min (the start part of chromatogram peak 4), the base peak is the segment ion at m/z 350.9 ($M-CH_3C=CCH_3COOH+Na^+$) and the relative abundance of the segment ion at m/z 245 is greater than that of m/z 227. In the MS/MS spectrum at retention time16.90 min (the tail of chromatogram peak 4), the base peak is the segment ion at m/z326.8 ($M^+-CH_3CHCH\ CH_3COOH$) and the relative abundance of the segment ion at m/z 245 is lower than that of m/z 227. Putting all the information together, the ion at m/z 451.1 is identified as qianhucoumarin H (at the start part of chromatogram peak 4) and pareruptorin E (at the tail of chromatogram peak 4).

IV CONCLUSION

Bai-Hua Qian-Hu, the dried roots of *P. praeruptorum* Dunn, is a rich source of pyranocoumarins. Six pyranocoumarins

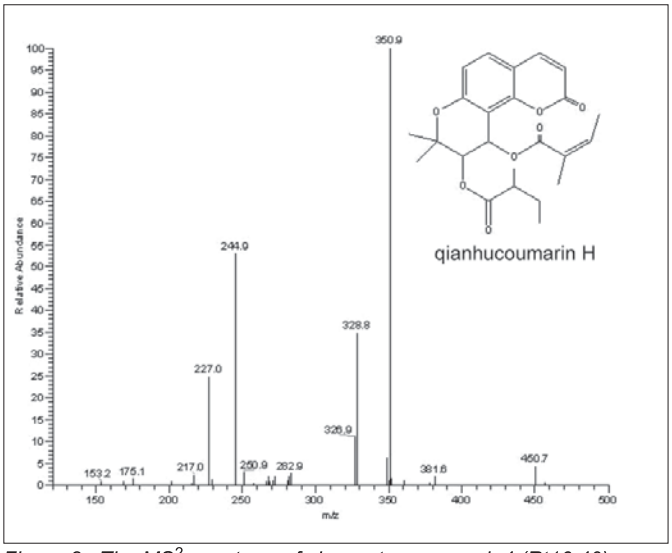


Figure 8. The MS^2 spectrum of chromatogram peak 4 (Rt16.40)

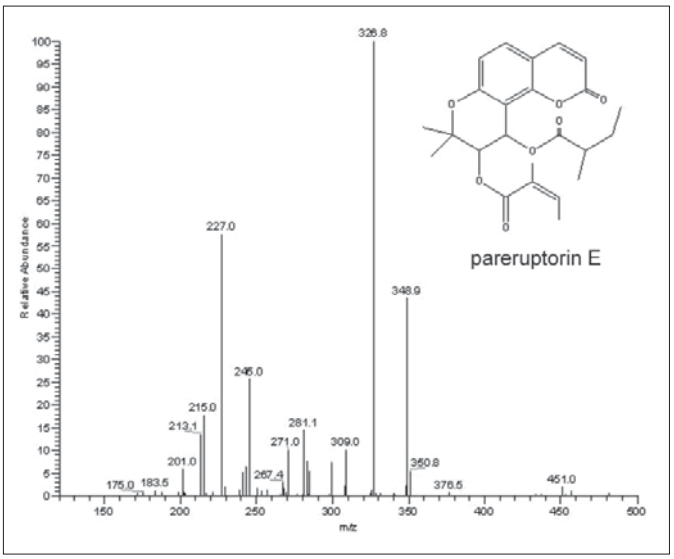


Figure 9. The MS^2 spectrum of chromatogram peak 4 (Rt16.90)

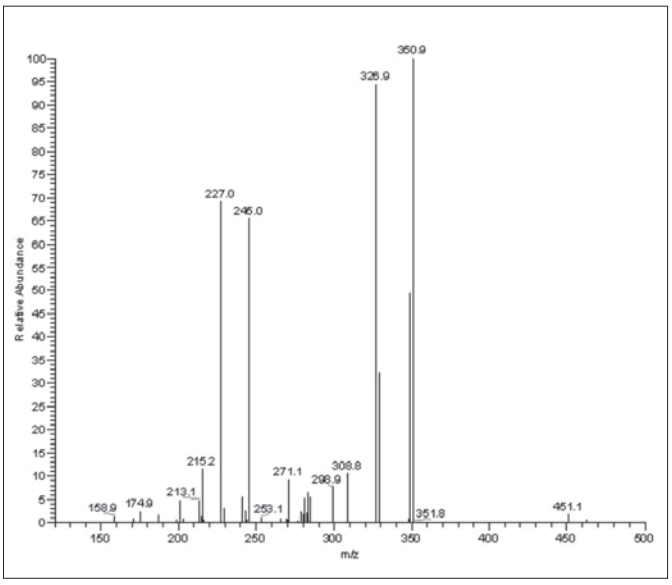


Figure 10. The MS^2 spectrum of chromatogram peak 4 (Rt16.68 min)

were identified by LC/MS/MS as pareruptorin A, pareruptorin B, peucedanumarin I, 3', 4'-diisovaleryloxy dihydroseselin, qianhucoumarin H and pareruptorin E. Pareruptorin A was found to be the most abundant component. The distinct product ions at m/z 245 and 227 indicated they have the same core structure, dihydroseselin. Three different MS/MS spectra were obtained in the LC-MS/MS experiment at the start, middle and tail part of chromatogram peak 4 that result in two isomers being identified. It is difficult to do by HPLC and other analytical methods. The method developed in this paper is a rapid and effective method for identification of pyranocoumarins of the roots of *P. praeruptorum* Dunn, especially when the standards can't be found.

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Extractives of Radix *Peucedani* (前胡) Stimulate Lung's Descending and Dispersing Function to Stop Cough and Respiratory Dyspnea

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Botanical Name: *Peucedanum praeruptorum* Dunn (白花前胡); *Peucedanum decursivum* Maxim (紫花前胡)
Plant Family: Umbelliferae
Pharmacopoeia Name: Radix *Peucedani*
Other Names: Qianhu, Hogfennel Root, Peucedanum Black Sampson, Niggerhead. Root
Brand Names: Tong Xuan Li Fei Pills; Qianhu[ST]

ABSTRACT

Qianhu is the dried root of *Peucedanum praeruptorum* Dunn or *Peucedanum decursivum* Maxim. It is a well-known traditional Chinese medicine officially listed in the Chinese Pharmacopoeia. This herbal medicine can be used as an expectorant and mucolytic. It is cold in nature and is suitable for clearing phlegm-heat in the lungs and for treating coughs with green and thick sputum due to pathogenic infection. In recent years, a number of pyranocoumarin substances which are antitussive as well as antitumor-promoting, have been identified and isolated in the ethanol extract of the herb. A study using *in vitro* cell culture reveals that some components in this herb were active against different types of human hepatocellular carcinoma cells.

Contraindications
No contraindication has been reported at the moment of this publication.

Undesirable Effects
Although no mention of toxicity has been reported, skin contact with the sap of a number of members in this genus is said to cause photo-sensitivity and/or dermatitis in some people.

Interaction with Conventional Drugs
No interaction with conventional drugs has been reported at the moment of this publication.

DESCRIPTION AND BACKGROUND

Plants of the genus *Peucedanum* (Family Umbelliferae) are small perennial shrubs growing in subtropical regions. An easily grown plant, it succeeds in any moisture-retentive soil in a semi shade to sunny position. Although damp thickets on hillsides, woodland and in waste places are also ideal sites for their growth; heavy clay soils are not suitable. Flowers of this plant are hermaphrodite and are pollinated by insects. It can be self-fertile. The herb preparations from *P. praeruptorium* are mainly from habitats in Zhejiang, Hunan and Sichuan provinces, and those from *P. decursivum* are from Zhejiang, Anhui and Jiangxi.

Radix Peucedani, also known as Qianhu (前胡) in Chinese or hogfennel root in the West, is the dried root of *P. praeruptorum* Dunn or of *P. decursivum* Maxim. The herb is irregular, cylindrical, conical and fusiform in shape with a slightly twisted appearance. The lower part of the herb is frequently branched and it could be 3 - 15 cm long with a diameter of around 1 - 2 cm. It looks blackish-brown or grayish-yellow in color with scars of a stem and fibrous remains of periclasia at the root stock. Freshly collected roots are normally very soft in texture but become hard and brittle when they are dried.

When stem and leaf of the plant have withered and before the floral stem grows, roots are dug, cleaned and dried under the sun. Roots of the plant are normally collected in

winter or spring. After the root bark is removed, the root is soaked in warm water and sliced for medicinal uses.

BIOACTIVE CONSTITUENTS

The genus *Peucedanum* is well known for its rich source of pyranocoumarin compounds[1]. The root of *P. praeruptorum* contains a number of pyranocoumarin substances; namely praeruptorin A, B and E (Figure 1)[2-4]. Both praeruptorin A and B were the first two components identified. Glycosides of pyranocoumarin, namely, praerosides II, III, IV and V (Figure 2) were also present in the herb[5]. It was reported that furanocoumaarin glycosides, such as praeroside I, marmesinin, isorutarin and rutarin (Figure 3), as well as coumarin glycosides, such as scopoline and skimming, have also been isolated from the root of this herb[6].

Other components found in this herb include qianhucoumarin A, psoralen, 5-methoxpsoralen, 8-methoxypsoralen, pteryxin, peuceanocoumarin II and β-sitosterol[7]. A coumarin derivative, identified as 9-angeloyloxy-10-oxo-dihydroseselin (Figure 4) was also reported to be present in the root of *P. praeruptorum*.

In the root of *P. decursivum*, a series of analogue compounds of pyranocourmarins such as decursin, decursidin, 7-angeloyloxy-6-seneescioyloxy-6,7-dihyroxanthyletin, 7-angeloyloxy-6-isovaleroyloxy-6,7-dihydroanthyletin, 7-senecioyloxy-6-hydroxy-6,7-dihyroxanthyletin and 7-hydroxy-6-senecioyloxy-6,7-dihyroxanthyletin were structurally identified and isolated[8-11].

Overall, the total content of the courmarins in these herbs is estimated to be 0.6 -1.1% (w/w).

CONTEMPORARY USES

Qianhu is commonly prescribed with Bai Qian as *"Er Qian"* which means 'the two Qian'. It has a bitter and pungent taste. A decoction of this herb is frequently used in the treatment of colds and headaches, coughing and asthma and tightness in the chest (dyspnea). Its applications as an antitussive, carminative, expectorant and febrifuge have been documented and are attributed to its cold nature. The herb is also claimed to be analgesic, antibacterial and antifungal.

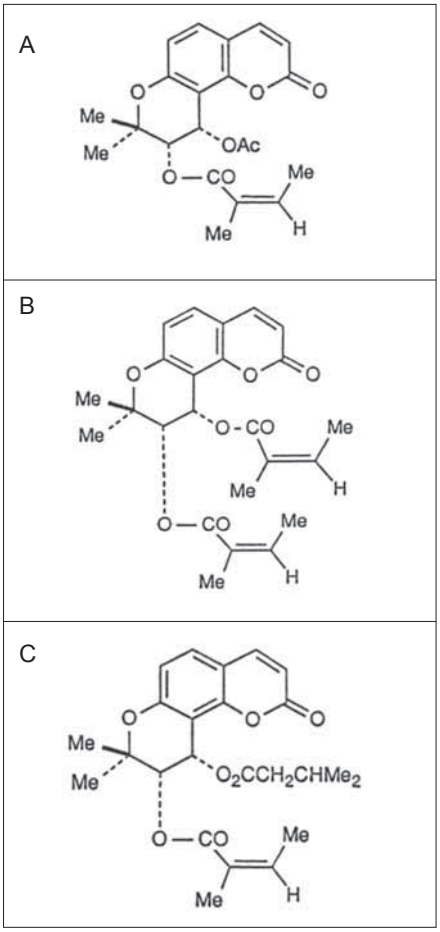

Figure 1. Chemical structures of some pyranocoumarin compounds identified in Qianhu.
*Frame **A:** Praeruptorin A;*
***B:** Praeruptorin B; **C:** Praeruptorin E*

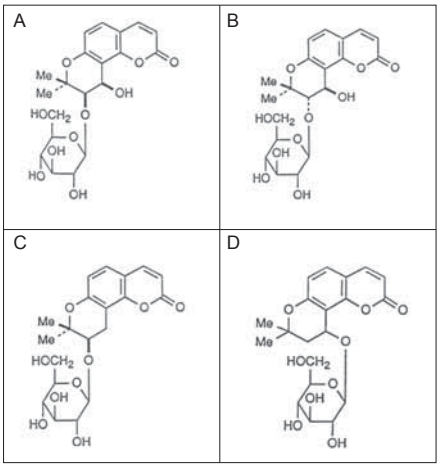

Figure 2. Glycosides of pyrano-coumarin in Qianhu.
*Frame **A:** Praerosides II; **B:** Praerosides III; **C:** Praerosides IV; **D:** Praerosides V*

MODE OF ACTION

Radix *Peucedani* is a Chinese herbal medicine of cold in nature. The pungent property of this herb gives it the capability to enter the lung meridian and to disperse the Lung-Qi. The direction of its' dispelling action is

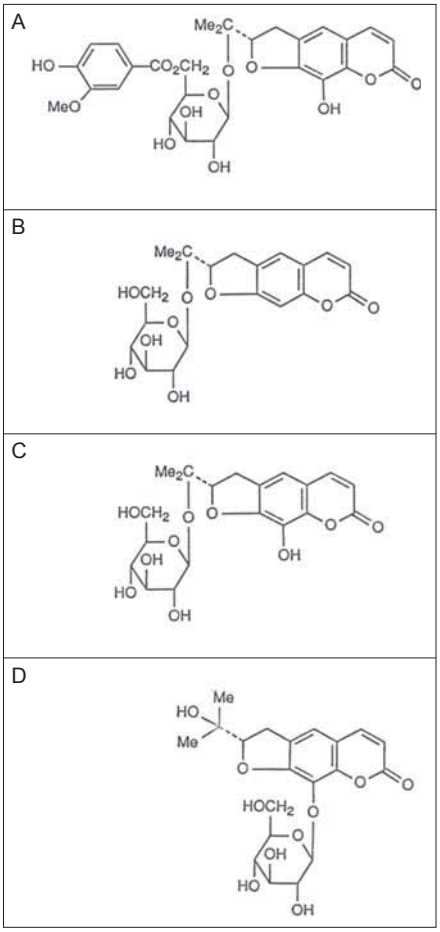

Figure 3. Chemical structures of furanocoumarin glycosides isolated from Qianhu.
*Frame **A:** Praeroside I; **B:** Marmesinin;*
***C:** Isorutarin; **D:** Rutarin*

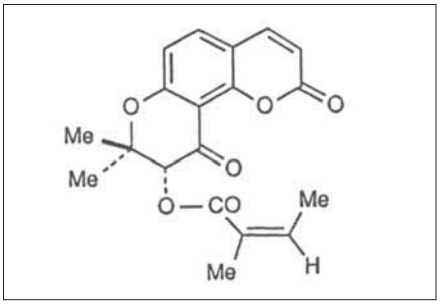

Figure 4. Chemical structure of coumarin derivative, 9-angeloyloxy-10-oxo-dihydroseselin, present in Qianhu

downward to accomplish heat removal and to relieve coughs and resolve heat phlegm[12]. Yang suggested that herbs that disperse or descend the lung-qi are particularly effective for relieving coughs. If they are combined with herbs that transform phlegm, clear heat or expel cold, they can be used for treating an acute or chronic cough in excess or deficiency syndromes, or for treating a cough caused by cold or heat in the lung[13]. Obviously, qianhu is one of the most favorable choices as it is cold in temperature and it disperses heat accumulated in the lung.

Antispasmodic and relaxant effects on smooth muscle

All three pyranocoumarin compounds, including praeruptorin A, B and E in the alcohol fraction of the root of *P. praeruptorum* were reported to show antispasmodic effects on smooth muscle of guinea pig ileum and taenia coli contracted after being exposed to acetylcholine and histamine[4]. Praeruptorin A, in particular, was the most effective to noncompetitively antagonize the action of acetylcholine in the small intestine[14].

Good relaxant effects of these pyranocoumarin compounds were also noted on isolated rabbit tracheas and pulmonary arteries[15].

Anticoagulation effects

A study on the effect of coumarine against human platelet aggregation induced by ADP *in vitro* showed that nodakenin and nodakenetin were most effective in inhibiting both the primary and secondary wave of aggregation[16].

Among the decurosides, decuroside III and decuroside IV showed the strongest inhibiting activity against aggregation of human platelets[17].

Anti-tumor activity

Studies conducted by Okuyama and his associates reported that among 95 extracts prepared from 14 kinds of Umbelliferous materials, they found that Qianhu was one of the most inhibitory on phospholipid metabolism in transformed cells. In the presence of these extracts, ^{32}Pi incorporation into phospholipids stimulated by tetradecanoylphorbol-13-acetate (TPA) was blocked[18]. Another cytotoxic study in Korea reported that growth of some human hepatocellular carcinoma cells were significantly affected by either methanol or aqueous extracts of *P. praeruptorum*[19].

CONTRADINDICATIONS

No contraindication has been reported at the moment of this writing.

UNDESIRABLE EFFECTS

No health hazards or side effects are known in conjunction with the proper administration of designated dosages. Light-skinned individuals may experience an increase in UV-sensitivity or dermatitis, due to the phototoxic effect of the pyranocoumarins.

INTERACTION WITH CONVENTIONAL DRUGS

No interaction with conventional drugs has been reported at the moment of this writing.

MODE OF ADMINISTRATION

This herb is almost obsolete as a drug in Western countries. In Asia, it is occasionally used as a constituent in medicinal preparations in combination with other herbs that resolve phlegm and stop coughing. It could be used orally as a cold extraction or infusion of the herb or as a pill.

DOSAGE

The recommended dosage is 6-10 g of decocted preparation.

REGULATORY STATUS

No information available.

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NEW PRODUCTS

ARCOXIA (MSD)

Active ingredient:
Etoricoxib

Presentation:
Available as 60 mg, 90 mg and 120 mg tablet

Pharmacological Properties:
Etoricoxib is a member of a class of arthritis/analgesia medications called Coxibs. ARCOXIA is a highly selective inhibitor of cyclooxygenase-2 (COX-2).

Indications:
Symptomatic relief of osteoarthritis and rheumatoid arthritis; Treatment of acute gouty arthritis; Treatment of acute pain, including that related to primary dysmenorrhea and minor dental procedures

Dosage and Administration:
Osteoarthritis - 60 mg once daily.
Rheumatoid Arthritis - 90 mg once daily.
Acute Gouty Arthritis, Acute Analgesia, Dental Pain and Primary Dysmenorrhea - 120 mg once daily (ARCOXIA 120 mg should be used only for the acute symptomatic period).

Contraindications:
ARCOXIA is contraindicated in patients with hypersensitivity to any component of this product; or with a history of asthma, urticaria, or other allergic reactions after aspirin or other NSAIDs. ARCOXIA should not be used as adjunctive therapy with other NSAIDs due to the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse reactions. However, ARCOXIA can be used concomitantly with low-dose aspirin for cardiovascular prophylaxis.

Precautions:
In patients with advanced renal disease, treatment with ARCOXIA is not recommended. Caution should be used when initiating treatment with ARCOXIA in patients with considerable dehydration. It is advisable to rehydrate patients prior to starting therapy with ARCOXIA. As with other drugs known to inhibit prostaglandin synthesis, fluid retention, edema and hypertension have been observed in some patients taking ARCOXIA. COX-2 selective inhibitors are not a substitute for aspirin for cardiovascular prophylaxis because of their lack of effect on platelets. Antiplatelet therapies should not be discontinued. ARCOXIA should be used with caution in patients who have previously experienced acute asthmatic attacks, urticaria, or rhinitis, which were precipitated by salicylates or non-selective cyclooxygenase inhibitors. Safety and effectiveness of etoricoxib in pediatric patients have not been established.

Side effects:
Asthenia / fatigue, dizziness, lower extremity oedema; hypertension; diarrhea, epigastric discomfort; heartburn, nausea; sinusitis; headache

Drug Interactions:
Warfarin (approximate 13% increase in prothrombin time & INR was associated with ARCOXIA 120 mg daily); *Rifampin* (a 65% decrease in etoricoxib plasma area under the curve when co-administered with ARCOXIA); *Methotrexate* (monitoring for methotrexate-related toxicity should be considered when ARCOXIA at doses greater than 90 mg daily); *Lithium* (reports suggest that non-selective NSAIDs and COX-2 selective inhibitors may increase plasma lithium levels.)

Forensic classifications:
P1S1S3

EZETROL (MSD)

Active ingredient:
Ezetimibe

Pharmacological Properties:
EZETROL is in a new class of lipid-lowering compounds that selectively inhibit the intestinal absorption of cholesterol and related plant sterols. Ezetimibe localizes at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood. Ezetimibe does not increase bile acid excretion (like bile acid sequestrants) and does not inhibit cholesterol synthesis in the liver (like statins).

Presentation:
Available as 10mg tablet

Indications:
Primary Hypercholesterolemia; Homozygous Familial Hypercholesterolemia; Homozygous Sitosterolemia

Dosage and Administration:
The recommended dose of EZETROL is 10 mg once daily, used alone or with a statin.

Contraindications:
Hypersensitivity to any component of this medication.

Precautions:
When EZETROL is to be administered with a statin, please refer to the Package Insert for that particular statin. When EZETROL is co-administered with a statin, liver function tests should be performed at initiation of therapy and according to the recommendations of the statin, consecutive transaminase elevations (≥3 X the upper limit of normal [ULN]) have been observed in patients receiving EZETROL with a statin. EZETROL is not recommended in those patients with moderate or severe hepatic insufficiency. Co-administration of EZETROL and fibrates is not recommended.

Side effects:
EZETROL administered alone - headache; abdominal pain, diarrhea
EZETROL co-administered with a statin - headache, fatigue, abdominal pain, constipation, diarrhea, flatulence, nausea, increased ALT, increased AST, myalgia.

Drug Interactions:
No clinically significant pharmacokinetic interactions have been observed between ezetimibe and drugs known to be metabolized by cytochromes P450 1A2, 2D6, 2C8, 2C9, and 3A4, or N-acetyltransferase. Concomitant cholestyramine administration decreased the mean AUC of total ezetimibe (ezetimibe + ezetimibe glucuronide) by approximately 55 %. The incremental LDL-C reduction due to adding ezetimibe to cholestyramine may be lessened by this interaction. No clinically significant pharmacokinetic interactions were seen when ezetimibe was co-administered with atorvastatin, simvastatin, pravastatin, lovastatin, or fluvastatin.

Forensic classification:
P1S1S3

TAMIFLU (Roche)

Active ingredient:
Oseltamivir phosphate

Presentation:
TAMIFLU 12 mg/ml powder for oral suspension is available in a bottle containing 30 g powder for mixing with 52 ml of water.

Pharmacological Properties:
Oseltamivir phosphate is a pro-drug of a potent and selective inhibitor of influenza virus neuraminidase enzymes. The active metabolite of oseltamivir inhibits neuraminidases of influenza viruses of both types A and B.

Indications:
TAMIFLU is indicated for treating or preventing influenza. It is indicated for the treatment in adult and children 1 year of age and older and prophylaxis in adult and adolescents 13 years of age and older.

Dosage and Administration:

Children (1-12 years old):
Treatment -

Body Weight	Dose for 5 days
15 kg	*30 mg bd*
15.1 kg - 23 kg	*45 mg bd*
23.1 kg - 40 kg	*60 mg bd*
> 40 kg	*75 mg bd*

Adults and adolescents (13 years old):
Treatment -
75 mg* dose of TAMIFLU twice daily for five days.
Prevention -
75 mg* dose of TAMIFLU once daily. Your doctor will recommend the length of time you will need to take TAMIFLU.
(Can use either capsule or oral suspension)*

IMPORTANT NEWS

NEW LABEL FOR ZOCOR FROM JULY, 2003

New Indication[1]

ZOCOR 40mg is now indicated for patients at high risk of CHD (with or **without hypercholesterolaemia**) including patients with:

- **Diabetes**
- **History of stroke**
- **Other cerebrovascular disease**
- **Peripheral vessel disease**
- **Existing CHD**

to reduce the risk of cardiovascular death, major cardiovascular events including stroke, and hospitalisation due to angina pectoris*[1].

Simplified Liver Function Monitoring

It is recommended that for daily dosage of up to ZOCOR 40mg, liver function tests (LFT) to be performed before treatment begins and thereafter when clinically indicated. This makes ZOCOR the statin with the **simplest** liver function monitoring requirement **without mandatory** regular follow-up LFT with a dosage up to 40mg per day[1].

The expanded indication & label change is a direct result of findings of the MRC/BHF** Heart Protection Study (HPS), the world's largest ever statin trial involving 20,536 patients with a mean duration of 5.3 years[2]. For details, please visit HPS trial web-site at **www.hpsinfo.org**

MSD

Committed to Bringing Out the Best in Medicine

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08-2004-ZCR-2003-HK-3020-J-(HK)

1. Hong Kong Physician Circular, ZOCOR.
2. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial, Lancet 2002;360:7-22.

* These effects do not replace the need to independently control known causes of cardiovascular mortality and morbidity such as hypertension, diabetes and smoking.

** MRC/BHF: Medical Research Council/British Heart Foundation

Efficacy, Evidence, Experience

ZOCOR® 40mg (simvastatin, MSD)

POWER FOR LONG-TERM SURVIVAL

NEW PRODUCTS

ARCOXIA (MSD)

Active ingredient:
Etoricoxib

Presentation:
Available as 60 mg, 90 mg and 120 mg tablet

Pharmacological Properties:
Etoricoxib is a member of a class of arthritis/analgesia medications called Coxibs. ARCOXIA is a highly selective inhibitor of cyclooxygenase-2 (COX-2).

Indications:
Symptomatic relief of osteoarthritis and rheumatoid arthritis; Treatment of acute gouty arthritis; Treatment of acute pain, including that related to primary dysmenorrhea and minor dental procedures

Dosage and Administration:
Osteoarthritis - 60 mg once daily.
Rheumatoid Arthritis - 90 mg once daily.
Acute Gouty Arthritis, Acute Analgesia, Dental Pain and Primary Dysmenorrhea - 120 mg once daily (ARCOXIA 120 mg should be used only for the acute symptomatic period).

Contraindications:
ARCOXIA is contraindicated in patients with hypersensitivity to any component of this product; or with a history of asthma, urticaria, or other allergic reactions after aspirin or other NSAIDs. ARCOXIA should not be used as adjunctive therapy with other NSAIDs due to the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse reactions. However, ARCOXIA can be used concomitantly with low-dose aspirin for cardiovascular prophylaxis.

Precautions:
In patients with advanced renal disease, treatment with ARCOXIA is not recommended. Caution should be used when initiating treatment with ARCOXIA in patients with considerable dehydration. It is advisable to rehydrate patients prior to starting therapy with ARCOXIA. As with other drugs known to inhibit prostaglandin synthesis, fluid retention, edema and hypertension have been observed in some patients taking ARCOXIA. COX-2 selective inhibitors are not a substitute for aspirin for cardiovascular prophylaxis because of their lack of effect on platelets. Antiplatelet therapies should not be discontinued. ARCOXIA should be used with caution in patients who have previously experienced acute asthmatic attacks, urticaria, or rhinitis, which were precipitated by salicylates or non-selective cyclooxygenase inhibitors. Safety and effectiveness of etoricoxib in pediatric patients have not been established.

Side effects:
Asthenia / fatigue, dizziness, lower extremity oedema; hypertension; diarrhea, epigastric discomfort; heartburn, nausea; sinusitis; headache

Drug Interactions:
Warfarin (approximate 13% increase in prothrombin time & INR was associated with ARCOXIA 120 mg daily); *Rifampin* (a 65% decrease in etoricoxib plasma area under the curve when co-administered with ARCOXIA); *Methotrexate* (monitoring for methotrexate-related toxicity should be considered when ARCOXIA at doses greater than 90 mg daily); *Lithium* (reports suggest that non-selective NSAIDs and COX-2 selective inhibitors may increase plasma lithium levels.)

Forensic classifications:
P1S1S3

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Pharmacological Properties:
EZETROL is in a new class of lipid-lowering compounds that selectively inhibit the intestinal absorption of cholesterol and related plant sterols. Ezetimibe localizes at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood. Ezetimibe does not increase bile acid excretion (like bile acid sequestrants) and does not inhibit cholesterol synthesis in the liver (like statins).

Presentation:
Available as 10mg tablet

Indications:
Primary Hypercholesterolemia; Homozygous Familial Hypercholesterolemia; Homozygous Sitosterolemia

Dosage and Administration:
The recommended dose of EZETROL is 10 mg once daily, used alone or with a statin.

Contraindications:
Hypersensitivity to any component of this medication.

Precautions:
When EZETROL is to be administered with a statin, please refer to the Package Insert for that particular statin. When EZETROL is co-administered with a statin, liver function tests should be performed at initiation of therapy and according to the recommendations of the statin, consecutive transaminase elevations (≥3 X the upper limit of normal [ULN]) have been observed in patients receiving EZETROL with a statin. EZETROL is not recommended in those patients with moderate or severe hepatic insufficiency. Co-administration of EZETROL and fibrates is not recommended.

Side effects:
EZETROL administered alone - headache; abdominal pain, diarrhea
EZETROL co-administered with a statin - headache, fatigue, abdominal pain, constipation, diarrhea, flatulence, nausea, increased ALT, increased AST, myalgia.

Drug Interactions:
No clinically significant pharmacokinetic interactions have been observed between ezetimibe and drugs known to be metabolized by cytochromes P450 1A2, 2D6, 2C8, 2C9, and 3A4, or N-acetyltransferase. Concomitant cholestyramine administration decreased the mean AUC of total ezetimibe (ezetimibe + ezetimibe glucuronide) by approximately 55 %. The incremental LDL-C reduction due to adding ezetimibe to cholestyramine may be lessened by this interaction. No clinically significant pharmacokinetic interactions were seen when ezetimibe was co-administered with atorvastatin, simvastatin, pravastatin, lovastatin, or fluvastatin.

Forensic classification:
P1S1S3

TAMIFLU (Roche)

Active ingredient:
Oseltamivir phosphate

Presentation:
TAMIFLU 12 mg/ml powder for oral suspension is available in a bottle containing 30 g powder for mixing with 52 ml of water.

Pharmacological Properties:
Oseltamivir phosphate is a pro-drug of a potent and selective inhibitor of influenza virus neuraminidase enzymes. The active metabolite of oseltamivir inhibits neuraminidases of influenza viruses of both types A and B.

Indications:
TAMIFLU is indicated for treating or preventing influenza. It is indicated for the treatment in adult and children 1 year of age and older and prophylaxis in adult and adolescents 13 years of age and older.

Dosage and Administration:

Children (1-12 years old):
Treatment -

Body Weight	Dose for 5 days
15 kg	*30 mg bd*
15.1 kg - 23 kg	*45 mg bd*
23.1 kg - 40 kg	*60 mg bd*
> 40 kg	*75 mg bd*

Adults and adolescents (13 years old):
Treatment -
75 mg* dose of TAMIFLU twice daily for five days.
Prevention -
75 mg* dose of TAMIFLU once daily. Your doctor will recommend the length of time you will need to take TAMIFLU.
(Can use either capsule or oral suspension)*

New Tamiflu Oral Suspension Now Available !

Significantly reduces impact of influenza in children as young as 1 year old [1]

Influenza-related otitis media in children

(n=26/217)

44% Reduction[1]

P<0.005

(n=50/235)

Multicenter, double-blind, randomized and placebo-controlled study of 452 pediatric patients aged 1 to 12 years with confirmed influenza. Patients were treated with Tamiflu 2 mg/kg twice daily or placebo twice daily for 5 days. There was a 21% incidence of otitis media in patients taking placebo vs. 12% in patients taking Tamiflu.

reduction in antibiotic use in children[1].

- 29% reduction in symptom severity in children taking Tamiflu and symptom relievers vs. children taking placebo and symptom relievers[1].
- Children experience a significant reduction (26%) in illness duration[1].
- Children return to normal activities almost 2 days earlier[1].

Reference:
1. Whitley RJ, Hayden FG, Reisinger KS, et. al. Oral Oseltamivir Treatment Of Influenza In Children. Pediatr Infect Dis J, 2001; 20: 127-33.

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Further information available.
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200306-ADV

Fast, Effective, Adjustable Asthma Control in One Inhaler [1,2]

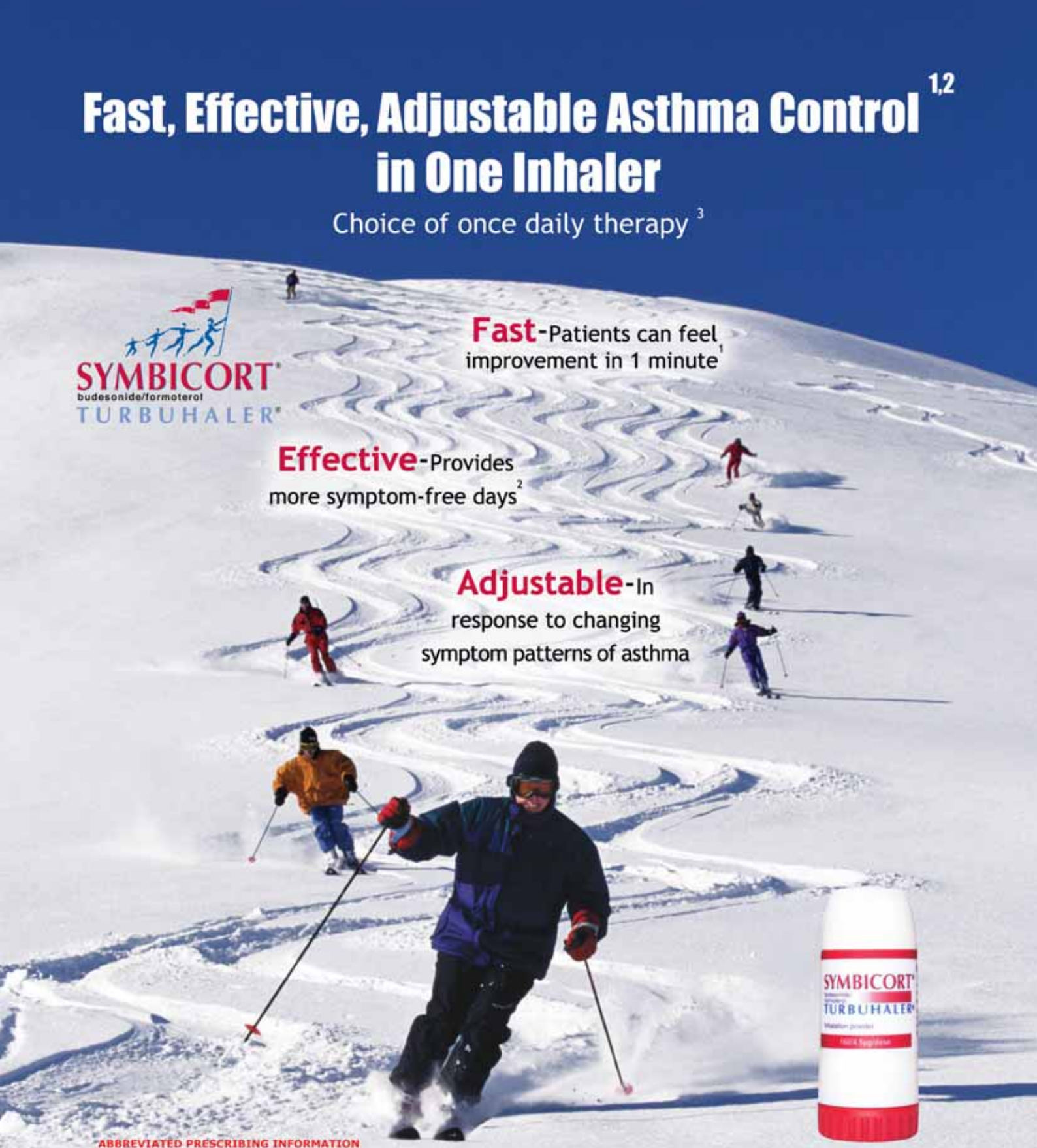
Choice of once daily therapy [3]

SYMBICORT®
budesonide/formoterol
TURBUHALER®

Fast-Patients can feel improvement in 1 minute [1]

Effective-Provides more symptom-free days [2]

Adjustable-In response to changing symptom patterns of asthma



ABBREVIATED PRESCRIBING INFORMATION

Symbicort Turbuhaler (budesonide and formoterol).

Presentation: Inhalation powder 160/4.5 µg/inhalation, 80/4.5 µg/inhalation (delivered dose).

Properties: Symbicort Turbuhaler is an inhaled combination medicinal product. It contains budesonide and formoterol, which show additive effects in terms of reduction of asthma exacerbations. Budesonide is a glucocorticosteroid with local anti-inflammatory effect. Formoterol is a selective β_2-adrenergic agonist that produces relaxation of bronchial smooth muscle. The bronchodilating effect sets in rapidly, within 1-3 minutes after inhalation and has a duration of 12 hours after a single dose. **Indications: Asthma** Regular treatment of asthma where use of a combination (inhaled corticosteroid and long acting beta-agonist) is appropriate; **COPD** Symptomatic treatment of patients with severe COPD (FEV_1 < 50% predicted normal) and a history of exacerbations, despite regular therapy with long acting bronchodilators. **Dosage:** Dosage is individual according to disease severity. If an individual patient should require dosages outside the recommended regimen, appropriate doses of beta-agonist and/or corticosteroids should be prescribed. **Asthma** *Adults and adolescents (12 years and above):* 1-2 inhalations twice daily. *Children (6 years and older):* 2 inhalations of low dose Symbicort (80/4.5 µg /inhalation) twice daily. **COPD** Adults: 2 inhalations of Symbicort (160/4.5 µg /inhalation) twice daily. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. When control of symptoms is maintained with the lowest recommended dosage, then the next step could include a test of inhaled corticosteroid alone. In usual practice when control of symptoms is achieved with the twice daily regimen, titration to the lowest effective dose could include Symbicort Turbuhaler given once daily, when in the opinion of the prescriber, a long acting bronchodilator would be required to maintain control. **Note:** To minimise oropharyngeal thrush, rinse the mouth out with water after each dosing occasion. Children under 6 years: Symbicort Turbuhaler is not recommended for children under 6 years. **Contraindications:** Hypersensitivity to budesonide, formoterol or inhaled lactose. **Warnings and Precautions:** It is recommended that the dose is tapered when the treatment is discontinued. The patient should seek medical advice if a previously effective dosage regimen no longer gives the same relief. There are no data available on the use of Symbicort Turbuhaler in the treatment of an acute asthma attack. Particular care is needed for patients who have transferred from systemic to inhaled glucocorticosteroids. Excessive doses of, or long term treatment with glucocorticoids may lead to signs or symptoms of hypercorticism, suppression of HPA function and/or suppression of growth in children and adolescents. The long-term effects of glucocorticosteroids in children and adolescents are not fully known. The growth of children and adolescents taking glucocorticosteroids in long term treatment by any route should be monitored. Symbicort Turbuhaler should be administered with caution in patients with severe cardiovascular disorders, diabetes mellitus, pheochromocytoma, untreated hypokalemia or thyrotoxicosis. **Pregnancy and lactation:** As with other drugs administered during pregnancy, the benefits for the mother should be weighed against the risks for the foetus. It is not known whether budesonide or formoterol passes into human milk. **Undesirable effects:** Common: Headache, palpitations, tremor, candida infection in the oropharynx, mild throat irritation, coughing, hoarseness. Uncommon: Tachycardia, muscle cramps, agitation, restlessness, nervousness, nausea, dizziness, sleep disturbances. Rare: Exanthema, urticaria, pruritus, skin bruising, bronchospasm. Other rare or very rare: (budesonide) Psychiatric symptoms such as depression, behavioural disturbances, signs or symptoms of systemic glucocorticosteroid effects, immediate and delayed hypersensitivity reactions (including dermatitis and angioedema), bruising. (formoterol) angina pectoris, hyperglycaemia, taste disturbances, variations in blood pressure, cardiac arrhythmias. **Interactions:** Beta-adrenergic blockers (including eye drops) can weaken or inhibit the effect of Symbicort Turbuhaler. Ketoconazole may increase systemic exposure to budesonide. This should be taken into consideration during long term treatment with ketoconazole. Other interactions are documented in the full prescribing information. "Symbicort" is a registered trademark owned by the AstraZeneca group of companies. Date of preparation of this abbreviated prescribing information: July 2003. Based on PLT 68 012 92.97 and 68 010 58.97 **References:** 1. van der Woude HJ et al. Am J Respir Crit Care Med 2002; 165 (8)(Suppl): A567. 2. Zetterström O et al. Eur Respir J 2001; 18: 262-268. 3. Buhl R et al. Am J Respir Crit Care Med 2001; 163 (Suppl 5): A864 + poster.

AstraZeneca

Further information is available on request:
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