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Pharmacist Forum on Standard Drug Formulary

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

Health service expenditure in Hong Kong was approximately 5% of the Gross Domestic Product (GDP). Compared against other advanced countries including reimbursement market, this percentage is reasonable. Why does our community still face healthcare financing issue? The answer is obvious: the lump sum is mainly from the government who has to be cautious on resource allocation. The growth of the aged population is four times higher than that of the other population groups, and the medical expenses involved are six times higher than for those under 65. It brings a significant up trend on the healthcare cost in the coming 10 years and, thus, the issues now lie in sustainability. At the opening speech of Hospital Authority Convention 2005, Dr York Chow, the Secretary for Health, Welfare and Food shared that a sustainable healthcare system requires the following essential elements:

- *A population that is knowledgeable about health and health risk factors, so that the general public can choose to adopt a healthy lifestyle, and take responsibility for their own health.*
- *A healthcare profession that views health promotion and preventive medicine as priorities, and exercises its practice professionally and ethically.*
- *A primary healthcare system that can provide a robust family and community medicine service affordable by all, and incorporating strong elements of health promotion and preventive care, with standards set for the care of different age groups and health status.*
- *A hospital service network that can provide emergency and secondary care within reach of the population in all districts, in order to enhance service access and family visitation.*
- *Mental health, elderly, long-term and rehabilitation care services that encourage home care with community outreach and professional support, with infirmary and hospice care in all districts to enhance maintenance of family support systems.*
- *The establishment of specialised tertiary centres and hospitals to develop and concentrate expertise, technology, special facilities and research.*
- *A well-integrated public and private sector that promotes healthy competition in terms of service quality and professional standards, and provides a choice for the public.*
- *A financing model that encourages appropriate use of healthcare services, ethical and effective professional care, reasonable and affordable contributions by users, and with targeted subsidies through public funds for the most needy and unfortunate patients and families.*

Spinning off from these rationales, a number of projects have been initiated by the Authority. It also has been proposed by the healthcare financing experts that medical insurance and taxation can help keep the system sustainable in the long run. The prologue that we can see recently is the raising of medical consultation fees and asking patient to share drug cost.

Hospital Authority Standard Drug Formulary is expected to roll out in mid July. The launch will first take place in New Territories East cluster and complete in four months' time. All medications that can be prescribed by HA doctor fall into 3 categories, namely Standard Drug (cost-effective drugs that can be provided to patients free of charge), Special Drug (only certain types of patients would enjoy free prescription), and Self-financed Item (SFI). The Hospital Authority Chief Executive, Dr William Ho, said the proposed formulary aims to ensure equitable access to cost effective drugs of proven efficacy and safety, through standardization of drug policy and utilization in all public hospitals and clinics. There is no doubt that our money should be used wisely, but the question is "how". Different people have different expectations. From the policy maker's perspective, the new system should open up more opportunities to gain access to a wider range of products for different types of patients - for those who are willing to pay for a better or surplus pharmaceutical service, they have a channel to do so and share the expensive drug cost; for those who cannot afford a better treatment choice, there is a safety net to help sponsor the cost. Patients shout loud to have more new drugs in the "free of charge" system, to extend the clinical indications of certain special drugs and to be informed better of their treatment options. The doctor may tell you that they absolutely wish but have no time to spend with patients to explain why they need to pay for their self-financed items. Some may say that they don't want their clinical judgment to be affected by the boundary of the Formulary. All in all, it is not always easy to achieve a nice balance.

It seems that everybody in the community focuses on the drug expenditure which was only 8.7% of total HA expenditure (including the cost of medical devices). Actually, like in many other counties, the key spending in the healthcare system is on human resources. How the Authority maximizes the value of HK$25 billion of staff cost (78% of total HA expenditure) is a real challenge. In 2004, there were not more than 290 pharmacists working in the HA setting. When compared with the group of 4,800 doctors and 19,000 nurses, we are actually a minority group of servants. However, it also means that there is much room for expansion and development. It is a time for us to ask for more - more responsibility and more value.

In the long run, if the government wants to maintain the high healthcare services limited resources, public-private partnership (PPP) will be the key operating priority to consider. Therefore, opportunity is not only within the Hospital Authority, but also in the private sector. Let me raise an example, non-urgent patients take up 70 per cent of the attendance in the accident and emergency (A&E) service. While the average cost of A&E consultation is HK$830, the A&E charge to patients is only HK$100. To the Authority, it is an abuse of the emergency service. To the patients, does the 10-minute consultation for their non-emergency minor illness worth that much? What sorts of OTC medications may patients receive from the A&E? I strongly believe that it is a time for the pharmacists in the primary care setting to ask for more - to take care of some of these patients.

Michael Leung
Managing Editor

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Editorial

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New Products

A Summary Report on the Open Forum on SFIs (Self-Financed Items) and Standard Hospital Authority Drug Formulary

Chiang, SC

I BACKGROUND

A draft consultation paper including the background and the objectives of developing a standard Hospital Authority Drug Formulary (the Formulary), guiding policy, value, review mechanism and content of the Formulary and implications was presented by Hospital Authority (HA) to Legislative Council Panel on Health Services on 31st January 2005. The HA had started consulting the staff within the organization and the public until 30th April, 2005. (for details of the consultation paper, please look up in http://www.ha.org.hk/hasdf/)

As the consultation paper also stated important policy directions about the classification of standard and non-standard drugs and proposed suggestions on how these could be supplied, pharmacists in Hong Kong would need to be engaged in the details and needed to formulate views about the entire issue.

II THE OPEN FORUM EVENT

In order to collect views from and facilitate discussion amongst pharmacists, an open forum was jointly organized by The Pharmaceutical Society of Hong Kong, the Practising Pharmacists Association of Hong Kong and the Society of Hospital Pharmacists of Hong Kong, in the evening on 23rd February, 2005 (Wednesday) at PSHK Club House in Jordan.

The forum started at 7.15p.m. with about 60 attendants, the majority of whom were community pharmacists. This was to be expected as the matter seemed to cause most direct impact on the community practice. However, as the discussion revealed, this was a subject that would affect all party players in the pharmaceutical field including hospital pharmacy practice, the pharmaceutical manufacturers, the chained pharmacy outlets, the Authorized Sellers of Poisons as well as other health care partners e.g. general practitioners, not to mention the patients and the public. Hence, it was an encouraging and healthy sign for the forum to have the presence of representatives from other practice areas, apart from the community to ensure more balanced perspectives in the discussion process.

The presidents from the three pharmacy professional organizations namely, Mr Benjamin Kwong (PSHK), Mr Billy Chung (PPAHK) and Mr K W Ng (SHPHK) started the forum discussion by briefing the background for the event. Additionally, participants were referred to the explanatory leaflet on the subject prepared and distributed by the Hospital Authority which briefly outlined the principles behind the HA Standard Drug Formulary policy, the classification of the Standard Formulary into general drugs and special drugs, as well as those non standard drugs which fell outside the Standard Formulary and would not be covered by the public health system. Those non standard drugs termed as Self-Financed Items (SFIs) by HA would, as the term suggested, require patients to make their own purchase. The leaflet also included an analysis on the pros and cons of the four options available to the patients for making these purchases.

III THE FORUM OBJECTIVES

The three presidents explained that the objective of the forum was for members to express their opinion and, if so decided, the three pharmacy organization could formulate a submission to reflect the collective views from the members of the pharmacy profession. Attendants were reminded that the submission should be made before the end of April and all comments were welcome but as responsible groups of professionals, we should be constructive in our suggestions. The floor was opened and a series of exchanges of communication and discussion points were raised.

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Major salient discussion points

- It was clarified that the HA Drug Formulary had adopted the principles from the WHO i.e. to provide an essential drug list needed for the population and it was noted that the HA Drug Formulary was more comprehensive than the WHO recommendation.

- All were aware that the matter on SFI and HA Drug Formulary was not only a strategic decision to control the drug expenditures in the public hospital system but would indeed evolve ultimately to become an important corner stone of a health care financing model in meeting the demands of drug supply for the general population in Hong Kong. This would in turn have long term implications affecting the dispensing workload pattern in the public hospitals and dispensing business in the community pharmacies.

- There was general consensus that the policy was well intended in order to maintain the financial sustainability of the health care system but there were concerns both from within the pharmacy profession and from outside the profession including those trying to implement the policy e.g. the director of Department of Health as well as the general public, as to how the patients could purchase the SFIs? How to ensure that these SFIs could meet quality standards without adversely affecting the patients' treatment and how to make available the SFIs to the patients at a fair price without having the need for the patients to shop around for price comparison?

- Members were concerned if HA had already decided on their preference on the four options rendering any efforts made by the community to assist in the implementation of dispensing SFIs in the community uneventful.

- Some members from the community practice opined that if these SFIs were released into the community pharmacy sector in significant volume, the community practice pharmacies would be driven by market force to raise their service standards, to lower the drug price, and could self regulate to prevent the use of fake or parallel imports. Business and professional incentives would attract more community pharmacists to become self employed and would be more ready to assume the ethical control over the daily operation of their pharmacies.

- Suggestions were generated to help patients to distinguish those community pharmacies with higher standards e.g. by wearing a white coat and/or pharmacist name badge, posting of performance pledge, lengthening of availability of pharmacists service hours so that patients can obtain a guaranteed dispensing service.

- There were concerns that the community could never compete with the public hospitals because they could not enjoy the lower drug prices packages as a result of bulk purchase contracts currently available to the public hospitals nor the big bonus discounts available preferentially to the general practitioners.

- There was suggestion that the community pharmacies could group their needs together and work out bulk purchase in a similar development direction initiated by certain groups of general practitioners. This would also help to enrich the influential power of the community pharmacists in drug sourcing and enable them to gain better control of the daily operation.

- There was recognition that certain cancer SFI drugs would never be dispensed in the community. The option of having the community pharmacy in the hospitals was considered but some members viewed that this set up would defeat the meaning of the geographical location of pharmacies in the community and the tender requirement for this community pharmacy set up in the public hospitals would be unfavorable to the independent or solo practice pharmacists most of whom would have practical difficulty in e.g. proving their financial ability or producing past track business experience.

- Suggestions were made that any SFIs sold in the public hospitals should be charged not at the original purchase price but with inclusion on the staff costs, handling costs, etc. in order to narrow the price gaps between the public and the community pharmacies and to avoid subsidizing the supply of these groups of drugs with public money.

- Lengthy discussion went on to address the root problems of the current unsatisfactory scenarios in the community practice. Suggestions included e.g. changing legislations to support the separation of dispensing from prescribing, reimbursing the community pharmacists to dispense the HA prescriptions, making the legislative requirement for the compulsory presence of the community pharmacists throughout the opening hours, granting special certificates to certain community pharmacies to handle the prescription drugs, influencing and persuading the ASPs (Authorized Sellers of Poisons) to let the pharmacists own the dispensing and handling of prescription drugs, educating the government and the public about the roles and functions of the community pharmacists in the primary health care, etc., etc.

- Members were reminded that the comments and suggestions from the pharmacists should not only address the needs of the pharmacy profession but must also ensure that patients' prime interests in getting the right drug at the right price with the right quality at the right standards in the right timing are assured. Without these in mind, the pharmacists would be seen protecting their own interests and forsaking the general interests of the public, for drugs are certainly not ordinary commodity but are special life long items required to restore and maintain health.

- There were written submission from those who could not attend the forum and their opinions were read at the Forum and incorporated in the above points in one way or another.

IV CONCLUSION

The discussion was well moderated with all participants having a fair share of opportunity and time to express their opinion. The participants hope that the three societies could make a joint submission. The three presidents reached a consensus to this but reiterated that sometimes, separate submissions by each society and even from individual members giving different perspectives on the matter might be a good strategic move. Meantime, the three societies would continue to collect other views from the members. The draft submission, may be separate or joint would be written and circulated for comments by the respective members before its final submission. The forum was adjourned at 9.20p.m on that day.

This report is contributed by ***Ms. S. C. Chiang***, Senior Pharmacist at the Chief Pharmacist's office. Ms. Chiang has been active all along in the pharmacy profession of Hong Kong. She wrote this as the SHPHK news reporter on behalf of HKPJ.

***** Written by SHPHK News Reporter on 25th Feb 2005 for and on behalf of HKPJ *****

Use of Herbal Products for Men's Problems

Chung, Racoon KC

Figure 1. Herbal product industry has being expanded very quickly.

Nowadays, herbal product industry is expanding at rocket speed. Many producers claim that their products can boost men's energy, alleviate male sex problems or manage prostate problems. Although there are great advances in western medicines in managing benign prostatic hyperplasia and erectile dysfunction, many patients still attempt to seek herbal products. The attractions may be due to the fact that herbal products are not strictly regulated by regulatory authorities, easy to obtain and, sometimes, less expensive than prescription drugs [1]. However, the efficacy of using these herbal products still remains uncertain. Most agents have not been studied extensively in clinical research. These perceived benefits are based on their cultural beliefs. Research findings frequently are preliminary in nature, often uncontrolled and published in journals not indexed in standard bibliographic databases [1]. In this article, the efficacy and safety of using these herbal products will be discussed.

I BENIGN PROSTATIC HYPERPLASIA (BPH)

There are several herbal products used for benign prostatic hyperplasia, including saw palmetto, beta-sitosterol, lycopene, pygeum, rye grass, nettle and pumpkin seed.

i) Saw Palmetto

Saw palmetto *(Serenoa repens)* is a palm-like plant native to North America (figure 2). It was traditionally used in the treatment of urinary tract problems. Nowadays, it is commonly used to treat BPH.

Saw palmetto was shown to improve urinary symptoms, such as frequent urination, painful urination, hesitancy, urgency and perineal heaviness [2]. Compared with placebo, saw palmetto significantly improved urinary tract symptoms by 28%, nocturia by 25%, peak urine flow by 24% and residual urine volume by 43% [3]. Men taking saw palmetto were nearly twice as likely to report improvement in symptoms as men taking placebo [3]. A 6-month double-blind randomized study comparing the effects of saw palmetto with those of finasteride with moderate BPH showed no significant difference in IPSS, quality of life and peak urinary flow rate improvement [4]. Patients taking saw palmetto gave rise to fewer complaints of decreased libido and impotence than those of finasteride [4]. However, patients taking saw palmetto showed smaller effect on prostate volume and no change in PSA level [4]. Another double-blind study showed that alfuzosin (an alpha-blocker) was more efficacious than saw palmetto in the treatment of urinary signs and symptoms of BPH [5].

The effects of saw palmetto may be due to the slowing of prostate cell proliferation by inhibiting fibroblast growth factor and epidermal growth factor and stimulating apoptosis [2, 7, 8].

The safety of saw palmetto was well demonstrated among 435 men in a 3-year study [6]. Adverse effects due to saw palmetto were generally mild and comparable with placebo [2, 4]. Dizziness, headache and gastrointestinal complaints such as nausea, vomiting, constipation and diarrhea are the most frequently reported adverse effects [2].

Figure 2. Saw Palmett (source: http://www.peaceandplenty.com/de/large_ saw_palmetto.html)

Saw palmetto was reported to prolong bleeding time [9]. Therefore, it should be used with caution with anticoagulant or antiplatelet drugs.

The common dosage is 160mg twice daily or 320mg once daily of a lipophilic extract containing 80 - 90% fatty acids [2].

ii) Beta-sitosterol

Beta-sitosterol is a plant sterol. Its chemical structure is similar to cholesterol with an ethyl group at position 24. Plant sterols were authorized by FDA in the use of labeling claims for reducing the risk of coronary heart disease [2]. Sometimes, African wild potato (figure 3) was used as a source of beta-sitosterol [2].

Figure 3. African wild potato (source: www.nbi.ac.za/ sisulu/tour3.htm)

A randomized double-blind placebo-controlled trial showed significant improvement in IPSS, peak flow and mean residual urinary volume in beta-sitosterol treatment group compared with placebo group [10]. In a systematic review, compared with placebo, beta-sitosterol improved urinary symptom scores by 35%, peak urinary flow rate by 34%, mean urinary flow rate by 47% and post-void residual urine volume by 24% [11]. However, beta-sitosterol did not significantly reduce prostate size [11].

Beta-sitosterol was shown to inhibit growth factors exerting anti-proliferative effects on the prostate in vitro [12]. It was also demonstrated to cause the shrinkage of prostate in animal (hamster) but this has not been shown in humans [2, 13].

Adverse effects due to beta-sitosterol were generally mild and comparable with placebo [11]. Gastrointestinal side effects are most common and impotence was reported in 0.5% of men on beta-sitosterol [11].

Randomized trials have shown that plant sterols and stanols lower blood concentrations of beta-carotene by about 25%, concentrations of alpha-carotene by 10%, and concentrations of vitamin E by 8% [14]. Ezetimibe was shown to produce significant reductions (41%) in beta-sitosterol concentrations [15].

The common dosage of beta-sitosterol for BPH is 60 - 130 mg of beta-sitosterol divided into 2 - 3 times daily [2].

iii) Lycopene

Lycopene is a carotenoid without provitamin A activity. It is the pigment present in many red fruits and vegetables [16].

Lycopene was commonly found in herbal products for prostate problems in Hong Kong. However, there are still no credible clinical researches supporting the use of lycopene in BPH [2]. It may be beneficial in prostate cancer management. A trial with small sample size (n=26) showed that patients with prostate cancer taking lycopene 15mg twice daily for 3 weeks before radical prostatectomy might decrease tumor growth compared with those with no supplementation [17]. A prospective cohort study suggested that lycopene or other compounds in tomatoes might reduce prostate cancer risk [18].

Lycopene had a very long history of use with respect to dietary exposure and even in the case of very high exposures from dietary sources. No indication of any significant adverse effects was suggested [19].

iv) Pygeum

An extract of the bark of the African plum tree *(pygeum africanum)* was commonly used for BPH (figure 4). Traditionally, the bark was collected and powdered and this was drunk as a tea to improve genitor-urinary symptoms [20].

Figure 4. Pygeum (source: http://www.numarkpharmacists.com/hn/Herb/Pygeum.htm)

Most studies on pygeum noted an improvement in nocturia compared with placebo [20]. In one newer multi-centre trial involving 85 patients, taking pygeum extract 50mg twice daily for 2 months was found to improve IPSS and quality of life 40% and 31% respectively [21]. Nocturnal frequency was reduced by 32%. However, post-voiding volume did not reach statistical significance [21]. In one meta-analysis, nocturia was reduced by 19%, residual urine volume by 24% and peak urine flow was increased by 23% in pygeum treatment group [22]. However, the ability to estimate its efficacy was limited by inadequacies in the reporting of outcomes [20].

Pygeum might inhibit prostate growth and cellular hyperplasia by inhibiting growth factors such as basic fibroblast growth factor, epidermal growth factor and insulin-like growth factor [2].

Adverse events due to pygeum were generally mild in nature and similar in frequency to placebo. The most frequently reported adverse events were gastrointestinal and occurred among 7 men in 5 trials [22].

For BPH, 75 - 200mg standardized lipophilic extract per day has been used [2]. 50mg twice daily and 100mg once daily were proven equally effective [23].

v) Rye grass

Rye pollen extract is prepared from the rye-grass, *secale cereale*. A specific extract (Cernilton®) is a registered pharmaceutical product in Western Europe, Japan, Korea and Argentina [2].

Rye pollen extract was comparable with pygeum in improving urological symptoms based on obstructive or irritative symptoms[24]. In one trial comparing rye pollen extract with pygeum, obstructive scale score improved 63% in rye pollen extract treatment group and 46% in pygeum treatment group and irritative scale improved 68% in rye pollen group and 40% in pygeum group [24]. In one double-blind, placebo-controlled study evaluating the effect of a 6-month course of rye grass pollen found the significant subjective improvement with treatment group (69% of patients) compared with placebo (30% of patient) [25]. However, rye grass pollen extract did not significantly improve objective measures such as peak and mean urinary flow rates when compared with placebo and the control study agents [24].

Rye pollen extract contains beta-sterols. There was some evidence that it might affect alpha-adrenergic receptors and relax the internal and external bladder sphincter muscles [24].

Rye pollen extract was well tolerated. The only adverse effect reported was mild nausea [24].

For BPH, a specific rye grass pollen extract (Cernilton®) 126mg three times daily has been used [2].

vi) Nettle

Extract from roots of the stinging nettle (figure 5) are often used in Germany for the treatment of BPH [20]. Although it was commonly sold in the market, its use was not well supported by clinical trials.

Figure 5. Nettle (source: http://www.numarkpharmacists.com/hn/Herb/Nettle.)

In one placebo-controlled study, liquid preparation of stinging nettle showed improvement in IPSS scores. However, this preparation was withdrawn from the market owing to its unacceptable taste [20]. Another placebo-controlled trial showed the improvement in peak urine flow and total voided volume in patients taking nettle extract capsules, but there was no difference in urologic symptoms and 24% of patients taking it withdrew from the study, partly due to unspecified side effects [20].

However, nettle extract was commonly used in combination with other agents and some showed positive results. In one randomized double-blind clinical trial comparing combination of extracts of saw palmetto fruit and nettle root with finasteride, the efficacy was shown to be equivalent and the combination was better tolerated [26].

The common adverse effects of stinging nettle root include GI distress, allergic skin reactions and hyperhidrosis [27]. In one six-month study in 4087 patients, only very few adverse events were reported [27].

vii) Pumpkin seed

Again, pumpkin seed (figure 6) was always included in the preparation for BPH. However, there was no convincing evidence supporting its use alone. In one small-scale randomized trial (n=55) evaluating the efficacy of pumpkin seed extracts, compared with placebo, preparation containing pumpkin seed and saw palmetto was found to improve self-rating of urinary symptoms (85% noted improvement in combination vs. 11% placebo), nocturia and residual urine volume (31% in combination vs 6.5% in placebo) [20]. However, the effect of pumpkin seed alone was difficult to be evaluated in this trial.

Figure 6. Pumpkin seed (source: http://www.boith.com/food/pumpkin%20seed%20and%20pumpkin%20seed%20kernels.htm)

No adverse effects and interaction with drugs were documented [27]. For BPH, pumpkin seed oil extract 480mg per day in 3 divided doses in combination with saw palmetto had been used [2].

II ERECTILE DYSFUNCTION (ED)

Panax ginseng, maca, suma, epimedium, muira puama and damiana are common herbs used in preparation marketed for erectile dysfunction. However, except a few herbs, most of the herbs are not well studied in human and their uses are only based on traditional beliefs or results from animal studies.

i) Panax ginseng

Ginseng has been used as Chinese medicine for centuries. It has been used as adaptogen for increasing resistance to environmental stress and as a general tonic for improving well-being [2].

Most of the researches on ginseng were on animals rather than on humans [1]. In one preliminary double-blind, placebo controlled, crossover study on human (n=45), mean international index of erectile function scores were significantly higher in the treatment group than in the placebo group [28].

How ginseng exert its effect on erectile dysfunction is not clear. Several studies indicate that ginseng increases levels of testosterone.

Table 1. Effectiveness and Safety of Herbs for Common Men's Problems

Herbs	Effectiveness*	Safety#	Adverse Effects	Cautions	Drug Interactions
Benign Prostatic Hyperplasia (BPH)					
Saw Palmetto (鋸棕櫚)	+++	+++	Dizziness, headache, GI	Bleeding problems	Antiplatelet, anticoagulant
Beta-sitosterol (African wild potato) (非洲星草)	+++	+++	GI	None reported	Vitamin E, alpha and beta carotene, Ezetimibe
Pygeum (非洲刺李)	+++	+++	GI	None reported	None reported
Rye Grass (黑麥草)	+	+	Nausea	None reported	None reported
Lycopene (番茄紅素)	+/-	+++	None reported	None reported	None reported
Nettle (蕁麻)	-	+	GI, skin problems	None reported	None reported
Pumpkin Seed (南瓜子)	-	+	None reported	None reported	None reported
Erectile Dysfunction (ED)					
Panax Ginseng (人參)	+++	+	Insomnia, tachycardia, palpitation, hypertension, hypotension, headache, diarrhea	Cardiovascular disease, bleeding problems, diabetics	Antiplatelet, anticoagulant, hypoglycemic drugs, immunosuppressants
Maca (安第斯人參, 馬卡)	+/-	+++	None reported	None reported	None reported
Suma (巴西人參)	+/-	+/-	Insufficient data	Insufficient data	Insufficient data
Epimedium (淫羊藿)	-	-	Dizziness, vomiting dry mouth, thirst, nosebleed. Large doses: respiratory arrest, spasm	Insufficient data	Insufficient data
Muira Puama (南美勃起樹)	+/-	+/-	Nervous, agitation	Insufficient data	Insufficient data
Damiana (透納樹)	+/-	+++	None reported	Diabetics	Hypoglycemic drugs

* +++ Likely effective + Probably effective +/- Insufficient data to rank - Probably ineffective

\# +++ Likely safe + Probably safe +/- insufficient data to rank - Probably unsafe

However, others report no such effects [1].

Panax ginseng (figure 7) is well tolerated. The most common side effect is insomnia [29]. Less common side effects include tachycardia, palpitations, hypertension, hypotension, edema, decreased appetite, diarrhea, hyperpyrexia, pruritus, rose spots, headache, vertigo, euphoria and mania [2].

In one randomized, double-blind, placebo-controlled study (n=30), ginseng, at doses of 200mg of ginseng extract, increases the QTc interval and decreases diastolic blood pressure 2 hours after ingestion in healthy adults on the first day of therapy [30]. However, there were no changes with prolonged use [30]. Therefore, it should be used with caution in patients with cardiovascular disease unless safety was demonstrated in such patients.

Figure 7. Panax ginseng (source: www.ooo.cz/zen-sen/)

Decreased blood coagulation had been reported in patients taking panax ginseng. Therefore, it is contraindicated in cases of hemorrhage or thrombosis and in patients taking anticoagulant or antiplatelet [2]. Ginseng was also demonstrated to reduce fasting blood glucose [31]. Therefore, it should be used with caution in diabetic patients taking hypoglycemic drugs. Theoretically, concurrent use of ginseng might have immune system stimulating properties and interfere with immunosuppressive therapy [2].

For ED, panax ginseng 900mg three times daily has been used [2].

ii) Maca

Maca (figure 8) is a root of *Lepidium meyenii* cultivated in the central Peruvian Andes [1]. Maca had been used for several thousand years by Peruvians as a "wonder drug" [1]. Although it is widely included in the preparation for ED and its prosexual effects were demonstrated in animals, it had not been proven to be effective for ED in human [1].

On the other hand, it was demonstrated to be effective in improving sexual desire in men in one small study. In a 12-week double-blind placebo-controlled, randomized trial (n=57), 40% and 42.2% of men taking 1500 or 3000 mg maca reported increase of sexual desire after 8 and 12 weeks of treatment respectively and the increase was not shown in placebo group [32].

Figure 8. Maca (source: www.abc.net.au/newengland/stories/ s778348.htm)

No adverse reactions were reported so far. For enhancing sexual desire in men, 1500 to 3000 mg daily in 3 divided doses has been used [32].

ii) Other herbs for ED

Although suma, epimedium, muira puama and damiana were used in preparation for ED, none of the above herbs were demonstrated to be effective in human. Their uses were only based on small animal studies or folk uses.

Suma, *pfaffia paniculata*, is called Brazilian ginseng. Traditionally, it is used orally as an immune enhancer or adaptogen to help the body adapt to all types of stress by enhancing or restoring the immune system [2]. There is insufficient data supporting its use in ED and its safety.

People commonly use epimedium, *epimedium grandiflorum*, orally for impotence and involuntary ejaculation. However, the use had not been well supported. However, extended use of epimedium may result in dizziness, vomiting, dry mouth, thirst and nosebleed [2]. Large doses of epimedium may cause respiratory arrest and exaggeration of tendon reflexes to the point of spasm [1]. There is insufficient data supporting the safety of using it in low doses.

Muira Puama comes from a small bush found in the rain forests of Brazil. Data supporting its use in ED was limited to a single study. Over 60% of 262 men reporting a loss of desire indicated improvement in subjects taking 1 - 1.5 g muira puama extract and over 50% of subjects indicated treatment with muira puama beneficial in attaining erection [1]. Mura puama may cause nervousness and agitation [1].

Damiana is a Mexican shrub and is traditionally used a sexual stimulant [1]. Data supporting its use in ED was lacking. In one small study (n=21) evaluating subjects with mild to moderate ED taking ArginMax® (combination of ginseng, ginkgo, damiana, L-arginine, vitamins and minerals) over a 4-week period, 88.9% improved in ability to maintain erection during sexual intercourse and 75% improved in satisfaction with their overall sex life [33]. Damiana is considered safe when used orally in amounts commonly found in foods as it has Generally Recognized As Safe Stats (GRAS) for use in foods in the US [2]. Theoretically, damiana may interfere with diabetes therapy due to hypoglycemic activity and should be used with caution in diabetics [2].

III CONCLUSION

Lots of herbal products in the market claimed that they are natural and free from adverse effects and their use was supported by the long history of folk use and clinical trials in human. However, this is not the truth. Most of the studies of herbal products were carried out on animals. Even if human studies are present, the results are limited by small sample size and questionable study designs. Most of the studies were published in journals not indexed in standard bibliographic databases [1]. Therefore the results and study designs are difficult to retrieve. Besides efficacy, safety data are lacking too. Moreover, natural products are not totally safe. Thus, it is inappropriate to recommend any herbal products for BPH and ED except for those products which have been well-studied and those patients who really want to seek alternatives. Saw palmetto, pygeum and beta-sitosterol are appropriate choices for BPH and panax ginseng is suitable for ED. But whenever any herbs are recommended, several factors should be considered. Firstly, herbs should not interact with the patients' medications and disease states. Secondly, patients should be reminded not to put too much expectation on the herbs. Thirdly, patients should not try taking herbs without telling their health care providers. Fourthly, patients should be told that safety of the herbs had not been well-studied and they should be advised to report any adverse effects encountered.

Raccoon Chung graduated from the CUHK and is currently working in a community pharmacy chain.

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Peritoneal Dialysis - Principles and Related Practical Issues

Chung, Kenneth

2 CE Units

I BACKGROUND

Renal disease is one of the leading causes of deaths in Hong Kong. Although it only ranked seventh in the list of diseases following the major three - malignant neoplasms, diseases of heart, and pneumonia, it claimed 1,000 out of 30,000 lives in the year 2003[1]. End stage renal disease (ESRD), one form of renal disease manifestations, is becoming more and more prevalent in the world. From the data of United States Renal Data System (USRDS), the number of cases was nearly doubled over six years from 1991 to 1997[2]. Dialysis and transplantation are the two treatments available for the management of patients with ESRD with peritoneal dialysis (PD) being one of the commonly adopted treatment modality. This article reviews the various issues concerning PD and aims to provide an update on the relevant information.

II END STAGE RENAL DISEASE (ESRD)

ESRD is a part of chronic kidney disease which describes the continuum of kidney dysfunction from early to late-stage disease. ESRD is defined as the glomerular filtration rate of patients less than 15mL/min [3,4]. In order to sustain life, patients need renal replacement therapy in the form of dialysis or transplantation. ESRD is associated with fluid and electrolyte abnormalities, anemia, cardiovascular disease, hyperparathyroidism, bone disease and malnutrition. These complications have to be managed. Therefore, Both drugs and dialysis are essential.

III PRINCIPLE OF PERITONEAL DIALYSIS

Peritoneal Dialysis is performed by introducing 1 to 3 liters of a dialysis fluid into the peritoneal cavity. The basic principle of PD is that the solute composition of the dialysis fluids infused into the peritoneal cavity tends to equilibrate with the plasma water solute composition during the dialysis. The walls of the peritoneal cavity are lined with a membrane called the peritoneum. During PD, the dialysis solution which contains a mixture of dextrose, salt and other minerals dissolved in water is placed in a person's abdominal cavity through a catheter. By diffusion and by ultrafiltration, waste products and extra body fluid are passed through the peritoneal membrane from the blood into the dialysis solution.

The crucial components of the PD system are peritoneal blood flow, the highly vascular membrane, and the flow rate and volume of the PD fluids[5]. Since neither peritoneal blood flow nor the vascularity of the membrane can be manipulated, the only factors that can be adjusted to achieve maximum solute and fluid removal are the flow rate and composition of the dialysis fluids. On the other hand, whether a patient can be placed on PD treatment depends on the membrane vascularity.

IV TYPES OF PERITONEAL DIALYSIS[5]

Peritoneal Dialysis is divided into two types; namely, Continuous Ambulatory Peritoneal Dialysis (CAPD) and Automated Peritoneal Dialysis (APD). APD refers to all forms of peritoneal dialysis that use a mechanical device to assist in the delivery and drainage of the dialysate from the peritoneal cavity[6]. APD can be furthered divided into Continuous Cycler-assisted Peritoneal Dialysis (CCPD), Nocturnal (Night-time) Intermittent Peritoneal Dialysis (NIPD) and Tidal Peritoneal Dialysis (TPD). The details of different PD methods are explained below and figure 1:

1. ***Continuous ambulatory peritoneal dialysis (CAPD)***
   Dialysate is always present in the abdomen. The dialysate is drained into the abdomen by gravity but not a machine. The dialysate is exchanged by draining and refilling 4 to 5 times per day. The abdomen is filled with dialysate overnight.

2. ***Continuous cycler-assisted peritoneal dialysis (CCPD)***
   Dialysis begins at bedtime when the patient gets connected to a cycler machine that will periodically replace the dialysate in the patient's abdomen with fresh dialysis solution while the patient sleeps. Usually the dialysate is changed 3 to 5 times during the night. In the morning the patient is disconnected from the cycler, leaving a fresh exchange of dialysis solution in the abdomen. This daytime exchange is drained at bedtime when the cycler machine is reconnected.

3. ***Nocturnal intermittent peritoneal dialysis (NIPD)***
   The patient is connected to the cycler only at bedtime as in the case for CCPD. The number of exchanges during the night is increased to 5 to 8 times or more. In the morning, before the patient is disconnected from the cycler, the abdomen is drained and is left dry during the day. NIPD is usually reserved for patients whose peritoneum is able to transport waste products very rapidly or for patients who still have substantial residual kidney function.

4. ***Tidal Peritoneal Dialysis (TPD)[7]***
   Tidal peritoneal dialysis is another variant of automated peritoneal dialysis which leaves a large portion of the dialysis fluid in contact with the peritoneum and exchanges a small portion of PD fluid; this eliminates the time between exchanges in which there is a minimal amount of fluid in the cavity. In some patients, pain or discomfort occurs with complete drain of the PD fluid or upon initiation of dialysis filling when the peritoneal cavity is empty. The use of tidal peritoneal dialysis can act as a modality to alleviate this pain[8].

V COMPOSITION OF PERITONEAL DIALYSIS FLUID

As mentioned previously, the solute composition of the peritoneal fluid is the main tool for removing excess water and waste products, supplying needed substances and restoring the

balance of disturbed solutes in uremic patients. The composition of PD fluid usually is standardized within certain limits of electrolyte content as mentioned in Table 1[9,10].

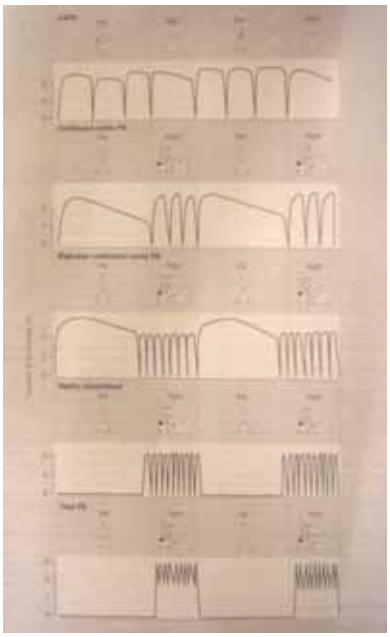


Figure 1. Various APD regimens compared with standard CAPD

Management of electrolyte balance is important for end stage renal disease patients since the kidney cannot carry out its normal function for electrolyte homeostasis. From Table 1, we can see that sodium and potassium have to be removed in order to maintain body homeostasis to try to achieve the normal plasma levels. Magnesium needs to be replenished and studies show that the small amount of magnesium present in the PD fluids (0.5 - 1.5 mEq/L) clinically is enough to elevate the magnesium level in patients[12,13]. The plasma calcium level in patients is lower than normal. It is due to the decreased calcium uptake from the gastrointestinal tract. Hypocalcaemia is a common feature in the pre-dialysis phase if oral calcium and/or vitamin D are not supplemented. On the other hand, the pH of the PD fluid is much lower than the physiological pH for maintaining the stability of the components, although it is quite contradictory since renal patients are at risk of developing metabolic acidosis due to decreased production of bicarbonate in the body. Consequently, lactate is normally added as a bicarbonate-generating compound to avoid the risk of precipitation during the preparation, sterilization and storage of the dialysis solutions if the latter are bicarbonate-containing[10]. Biocompatibility issue also arises due to the low pH of PD fluids. The pH of the solution has to be kept low to prevent caramelization* of glucose during the heat sterilization process[14].

Table 1. Electrolyte Composition of Patient Plasma Level vs. PD Fluid

Solute	Normal Plasma Level (mEq/L)[11]	Patient Plasma level (mEq/L)	PD Fluid (mEq/L)
Sodium	134 - 149	135 - 142	132 - 134
Potassium	3.5 - 5.2	4 - 6	0 - 2
Calcium	4.4 - 5.2#	2.7 - 3.3	2.5 - 3.5
Magnesium	1.3 - 2.1#	1.1 - 1.4	0.5 - 1.5
Chloride	95 - 108	95 - 100	95 -106
Lactate	-	-	35 - 40
pH	7.3 - 7.4	~7	5.5

 # Values are converted from mg/dL to mEq/L by equation listed in Drug Information Handbook

Most PD fluids have similar electrolyte contents. However, several large pharmaceutical companies produce PD fluids sterilized in varying volumes with different concentrations of glucose as the osmotic agent. There are now more alternative substances such as glycerol, amino acids and glucose polymers being used as osmotic agents. The difference in osmotic agents will be discussed later.

VI DIFFERENT TYPES OF PERITONEAL DIALYSIS FLUIDS

The PD fluids used in Hong Kong public hospitals are mainly supplied by three companies - Baxter®, Fresenius® and Gambro®. There are various brands with different composition as listed below Table 2.

Different calcium concentrations, glucose concentrations and volume are used according to the needs of patients. If a patient is hypocalcemic, PD fluid containing higher calcium content will be used for replenishment of calcium ions. As glucose is an osmotic agent, a higher concentration of glucose can be used to remove more water from a patient. If a patient has a heavy water load, PD fluid of a higher glucose concentration should be used. The volumes of PD fluids to be used depend on the modes of PD. For example, 2L is used for CAPD while larger volumes may be used for APD. It also depends on the time of administration. If the PD fluid will remain in the peritoneal cavity for a longer time, e.g. overnight, a larger volume should be used.

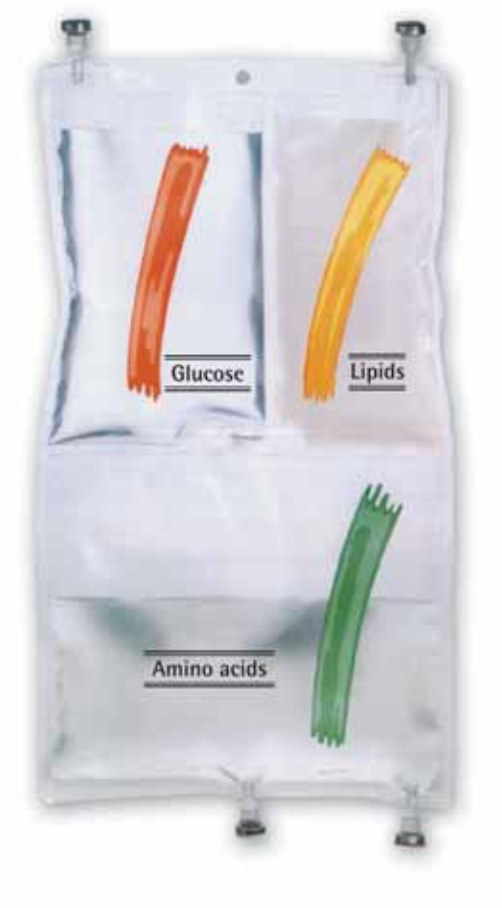
Table 2. Comparison of Different Brands of Peritoneal Dialysis Fluids available in Hong Kong

Companies	Brands	Osmotic agent	Concentration	Calcium Content (mEq/L)*	Osmolarity (mosmol/L)
Baxter®	Spike	Glucose	1.5%	2.5/3.5	344-346
			2.5%	2.5/3.5	395-396
			4.25%	2.5/3.5	483-485
	Ultra-bag	Glucose	1.5%	2.5/3.5	344-346
			2.5%	2.5/3.5	395-396
			4.25%	2.5/3.5	483-485
	Extraneal	Icodextrin	7.5%	3.5	282-286
	Nutrineal	Amino acids	1.1%	2.5	367
Fresenius®	Andy Disc	Glucose	1.5%	2/3.5	35 6-358
			2.3%	2/3.5	399-401
			4.25%	2/3.5	508-511
	Safe lock	Glucose	1.5%	2/3.5	356-358
			2.3%	2/3.5	399-401
			4.25%	2/3.5	508-511
Gambro®	Gambrosol trio	Glucose	Varies#	Varies^	Varies@

* The "/" separates two calcium contents, one is for low calcium content and the other is for standard calcium content
# Change with different mixing methods (1.5, 2.5, 3.9%)
^ Change with different mixing methods (2.62, 2.7, 2.76 mEq/L)
@ Change with different mixing methods (356, 408, 482 mosmol/L)
There are three compartments - A, B & C. The two smaller compartments (A and B, B is of larger volume) each contains 50% glucose solution and sodium chloride and a larger third compartment (C) contains the electrolyte solution. After breaking the frangible pin between compartments A and C and thoroughly mixing the two fluids a PD fluid containing 1.5% glucose (2.76 mEq/L calcium, 356 mosmol/L) will be produced. Similarly mixing the contents of compartments B and C will produce a PD fluid containing 2.5%glucose (2.7 mEq/L calcium, 408 mosmol/L). Finally by breaking both frangible pins and mixing the contents of all three compartments will produce a solution containing 3.9% glucose (2.62 mEq/L calcium, 482 mosmol/L).
(Reference: Product information of Gambrosol trio)

** Caramelization is defined as the thermal degradation of sugars leading to the formation of volatiles (caramel aroma) and brown-colored products (caramel colors). The process is acid or base catalyzed and generally requires temperatures >120ºC at pH<3 or >9.*

NuTRIflex® Lipid



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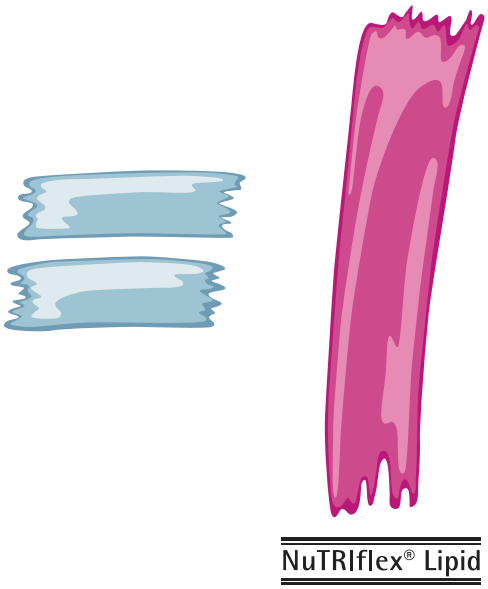

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PD entails a closed system, in which fluid is initially instilled by gravity into the peritoneal cavity and then drained out after several hours. The basic PD system consists of a collapsible plastic bag containing 1 L to 6 L PD fluid, a transfer set, a Tenckhoff catheter or other catheter. Different brands contain different devices to serve various purposes. One of the major purposes is to reduce the risk of PD-associated peritonitis. The Spike of Baxter® is the most common form of device. It consists of a rigid pointed hollow plastic tube. The point of entry of the spike to the bag of dialysis fluid is protected by a barrier consisting of two small sponges soaked in povidone iodine. On the other hand, the Safe Lock system (Figure 2) of Fresenius® is a luer lock system with sprayed antiseptic preparation consisting of an alcoholic solution containing phenol. For Gambro, the luer lock system is a protective povidone iodine laden clam shell[10].

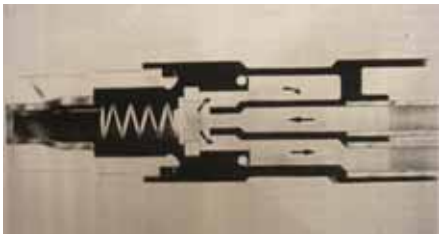

Figure 2. "5F" Safety lock connector

The more recent concept is the 'Y' system (Figure 3). This Y or disconnect systems free the patient from carrying the empty fluid bag during the long dwell period. This system was first described in Italy. The dialysis fluid transfer set may be formed into a 'Y' shape, to which a full bag and an empty bag are placed at either end of the upper limbs of the 'Y' while the lower limb of the 'Y' is connected to the patient via a connector. This concept (flush & fill, see Figure 4) is that the delivery of fluid into the patient is preceded by running out spent dialysate into a waiting empty bag, carrying with it any contaminating bacteria introduced by 'touch' contamination of the connection. The Baxter® Ultra bag and Fresenius® Andy Disc are variations of the 'Y' system. This system has resulted in reduction in the frequency of peritonitis compared to standard CAPD[10].

Gambrosol trio is filled in a three-compartment bag. The two smaller compartments each contains 50% glucose solution and sodium chloride and a larger third compartment contains the electrolyte solution. By breaking the frangible pin between different compartments, glucose of different concentrations can be produced. The manufacture and storage of conventional PD fluids leads to the formation of cytotoxic glucose degradation products (GDPs) or advanced glycation end products (AGEs)[15,16]. The GDPs will damage the peritoneum and decrease its capacity to perform ultrafiltration. The Gambrosol trio 3-compartment bag separates the components and reduces the formation of GDPs and AGEs; thus improving the biocompatibility of the solution so that patients can remain on PD for longer. It is also convenient for prescribers since the concentration of the osmotic agent can be adjusted by the 3-compartment system.

Figure 3. "Y" Set

From table 2, there are 3 different osmotic agents - glucose, icodextrin and amino acids. Glucose is the most common out of the three. Related problems include hyperglycemia, hyperinsulinemia[17] and formation of GDPs. Hyperlipidemic effect was also demonstrated in several studies. These effects were attributed to the continuous peritoneal absorption of glucose. Given these backgrounds, icodextrin and amino acids have been suggested as alternatives to glucose as osmotic agents. Extraneal of Baxter® contains icodextrin 7.5%. Icodextrin is a glucose polymer which is a mixture of polysaccharides consisting of linked glucose residues of varying chain length obtained by the hydrolysis of corn starch. Some experts queried the use of icodextrin as some trials found accumulation of poorly metabolisable polymers in the body[18] although some trials showed that a 8% glucose polymer solution was comparable to the 4.25% glucose solution in terms of ultrafiltration[19]. One important concern with the use of icodextrin is allergic reaction. Up to 15% of patients on icodextrin may experience skin reactions, which may be serious in about one-third of cases[20].

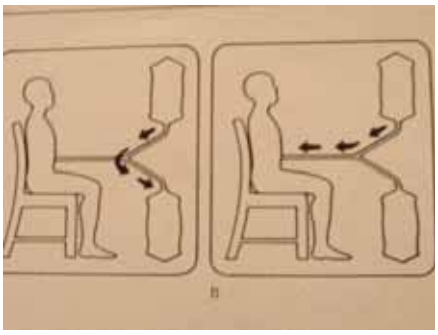

Figure 4. Flush & fill concept

The Nutrineal of Baxter® contains amino acids as the osmotic agent. It has several advantages over the conventional PD fluids that use glucose as the osmotic agent. The absence of glucose improves blood glucose control in diabetic patients and the pH is more physiological. Moreover, on nutritional side, the use of amino acid dialysate has been shown to improve the nutritional status of malnourished CAPD patients[21]. In terms of ultrafiltration, Amino acid 1.1% has similar osmolarity as 1.5% of glucose. In a trial, a 2% amino acid-based solution induced equivalent amounts of ultrafiltration and removal of urea, creatinine and potassium compared to a 4.25% glucose solution over a 6-hour dwell time[22].

VII ADVANTAGES AND DISADVANTAGES OF PERITONEAL DIALYSIS

The main advantage of PD is that it is relatively simple to teach, so patients can quickly be established on home dialytic therapy. Unlike hemodialysis, PD usually does not require specific and complex equipment, and the therapy results in continuous steady-state biochemical and fluid status, therefore it can avoid the fluctuation of intermittent haemodialysis[23]. The cost of PD is lower, for example, the cost of CAPD is at least 25% lower than that that for in-hospital haemodialysis[24]. Moreover, patients experience better with PD. In a trial with 736 patients, patients receiving PD rated their care higher than those receiving haemodialysis[25].

The main disadvantage is related to infections, mechanical and metabolic complications inherent in the technique, and a higher rate of technique failure and the need to transfer to haemodialysis[26].

VIII FUTURE OF PERITONEAL DIALYSIS

There has been a huge expansion in both the clinical and research areas of PD over the past 20 years. The technique is now used worldwide, mainly in the form of CAPD, but the use of APD is increasing. Dialysis, drug treatment and dietary considerations are the three main components of the management of patients with end stage renal disease. The implementation of clinical practice guidelines (CPGs) to guide rational treatment of patients is a relatively new concept[27]. In 1997, the National Kidney Foundation instituted the Dialysis Outcomes Quality Initiative (DOQI) and commenced the development of CPGs to guide the practice of dialysis therapy. Prevention of PD-associated peritonitis is also a major issue. It is hoped that the advance in technology will continue to improve the treatment outcomes and patients' quality of life and reduce the cost of treatment.

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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!

Questions for Pharmacy Central Continuing Education Committee Program

2 CE Units

Peritoneal Dialysis - Principles and Related Practical Issues

1. Which of the following statements concerning end stage renal failure (ESRD) is false?

A. The global prevalence of ESRD is on rising trend.
B. Dialysis and transplantation are the two treatments available for the management of patients with ESRD.
C. ESRD may be associated with hypertension or heart failure.
D. It is a term used to cover the continuum of kidney dysfunction from early to late-stage disease.
E. Both drugs and dialysis are essential to manage fluid and electrolyte abnormalities in ESRD patients.

2. Which component listed below is not a factor affecting the ultrafiltration of a peritoneal dialysis system?

A. Peritoneal blood flow
B. Flow rate of peritoneal dialysis fluid
C. The system connecting the dialysis bag and the peritoneum
D. Volume of peritoneal dialysis fluid
E. Vascularity of peritoneal membrane

3. What is the major difference between Continuous Ambulatory Peritoneal Dialysis (CAPD) and Automated Peritoneal Dialysis (APD)?

A. APD can be further divided into 3 types of dialysis.
B. They use different peritoneal dialysis fluids.
C. The abdomen is filled with dialysate overnight for CAPD which is not the case for APD
D. They are used according to different degree of severity.
E. APD employs a mechanical device to assist in the delivery and drainage of the dialysate while the dialysate is drained into the abdomen by gravity in CAPD.

4. Which electrolyte listed below has to be replenished in an ESRD patient?

A. Sodium
B. Magnesium
C. Potassium
D. Chloride
E. Lactate

5. Why is the pH of the PD fluid much lower than the physiological pH?

A. For management of electrolyte balance
B. Due to the presence of lactate as a buffer
C. For maintaining the stability of the components
D. For correcting metabolic acidosis of the patient
E. For increasing production of bicarbonate ions in patient's body

6. Which of the followings are the osmotic agents being used in the commercially available peritoneal dialysis fluids?

i. Glucose
ii. Amino Acids
iii. Propylene glycol
iv. Icodextrin
v. Povidone iodine

A. i & ii
B. ii & iii
C. i, ii & iii
D. i, ii & iv
E. All of the above

7. Which of the following(s) is/are method(s) used by different brands of peritoneal dialysis fluids to reduce the risk of peritoneal dialysis associated peritonitis?

A. A 3-compartment system
B. A protective povidone iodine laden clam shell
C. A 'Y' system
D. b & c
E. None of the above

8. Which statement below is incorrect concerning the 3-compartment system in Gambrosol trio?

A. To prevent caramelization of glucose during the heat sterilization process
B. To reduce the production of cytotoxic glucose degradation products
C. To improve the bioavailability of peritoneal solution
D. To produce different concentrations of osmotic agent
E. To produce different volumes of peritoneal solution

9. What of the followings is true about the Nutrineal of Baxter®?

A. It contains icodextrin 7.5%.
B. A 1.1% amino acid solution has a similar ultrafiltration capacity as a 4.25% glucose solution.
C. It can be used to improve the nutritional status of malnourished CAPD patients.
D. Glucose and amino acids are combined to produce the desired osmotic effects.
E. The occurrence of allergic reaction is a major limitation associated with the use of Nutrineal.

10. Which is not an advantage of peritoneal dialysis?

A. Peritoneal dialysis does not require specific and complex equipment.
B. Patient can be established on home dialytic therapy.
C. The cost of peritoneal dialysis is lower.
D. Peritoneal dialysis can avoid the fluctuation of intermittent haemodialysis.
E. None of the above

Answers will be released in the next issue of HKPJ.

Answers for the past issue (Oct-Dec2004)

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1)B 2)A 3)D 4)C 5)E 6)C 7)B 8)A 9)E 10)C

Therapies for Chronic Hepatitis B Virus Infection

Hui, Chee-kin; Lau, George KK

I INTRODUCTION

Hepatitis B virus (HBV) infection is one of the most common viral infections in humans. Approximately 2 billion people have been infected with HBV and 350 million of them became chronically infected. Among them, around 25-40% will eventually die of liver disease (viz. cirrhosis with or without hepatocellular carcinoma); the death rate being 50% for males and 15% for females[1]. The ultimate goals of treatment are to achieve e-seroconversion in chronic hepatitis B e-antigen positive patients, sustained suppression of HBV replication, and remission of liver disease. The agents currently available for the treatment of chronic HBV infection are divided into 2 main groups. The immuno-modulators, which include interferon-α, thymosin α1 and nucleoside analogues, among which lamivudine, adefovir dipivoxil and famciclovir are the most well known. At present, however, only interferon, lamivudine and adefovir monotherapy have been approved for the treatment of chronic HBV infection. The immunomodulators act by promoting cytotoxic T cell activity for lysis of infected hepatocytes and by stimulating cytokine production for control of viral replication. Nucleoside analogues, on the other hand, act by suppressing HBV replication at the level of DNA synthesis, and in addition there is evidence that they may enhance immune clearance of hepatocytes.

However, not all patients with chronic hepatitis B infection respond to these treatments. With the future introduction of new anti-viral, such as entecavir, clevudine, telbivudine, tenofovir, pegylated interferon and others, one would anticipate more clinical trials be conducted to investigate the effectiveness of the use of these agents, either as monotherapy or combination therapy with approved agents. The rest of this review will focus on emerging new therapies for chronic HBV infection.

II INTERFERON

Interferon-α2b is the first drug to be approved by the US Food and Drug Administration for treatment of chronic HBV infection followed by lamivudine and most recently adefovir. However, the efficacy of interferon, defined as sustained loss of HBeAg and HBV DNA, is limited. In a meta-analysis of 15 randomized, controlled trials, loss of HBeAg and HBV DNA in HBeAg positive patients is seen in 33% and 37% on interferon-treated patients compared to 12% and 17% of untreated patients, respectively [2]. In Caucasians, the long-term durability of HBeAg is as high as 90%, while around 20-70% of patients with loss of HBeAg and anti-HBe seroconversion will eventually lose HBsAg [3,4]. While in those with detectable HBV DNA after HBeAg seroconversion, the HBV DNA will be undetectable in 60-100% of those who lose hepatitis B surface antigen (HBsAg). In HBeAg negative variants (precore mutants and others), prolonged interferon at a dose of 3-5 MU thrice weekly for at least 12 months results in a sustained biochemical remission in 15-25% of patients [5,6]. Factors that predict a favorable response to interferon include low pretreatment level of HBV DNA (<200 pg/ml), high levels of serum aminotransaminase (>100 U/L), and evidence of necroinflammatory activities in the liver [7]. In contrast, male sex, length of chronic state, Asian origin, precore mutants, and human immunodeficiency virus (HIV) co-infection are factors associated with poor response to interferon [8]. In a recent study from Taiwan, patients with genotype B were more likely to respond to interferon than those with genotype C [9]. However, recent data suggest that spontaneous seroconversion is also greater with genotype B [10].

The rate of achieving HBeAg seroconversion in Asian patients has been low [12]. This difference between Asian and Caucasian patients is thought to be related to the duration of the chronic state. While HBV is acquired by Asians perinatally, Caucasians acquire HBV predominantly in their adolescent or adulthood. In perinatally acquired infection, infection is followed by a lengthy period of immune tolerance during which the HBV DNA is high while the serum ALT levels are normal or near normal and liver necroinflammation is minimal [12,13,14]. Whereas in the latter, there is more active host immune response directed towards clearance of the infection with raised ALT levels [15].

III PEGYLATED INTERFERON-α

Pegylated-IFN-α-2a and pegylated-IFN-α-2b joins a growing number of therapeutic agents that are pegylated by incorporation of a polyethylene glycol (PEG) moiety into the active product. Pegylated-IFN-α-2a is the only pegylated interferon that has recently been approved for treatment of chronic hepatitis B in Hong Kong. Pegylation of the IFN-α molecule is undertaken primarily to enhance the pharmacokinetic properties of unmodified IFN-α, which enables once a week dosing. Pegylated-IFN-α enables sustained absorption, limited volume of distribution and a prolonged half-life compared with unmodified IFN-α. Most adverse events related to PEG-IFN-α were those commonly associated with interferon-based treatment, such as flu-like symptom, headache, myalgia and fatigue. In the search for improved therapies for chronic HBV infection, phase III clinical trials on pegylated interferon-α-2a have recently been completed.

Two randomized, prospective study comparing the use of pegylated interferon α-2a vs. combination pegylated interferon α-2a and lamivudine vs. lamivudine monotherapy alone in 814 hepatitis B e antigen (HBeAg) positive and 537 HBeAg negative chronic HBV patients have convincingly shown the superiority of pegylated interferon α-2a over lamivudine in the treatment of chronic HBV infection [37,38]. In both studies, the majority of recruits were Asian (87% and 60% in HBeAg-positive and HBeAg-negative studies respectively) [37,38] and a higher response rate can be achieved with pegylated interferon α-2a monotherapy or combination therapy than with lamivudine monotherapy in both HBeAg positive (Table 1) and HBeAg negative patients (Table 2). This response is sustained for 24 weeks after cessation of therapy and the addition of lamivudine, however, did not improve the response rate. HBsAg seroconversion occurred in a significantly higher proportion of patients treated with pegylated interferon α-2a with or without lamivudine than with lamivudine alone. No unexpected adverse events were reported and most were mild in nature. Serious adverse events and withdrawals for safety reasons were low across the treatment groups (2-6%).

In another study on 100 HBeAg

Table 1. Outcome of peginterferon alfa-2a on hepatitis B e antigen positive patients at week 72.

Endpoints	Peginterferon alfa-2a (n=271)	Peginterferon + lamivudine (n=271)	Lamivudine (n=272)
Co-primary endpoints			
HBeAg seroconversion	32% (p<0.01)*	27% (p=0.023)*	19%
HBV DNA < 100,000 copies/ml	32% (p=0.012)*	34% (p=0.003)*	22%
Secondary endpoints			
HBeAg loss	34% (p<0.001)*	28% (p=0.043)*	21%
ALT normalization	41% (p=0.002)*	39% (p=0.006)*	28%

Note:
HBeAg = Hepatitis e antigen
ALT = alanine transaminase.
**compared with lamivudine therapy*

positive chronic hepatitis B patients comparing the use of staggered combination pegylated-IFN-α-2b for 32 weeks plus lamivudine for 52 weeks versus lamivudine monotherapy for 52 weeks, the sustained virologic response with combination therapy was 36% and 14% for lamivudine monotherapy [39].

These 3 studies demonstrated the superior efficacy of pegylated-IFN over lamivudine as a treatment option for chronic HBV.

IV NUCLEOS(T)IDE ANALOGUES

Lamivudine, the (-) enantiomer of the deoxycytidine analogue 2'-deoxy-3'-thiacytidine, competitively inhibits viral reverse transcriptase and terminates proviral chain DNA viral extension [16,17]. Because of its mode of action, lamivudine is equally effective in Asians and Caucasians. Lamivudine can induce a rapid 2-3 log decrease in serum HBV DNA levels in patients with chronic HBV [18].

Several randomized trials in HBeAg-positive patients demonstrated that a one-year course of lamivudine can induce HBeAg seroconversion in 16-18% of the patients [19,20,21]. It was able to decrease the serum HBV DNA levels to undetectable levels in about 93% to 100% of patients. However, after the discontinuation of therapy, HBV DNA reappeared in most patients, therefore, resulting in a prolonged duration of treatment with lamivudine. The most important predictor of a favourable response following lamivudine treatment is a high pretreatment ALT level with the rate of HBeAg seroconversion being 2% in those with normal ALT as compared to 47% in those with ALT levels five times the upper limit of normal (ULN) [22].

The sustained seroconversion rate of HBeAg to anti-HBe increased during the second year of treatment, from 17% to 27% [23]. The durability of HBeAg seroconversion in patients receiving 3 to 4 years of lamivudine range from 38% and 73% [24,25]. On the other hand, a mean duration of treatment of 9.3 months showed cumulative relapse rates of 37.5% at one year and 49.2% at two years [26]. A sustained virological and biochemical response was maintained in 11-20% with a relapse rate of 48% after six months of follow-up rising to 74% by 12 months [27,28,29].

Unlike interferon, lamivudine can also suppress HBV replication in patients with precore mutants [30]. The initial response in these patients to lamivudine is similar to those reported in HBeAg positive patients. Biochemical and virological response was seen in 60-70% of patients after 52 weeks of treatment but 90% of these patients relapsed after lamivudine was discontinued.

One major drawback of lamivudine treatment is the development of drug resistant HBV after 6 to 9 months of treatment. The lamivudine-resistant viruses have a characteristic amino acid substitution in the tyrosine-methionine-aspartate-aspartate (YMDD)-motif of the RNA-dependent DNA polymerase [31,32]. The methionine at codon 204 is either replaced by an isoleucine (rtM204I) or by a valine (rtM204V). In addition, the rtM204V mutation is frequently accompanied by a leucine-180-to-methionine (rtL180M) substitution. The mutation at the YMDD motif of the polymerase gene is noted after the first 6 months of treatment. The risk of mutation increases with the duration of treatment. At the end of the first, second, third and fourth year of treatment, the incidences of resistance are: 15-32%, 38%, 56% and 67% respectively [33].

Adefovir dipivoxil or bis-pivaloyloxymethy-9 (2-phosphonyl-methoxyethyl) adenine (PMEA) is a phosphonate of an acyclic nucleotide analogue. The drug, unlike other nucleoside analogues, contains a phosphate group already and requires an additional phosphorylation step before it becomes active. This is preceded by the removal of the bis-pivaloyloxymethyl moiety. Adefovir dipivoxil other than acting as a DNA chain terminator, is also thought to stimulate natural killer cell activity and to induce endogenous interferon production [34]. Adefovir has been shown to inhibit the amplification of cccDNA although the *de novo* formation of cccDNA cannot be prevented in duck HBV-infected hepatocytes.

In Phase I/II studies, treatment with adefovir results in significant reduction of HBV DNA within 1-2 weeks. In a Phase III placebo-controlled trial, adefovir 10 mg daily given for 48 weeks in 172 patients was associated with significantly better histological improvement (53% vs 25%), a higher rate of HBeAg seroconversion (12% vs 6%), a three logarithmic reduction of HBV DNA levels and a higher chance of normalization of ALT levels (48% vs 16%) when compared with 170 patients receiving placebo [35]. Importantly, adefovir is also active against lamivudine-resistant YMDD mutants.

There were apparently no adefovir-resistant mutations observed up to 135 weeks of treatment. It is associated with much lower rate of resistance development (~6%) after 3 years of therapy. The low rate of resistance to adefovir may be related to the close resemblance of adefovir to its natural substrate and/or the flexible acyclic structure of the adefovir molecule allowing multiple binding modes. Both these conditions may subvert the steric hindrance between the mutant amino acid side chain and agents like lamivudine that account for drug resistance [36].

Severe renal toxicity has been observed in patients receiving higher doses (60-120 mg daily) of adefovir in trials for patients infected with human immunodeficiency virus (HIV). The renal toxicity is mediated through the human renal organic anion transporter 1 (hOAT1) and may result in proximal renal tubular dysfunction. To date, no clinical renal toxicity has been observed with the 10 mg daily dose. Furthermore, treatment with adefovir 10 mg daily for 144 weeks has been shown to increase

Table 2. Outcome of pegylated interferon alfa-2a on hepatitis B e antigen negative patients at week 72.

Endpoints	Peginterferon alfa-2a (n=177)	Peginterferon + lamivudine (n=179)	Lamivudine (n=181)
HBV DNA < 20,000 copies/ml	43% (p=0.007)*	44% (p=0.003)*	29%
ALT normalization	59% (p=0.004)*	60% (p=0.003)*	44%

Note:
HBeAg = Hepatitis e antigen
ALT = alanine transaminase.
**compared with lamivudine therapy*

HBeAg loss and seroconversion rates. A continued reduction in serum HBV DNA and ALT normalization can be observed as well [36].

Entecavir is a carbocyclic 2'-deoxyguanosine analogue with potent anti-hepadnaviral activity {1s-(1,3d,4β-2-amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6H-purin-6-one monohydrate}. In chronically infected woodchucks, treatment with entecavir resulted in a 2-3 $\log_{10}$ reduction in serum WHV-DNA, which rebounded on stopping treatment [40]. Similar results were obtained with the duck animal model [41]. Entecavir was shown to be well tolerated, with no evidence of resistant mutants in two groups of woodchucks maintained on the drug for 14 and 36 months, respectively; 50% of the animals from the first group (withdrawn from therapy) had a sustained antiviral response 28 months later, whereas in the group treated longer, two-thirds of the animals had DNA levels near the lower limit of detection for 2 years [42].

Phase III trials of 0.5 mg entecavir versus lamivudine showed a stronger suppression of HBV DNA levels with entecavir but similar HBeAg seroconversion rate between the two drugs. However, entecavir had a better resistance profile when compared to lamivudine with no evidence of entecavir resistance in nucleoside analogue naive patients and only a 6% incidence of entecavir resistance in lamivudine refractory patients after 48 weeks of entecavir therapy. Phenotypic resistance to entecavir required the presence of pre-existing lamivudine resistance mutation [43].

Telbivudine (β-L-2'-Deoxythymidine) is one of three L-nucleosides that specifically inhibit HBV replication. The other two members are β-L-2'-deoxycytidine and β-L-2'-deoxyadenosine [44]. The anti-HBV activities are conferred by the common hydroxyl group in the 3'-position of the β-L-2'-deoxyribose sugar of the molecules. β-L-2'-deoxythymidine has been demonstrated to have an eight logarithmic reduction in HBV DNA levels in woodchuck models. Phase I/II clinical trials with β-L-2'-deoxythymidine show a marked dose-proportional antiviral activities with 4 weeks of the 800 mg daily dose causing a 4 log reduction in median HBV DNA levels. No side effects have been observed. The lack of side effects may be related to the L-configuration of the molecule [45].

V COMBINATION THERAPY

To date, monotherapy for the treatment of HBV is still far from ideal, mainly because of the emergence of drug-resistant viruses. The future probably lies in combination therapy. There are at least three beneficial effects of using combination therapy. Different agents acting at different sites of the viral replication cycle may have additive or even synergic effects. The side effects of individual agents may be lessened if a lower dose can be used when combined with other agents. Finally, more effective viral suppression should minimize the risk of viral mutations.

The first approach is the combination of immunomodulation with viral suppression. The combination of IFN-α and lamivudine has been investigated in two multicentre trials for treatment-naive patients and for non-responders to previous IFN-α treatment [46,47]. However, the efficacy of this form of combination therapy is not significantly better than monotherapy with either agent alone. Even though pegylated IFN-α has been shown to be more efficacious than traditional IFN for hepatitis B, studies combining longer duration treatment of pegylated IFN-α-2a with lamivudine have not shown a significant increase in the rate of virologic response when compared with pegylated IFN-α-2a monotherapy alone [37,38].

The second approach to combination therapy is the combination of two or more nucleoside analogues as in the treatment of HIV. The ideal combination should be of two or more highly potent nucleoside analogues acting on different sites of the HBV replication cycle to achieve maximal viral suppression and to ensure effectiveness against any pre-existing drug-resistant mutant HBV. One such combination that has been shown to be effective in preliminary study is emtricitabine plus adefovir combination [48].

VI CONCLUSION

IFN-α or nucleoside analogue monotherapy treatments are effective in suppressing HBV replication, leading to HBeAg seroconversion, normalization of ALT levels, improvement in histology and in some cases even loss of HBsAg (Table 3). However, such favorable outcomes are attainable in only about a third of those treated, at the best of times. In spite of this, certain groups of patients have benefited tremendously from the use of nucleoside analogues, such as those with decompensated cirrhosis and chronic HBV patients undergoing liver transplantation, when there was little hope for them before.

The introduction of pegylated interferon α-2a offers significantly improved efficacy over both adefovir dipivoxil and lamivudine in terms of HBeAg seroconversion, HBsAg clearance and drug-resistant profile. The ability of pegylated interferon α-2a to sustain biochemical, virologic and HBsAg response rate is a major advance over the currently available therapies. The rate of sustained response after 1 year of therapy with pegylated interferon α-2a seems to be higher than with lamivudine or adefovir and can be achieved with a defined duration of therapy [49]. Pegylated interferon alfa-2a can be used as a first line therapy in the treatment of chronic HBV infected patients [49].

Patients who do not respond to monotherapy treatment protocols may benefit from combination therapies, as has been the case in HIV treatment. Drugs acting through different antiviral mechanisms may supplement each other, by additive or synergic effects. If successful, these may reduce the duration and cost of treatment, lessen the impact of side-effects, and more importantly prevent the emergence of drug-resistant variants of the virus. Combination therapies in Phase II and III clinical studies at the moment will hopefully prove successful and lead to the selection of the optimum cocktail of drugs and duration of treatment.

Remark: ***Dr. CK Hui*** has no conflict of interest. Dr. George Lau is an investigator for Roche Pharmaceuticals.

Table 3. Summary of antiviral results with nucleoside analogue.

48 Weeks results	Lamivudine 100 mg/day	Emtricitabine 200 mg/day	Adefovir 10 mg/day	Emtricitabine 200 mg/day + adefovir 10 mg/day	Telbivudine 200 mg/day	Entecavir 0.5 mg/day
Histologic improvement (%)	62	62	53	-	-	72
Median change in HBV DNA from baseline, $\log_{10}$ copies/ml	-5.5	-3.2	-3.5	-5.3	-6.4	-7.0
HBV DNA < 400 copies/ml (%)	38	56	21	79		69
HBeAg seroconversion (%)	18	12	12	14	25*	21
Resistance	14	12	0	0		0

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Computational Methods and Tools of Molecular Docking for Rational Design and Discovery of Drug

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Virtual screening is a new approach in the pharmaceutical industry as a cost-cutting and effective technology for searching for novel lead compounds. The binding of small molecule ligands to large protein targets is central to numerous biological processes. The accurate prediction of the binding modes between the ligands and a protein, the docking problem, however, is of fundamental importance in modern structure-based drug design. Here, the principle of docking is reviewed. Various algorithms employed in searching and evaluating the binding mode of small molecules are described. After a summery of some popular docking softwares, such as DOCK, AutoDock, GOLD and so on, several applications of these softwares are outlined.

I INTRODUCTION

The process of drug discovery consists of seven steps: disease selection, target hypothesis, lead compound identification (screening), lead optimization, pre-clinical trial, clinical trial, and pharmacogenomic optimization. Traditionally, these seven steps are carried out sequentially, meaning one step after another [(1)]. The entire progress from step 1 to step 7 for traditional development of a new drug takes between 10 to 16 years and costs an average of US$500 - 800 billion. Previously, the main bottlenecks for new drug design were the cost and time of finding and testing new chemical entities (NCE). The average cost of creating a NCE in major pharmaceutical companies was estimated to be about US$7,500 m per compound [(2)]. The increasing economic pressure on pharmaceutical industry to discover better therapeutic agents in a faster and more efficient way has led to the development of new methods aiming to discover new lead compounds. Efforts have been made and led to innovative approaches in new drug design, such as combinatorial chemistry [(3)] and virtual screening [(4)]. Virtual screening as illustrated in Figure 1 is the use of a high-performance computer to analyse large number of chemical compounds in order to identify possible drug candidates, and it is a technology that complements the advance of high throughput chemical synthesis and biological assay. Several reviews on virtual screening for the design of new drugs have already been published [(5-7)].

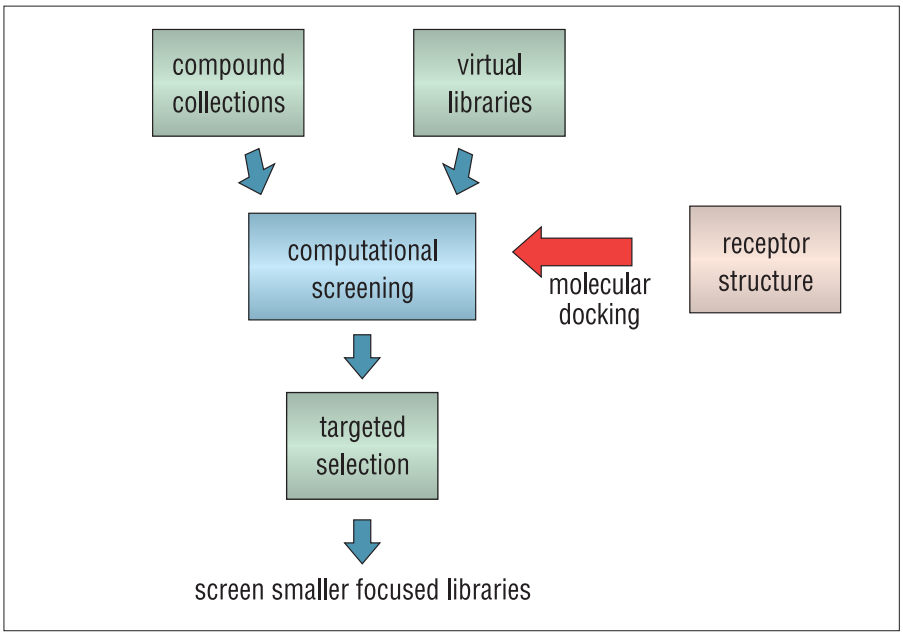

Figure 1. Roles of computation in drug discovery.

The virtual screening and other new technologies have led to many breakthroughs in drug design [(5)]. Its' key approach is by means of docking a small molecule to the binding site of a protein. There is a lot of software that can carry out the docking calculation and predicting the orientation of a drug molecule.

II PRINCIPLE OF MOLECULAR DOCKING

Since it was pioneered during the early 1980s [(8)], molecular docking has become a highly active area of research [(4)]. Molecular docking can be defined as the prediction of the structure of receptor-ligand complexes, where the receptor is usually a protein and the ligand is a small molecule or another protein. It is the process by which two molecules fit together in 3D space. In general, the aims of docking studies include [(1)] accurate structural modeling and [(2)] correct prediction of activity [(9)].

For the interaction between an enzyme and an inhibitor, a docking study aims at predicting the structural

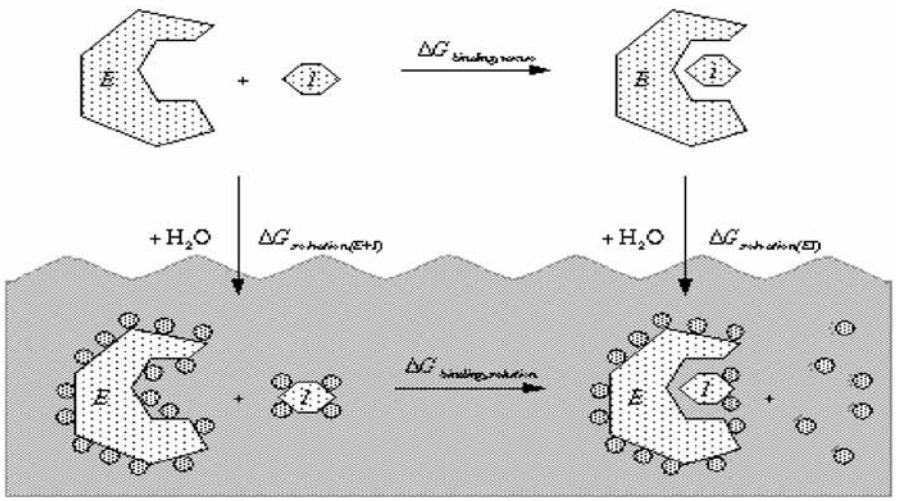

Figure 2. Thermodynamic cycle of the binding of an enzyme and an inhibitor in solvated phase and in vacuo. E = enzyme, I = inhibitor.

changes after the enzyme and inhibitor come across to form a complex under the equilibrium conditions. Figure 2 shows the thermodynamic cycle for the binding of an enzyme, *E* and an inhibitor, *I*, in both the solvated phase and *in vacuo* [10]. Note the solvent molecules are indicated by filled circles: they tend to be ordered around the larger molecules, but when *E* and *I* bind, several solvent molecules are liberated and become disordered. This is an entropic effect and is the basis of the hydrophobic effect. The solvent ordering around *E* and *I*, when both bound and unbound, is strongly influenced by the hydrogen bonding between these molecules. These hydrogen bonds between solvent and *E*, and solvent and *I*, contribute enthalpic stabilization, and is something that can be estimated from free energy function.

According to Hess's law of heat summation, the change in free energy between two states will be the same, no matter what the path. Hence, the free energy of binding in solvent could be calculated by the following equation:

$$G_{binding,solution} = G_{binding,vacuo} + G_{solvation(EI)} - G_{solvation(E+I)}$$

Since we can calculate $G_{binding,vacuo}$ from the docking simulation, and can estimate the free energy change upon solvation for the separate molecules *E* and *I*, and for the complex, *EI* , $G_{solvation(EI)}$ and $G_{solvation(E+I)}$ respectively, then it is also possible to calculate the free energy change upon binding of the inhibitor to the enzyme in solution, $G_{binding,solv}$. Thus, we can estimate the inhibition constant, K_i, for the inhibitor, *I*. To predict the structure of the enzyme and inhibitor complex does not require any information about the K_i. However, to predict the binding affinity of enzyme and inhibitor requires the value of K_i.

III IDENTIFYING A BINDING SITE

Identification of the molecular features that are responsible for special molecular recognition is very complex and even more complicated for simulation on a computer. Kuntz *et al* divided the docking problem into three basic subproblems [11]. The first one is finding a useful way for representing molecules and molecular features. The second is that docking requires methods for the juxtaposition of ligand and protein for generating orientations. The last one is to find the scheme for evaluation of the complementary parts. Although the problem is divided, the subproblems are still complex issues. In order to make the docking problem tractable, different simplifications have been employed in different docking software. Whatever the simplification used for docking and whatever the nature of the bonding partners, certain problems must be explored by docking method, and some features are common to all procedures. In the simplest form, they may be summarized as "searching or docking and scoring". Therefore, docking software can be separated functionally into roughly two parts: docking and scoring. These two parts are somewhat independent of each other. The docking part is the routines which determine the orientation of small molecule (drug candidate or ligand) relative to the protein molecule (receptor). The scoring part is the routines which evaluates (scores) a ligand orientation.

IV DOCKING ALGORITHM AND SCORING

i) Searching algorithm

Determining the correct binding mode of a molecule means finding the correct orientation and the conformation of the docked molecule because most ligand molecules are flexible. The inclusion of the flexibility is an important issue in docking, because the lock-and-key-type binding between rigid bodies is not sufficient enough for describe all the aspects of the interaction of ligand and receptor and significant conformational changes may occur on binding. A number of different algorithms have been developed to treat the flexibility of the ligand, which can be divided into three basic types of searches [12]: systematic, random or stochastic, and deterministic searches. Systematic search algorithms try to explore all the degrees of freedom in a ligand molecule. That means each formal degree of freedom is explored in a combinatorial fashion during the search. As the number of degrees of freedom increase, the number of evaluations needs to increase more rapidly. Therefore, termination criteria are inserted into the algorithm to avoid searching unnecessary conformational space. An example of a systematic search is an incremental construction algorithm. This algorithm can be carried out in different ways. One popular method is docking different molecular fragments into the active site region and then linking them covalently. An alternative way is anchor-first-search in which the ligand is divided into rigid (anchor) and flexible parts (side chains). Once the anchor is identified, it is fitted into the active site firstly. Next, the side chains are added in an incremental fashion [13-15]. Stochastic algorithms operate by making random changes to each of the degrees of freedom. Two popular examples of stochastic algorithms are Monte Carlo methods [16,17] and evolutionary algorithms [18-20]. In the deterministic searches the initial state determines the changes that are made to generate the next state whose energy is no more than that of the initial state. The final state converges at the minimum of the energy surface. A problem with the deterministic algorithms is that they are often unable to cross high energy barriers within feasible simulation time periods and therefore the final state may reach the local but not the global minimum of the energy surface. To deal with this problem, different approaches are

Table 1. Flexible ligand search algorithms		
Systematic	**Stochastic**	**Deterministic**
DOCK [22,23]	AutoDock [16]	DOCK
FlexX [24]	MOE-Dock [30]	Glide
Glide [28]	GOLD [27]	AutoDock
Hammerhead[29]		Hammerhead
FLOG [25]		MOE-Dock

developed to increase the ability to cross the barriers or decrease the height of the energy barriers. Examples of deterministic search algorithms are energy minimization methods and molecular dynamic simulations. The systematical search algorithms are used by DOCK [21-23], FlexX [24], FLOG [25] and other software, and the stochastic algorithms are employed by AutoDock [16] and GOLD [27]. The summary of the ligand flexibility algorithms is listed in Table 1.

ii) Scoring function

Generating a broad range of binding modes is ineffective if there is no accurate and efficient model to rank each conformation. Scoring involves evaluating the fit for the docking molecules from the database, and ranking them accordingly. Ideal scoring should be able to distinguish the experimental binding modes from all other modes explored through the searching algorithms. However, estimating binding free energies accurately, which is the role of scoring function, is a time-consuming process. The rigorous scoring function, such as free-energy simulation [33,34], should usually be computationally expensive without reducing its complexity. The need for a simple, yet acute, scoring function for docking research has led to a number of different functions which can be divided into three groups; namely, molecular mechanics (MM) force fields, empirical free energy and knowledge based functions. The popular examples of MM force fields scoring function are AMBER [35], OPLS [36], and CHARMM [37]. Both MM force fields and empirical schemes are based on physical interaction terms, such as Coulomb, van der Waals and hydrogen bonding terms. In empirical scoring functions each term is multiplied with a coefficient and the products are summed to give the final score. Different with the empirical function, the MM methods use the terms that are directly derived from physical chemical theory. The knowledge based scoring functions are derived using statistics for the observed frequencies of atom-atom interactions in known structure of protein-ligand complexes. Examples of these scoring functions are DrugScore [38] and potential of mean force (PMF) [39-41].

For a comprehensive overview of searching algorithms and scoring functions in docking, the reader can refer to several recent reviews [31, 32].

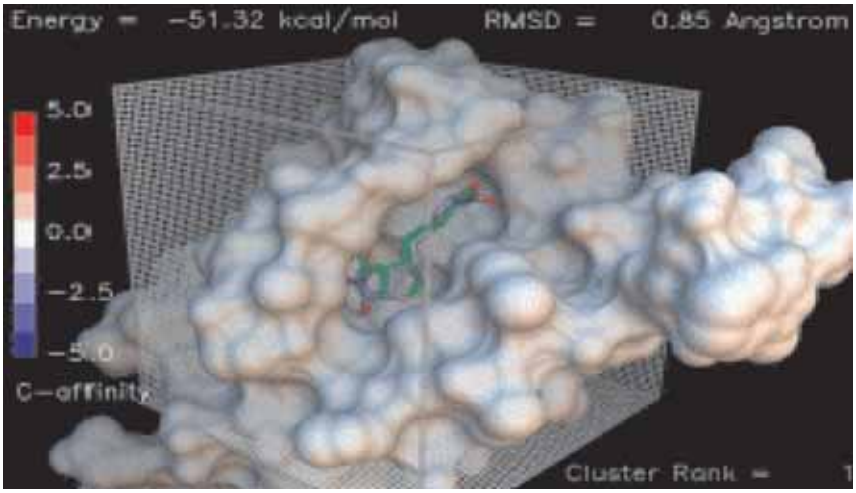

Figure 3. 3-D illustration of Biotin binding to Streptavidin. This 3-D diagram shows the ligand biotin and its final docked conformations after 100 AutoDock dockings to streptavidin. The order of conformations in this animation is from lowest energy to highest. The crystal structure conformation of biotin is shown in green. Note the beautiful, elongated binding cleft. To give an idea of scale, the sides of the grid shown in the background are 22.875 A long [47].

In the following, only two popular docking softwares, i.e. DOCK and AutoDock will be introduced.

V MOLECULAR DOCKING SOFTWARE

Three-dimensional molecular structure is one of the foundations of structure-based drug design. Often, data are available for the shape of a protein and a drug separately, but not for the two together. With the steady increase in readily available computer power, computational tools have come to play an important role in the field of drug discovery. DOCK is perhaps the most common program employed in pharmaceutical research [8]. The program DOCK searches the geometrically allowed binding mode of ligand and receptor according to the following steps. Firstly, it generates sets of spheres to represent the active sites in the cavity of the receptor. Next, the program searches the conformation and orientation of the ligand and matches them into the sphere sets. Finally, it scores the conformation and orientation data. Originally, the early version of DOCK treated both the receptor and ligand as rigid bodies. However, the recent versions of DOCK (version 4.0 [23] and 5) include the flexibility of the ligand using a modified scoring function which is a forced field based score and includes a term for the intra-molecular potential of the ligand. The searching algorithms have been reviewed by Ewing *et al* [22]. DOCK 5 uses the same searching algorithms and scoring functions as the DOCK 4.0. The extension of DOCK 5 is the inclusion of the generalized-Born GB/SA [43] continuum model into scoring function [44].

The DOCK program is able to investigate not only a single ligand molecule but also a database of ligands, and therefore it is favorable for high throughput virtual screening. On the other hand, the accurate scoring functions that are usually time consuming, are not fitted for the database searching mode. The successful application of DOCK has been demonstrated by the discovery of several novel enzyme inhibitors. Unfortunately, these inhibitions are only effective at micromolar concentrations [45,46].

The program AutoDock was originally written in FORTRAN-77 in 1990 by David S. Goodsell in Arthur J. Olson's laboratory in Research Institute

of Scripps Clinic, CA [26,47]. It was designed to perform automated docking of ligands (small molecules like a candidate drug) to their macromolecular targets (usually proteins, sometimes DNA, Figure 3). The original AutoDock supported only one search method [26], although version 3.0 [19] now has several search methods. A new search method contained in AutoDock 3.0 is a hybrid one that implements an adaptive global optimizer with local search. In this implementation of AutoDock the ligand is flexible and the receptor is rigid and is represented as a grid. In the AutoGrid procedure the energy of interaction of probe atom and protein at each grid point is calculated and assigned to the point. The rapid energy evaluation is achieved by precalculating atomic affinity potentials for each atom type in the substrate molecule in the manner described by Goodford [42]. Both DOCK and AutoDock implemented scoring functions use the Coulomb and van der Vaals terms of force field functions.

The main purpose of AutoDock is to provide an automated procedure for predicting the interaction of ligands and receptors. Indeed, it can be a valuable tool in the x-ray structure determination process itself: given the electron density for a ligand, AutoDock can help to narrow the conformational possibilities and help identify a good structure. Compared with DOCK, the AutoDock is a relatively integral software package, because the whole simulation process can be done within the AutoDock package while the calculation of DOCK is unable to start without the support of some other software. Preparation for ligand and receptor molecules can not be done by DOCK itself.

Besides the two computational tools described above, there is other software available for molecular docking. A brief description of these software programs is shown in Table 2.

VI ADVANTAGES AND DISADVANTAGES OF COMPUTATIONAL SCREENING

Structure-based virtual screening by computer has a lot of advantages. It is an achievable and useful tool for drug discovery despite of its technical limitations. In the long run, it is cheaper and more rewarding. But like any other simulation methods and modeling techniques, virtual screening has to be confirmed by experimental work and studies.

VII TRENDS AND OUTLOOK

Exploit expanding computing resources to improve docking/scoring functions and to improve receptor representations. To meet this objective, development of better software is unavoidable. Routine data mining by computation would be a worthwhile exercise. Virtual screening of receptor-ligand complementarity for achieving good subset selection and to point towards better scoring functions will become the core of drug discovery and improvement. When better software becomes available, virtual screening will also be applied to the evaluation of potential compounds for their suitability to be used as drugs, screening of very large virtual libraries and routine screening across other macromolecules.

Table 2. Examples of software packages for molecular docking

Program	Particular Features
Dock	A pioneer-software of molecular docking. The latest version of Dock 5 includes rigid orienting of ligands to receptor spheres, AMBER energy scoring, GB/SA salvation scoring, contact scoring, interal non-bonded energy scoring, ligand flexibility. It supports ligands database searching mode. Free of charge for academic use.
AutoDock	On-line documention, examples, animations, references and useful parameters. A useful set of compilation instructions have been compiled and made available online. Only free of charge for academic purposes.
HotDock	A tool for interactive visualisation, teaching and communication of Molecular Docking behavior and concepts. It allows for the loading of 3D molecular structures and visually/interactively simulates a docking process, by means of a collision detection based on the structural properties of the loaded molecules. The program's focus is protein-ligand docking, but may also be used to simulate protein-protein docking as well.
IDock	NCSA's molecular Docking software initiative. The IDock code is an adaptation of the existing GROPE system, designed to run now on the ImmersaDesk high performance graphics workstation. The code allows for the display of ball and stick images and also Connolly surfaces. Recently incorporated into the famework has been the PHANToM force-feedback device from SensAble Technologies.
FlexX	A program for automatic prediction of receptor-ligand interactions developed by M. Rarey, B. Kramer, C. Lemmen, T. Lengauer, C. Hiller, F. Sonnenburg and M. Zimmermann. The program is suitable for suitable for docking small but completely flexible ligands (up to 30 rotatable bonds). Uses a heuristic energy function that provides energetic flexibility. The Web site provides some background, a user guide and a download facility.
AMMD	A fast docking program which uses FFT's to calculate the interaction energy between molecules without requiring cutoffs or other aphysical approximations. Dynama can treat ligand flexibility, and by approximating the partition function, it can include free energies of solvation and solvent exclusion effects in a screening calculation. In a nutshell: • Fast long range electrostatics and nonbonded terms. AMMP runs without cutoffs in times comparable to or better than an 8 Angstrom cutoff in other programs. • Stable, numerically accurate, molecular dynamics. AMMP is stable with difficult problems such as parallel stranded DNA. • Flexible choice of potential functions. In addition to standard formulations, AMMP has non-point charges, explicit Debye screening, accurate polarization models, non-harmonic bond and angle formulations, and coupled bond-angle terms available. • Calculates partial charges for new molecules. • Embedding and homotopy methods for rapid model building. • Self-contained, and can be embedded in other programs.
Glide	A speedy and easy use docking program for identifying ligand binding modes through Monte carlo sampling, predicting binding affinities with accurate scoring function. The program can be setup and visualized easily. Grid-based approach for evaluating nonbonded interactions between ligand and receptor. 'Fast-mode' library screening and automated docking are available.

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Pharmacy Central Continuing Education Committee (PCCC) Annual Report 2004

PCCC ACTIVITIES IN YEAR 2004

i) Committee meetings

There are 10 Committee Meetings held in Year 2004. The Committee consists of Executive Committee Officers and Committee Members in Year 2004 and is shown in panel 1.

ii) Seminars

Early in Year 2004, PCCC collaborated with the Hospital Authority and the 3 professional pharmacists bodies to hold seminars and workshops for pharmacists to gain necessary knowledge and skills to participate in the Public Private Partnership Program (4P) - Drug Compliance and Counseling Scheme (DCCS) to offer patient counseling service at the community sector. More than 300 registration forms had been received and there are more than 100 pharmacists who have successful completed the seminars and workshops. Table 1 is a list of the seminars held in Year 2004. All seminars are overwhelmingly booked and the number of attendants is more than 200 each time.

iii) Articles

A total of 10 CE articles have been issued in Year 2004.

iv) Website

Maintaining an effective and efficient communication channel with our members is always important. We have recently been constructing our website which is intended for online CE activities. The website with a domain name of pccchk.com will be officially opened in March 2005. Since the maintenance of a website is very demanding in both resources and manpower, a maintenance subcommittee has been formed to look after the website and the online CE activities particularly.

v) Survey

Several pharmacy professional organizations in Hong Kong have embarked on a proposal to require members of the respective professions to receive continuing professional development (CPD), with the ultimate objective of making CPD mandatory. At a recent meeting, the Pharmacy and Poisons Board has considered the subject again and would like to explore the need for CPD for the pharmacist profession. A working group within the Pharmacy and Poisons Board including the pharmacists board members was formed for this purpose. The Hong Kong Pharmacy Consortium (comprised of the heads of the 6 major pharmacy organizations in Hong Kong, namely, the Department of Health, the Hospital Authority, the School of Pharmacy of the Chinese University of Hong Kong, the Pharmaceutical Society of Hong Kong, the Practising Pharmacists Association of Hong Kong and the Society of Hospital Pharmacists of Hong Kong) also supported this direction to explore the need for CPD and recommended a survey to be carried out to obtain the opinion from the registered pharmacists in Hong Kong. The PCCC has been assigned with this task of conducting the survey.

This survey is conducted via questionnaire and the questionnaire consists of three parts. The first part is to collect the demographic data, the second part is to collect the views about the CPD requirement for pharmacy registration and the last part is to explore the views on the proposed plan of the implementation of CPD. This questionnaire has been sent out to all registered pharmacists and the results are being analyzed at the moment and the overall findings will be published in the Hong Kong Pharmaceutical Journal soon.

Panel 1. PCCC Executive Committee Officers and Committee Members in Year 2004

Chairman:	Dr. Warren TSANG	***CE Article Coordinators:***	Mr. So Ho CHUNG Dr. Ophelia YIN
Vice-Chairman:	Mr. Rowget YOUNG	***CE Seminar Coordinators:***	Dr. Benjamin LEE Mr. Charles LO Ms Charmaine CHAN
Honorary Secretary:	Dr. Mary Au YEUNG	***I.T. Officers:***	Mr. Chi Kit CHAN Mr. Dave YUEN
Honorary Treasurer:	Ms Dorothy CHIN	***Membership Coordinator:***	Ms Jaime CHU

Table 1. Seminars held in Yeaar 2004 by PCCC

Date	*Seminars*
31 Mar 2004	Drug selection principles for epilepsy
14 Apr 2004	Module I: Asthma seminar (4P)
19 Apr 2004	Module I: Hypertension seminar (4P)
26 Apr 2004	Module I: Diabetes mellitus seminar (4P)
24 Apr 2004	Workshops on asthma, hypertension and diabetes (4P)
20 May 2004	Module II: Experience sharing on interpersonal communication skills in HA (4P)
20 Jul 2004	Dementia and alzheimer's disease - aetiology, symptoms and treatment
24 Sep 2004	Attention deficit hyperactivity disorder
17 Nov 2004	An update on lamivudine, adefovir & new antiviral drugs
23 Nov 2004	1. The importance of bio-equivalence in drug selection 2. Does it matter how you lower blood pressure - insight from the LIFE study
6 Dec 2004	1. Updates on influenza vaccines 2. HA influenza vaccination program
15 Dec 2004	Common Illnesses in Children

The Pharmaceutical Society of Hong Kong President Report 2004

Kwong, Benjamin

December 11 2004

The Year 2004 is a year of uncertainty and changes. The society recovers from the SARS trauma and the economy only starts picking up at the beginning of the last quarter of 2004. We also witnessed the change of an era in the health care arena. With the new Secretary of Health, Welfare and Food being appointed, and the newly elected Health constituency Legislative Councillor elected, PSHK anticipates that another wave of changes is imminent.

The Pharmaceutical Society of Hong Kong took 2004 to be a year of consolidation. With the meticulous effort of the General Council, we maintain a healthy membership base to support the work and the direction of the PSHK. Our P & P Board members have worked hard and cohesively to nourish a suitable environment to make changes in our future professional development. We have initiated the review of the existing pre-registration requirements and standards. We also facilitate the awareness of our members on the issue of mandatory continuing professional education. Without losing the momentum, PSHK is actively pursuing down-regulating of prescription drugs or vice versa up-regulating OTC items to Part I poison classification.

PSHK further enhances the electronic tool to improve the mean of communication among members. We have upgraded the e-mail storage capacity for our members. We disseminate news to members via e-mail and our newsletter is published on our web site. We will continue promoting to members to use e-mail more regularly so that there is no break down on the communication between the General Council and the members.

With the imminent wind-up of the Old-aged home (OAH) project, PSHK has gained valuable experiences in planning the development of pharmaceutical care in OAH. PSHK will continue to explore any future opportunity to further develop and strengthen the pharmacist role in the OAH setting. This is an area of future development as by 2015, our old-aged group population will be increased exponentially.

This year we have strengthened our tide with the Police Force in matters relating to drug abuse. There is a trend in teenage drug abuse and expertise in this area is very much needed if we want our society to be healthy. Apart from the Police Force, we are doing our best to strengthen our relationship with all the various stakeholders in the health care setting.

PSHK promulgates the importance of standard and the necessity of it in our modern society. It can be a useful tool to assist our profession to develop further and better. It will increase the trust from the end-users on our services provided. It also pushes us to improve and increases our awareness of self-discipline. With the development trend is on primary health care in the coming years, PSHK should anticipate areas where pharmacists need to improve if we want to have resources, at least, in developing our role in the primary health care model. We may have to shift our paradigm from drug oriented to health oriented. We should not forget health should be viewed globally. We should not just concentrate on physical health. We need to address others as well, namely mental health, spiritual health, psychological health, environmental health and public health. Pharmacists have ample of opportunities in these areas. PSHK will continue to seek out opportunities in area where pharmacists could and are ready to involve.

Globalisation is coming and it will cause major changes to our societal structure and to profession's protectionism. If we do not equip ourselves and get ready to face this challenge, the profession will be endangered. Look around the world and you will see our counterparts are all taking measures one way or the other to prepare for the change.

I believe in the coming new PSHK Council members as they all will do their best to serve you and lead the profession to develop further and better.

I would like to take this opportunity to thank all the Council Members of the Year 2004 of their hard work and dedication to the PSHK. Without their support, I would not be able to lead the Society to meet our members' expectations.

Be ACTIVE and SHARE with us your vision.

Benjamin Kwong
President, The PSHK

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General Council members of Pharmaceutical Society of Hong Kong 2005

President:	Mr. Benjamin Kwong	***Other GC members:***	Mr. Rico Yau
Vice President:	Mr. Warren Tsang		Mr. Ken Hau
Hon. Treasurer:	Mr. John Lau		Mr. Henry Lau
Hon. Secretary:	Ms. Ritchie Kwok		Mr. Philip Chiu
P&P Board member:	Mr. Peter Leung		Mr. Chi Kit Chan
P&P Board member:	Mr. Peter Chua		Mr. Chi Ming Wong
P&P Board member:	Mr. Perry Sit		Ms. Candy Tai
			Ms. Manda Young

Revisions of the CUHK Pharmacy Curriculum - Responding to Changes in Pharmacy Practice

Ho, Susan S.S.

I INTRODUCTION

As the Year 2005 marks the 10th Anniversary of the graduation of the first batch of locally trained pharmacy students, it is timely to reflect on the changes that have occurred in local pharmacy education in the past 10 years. Because the CUHK is the only local university offering a full-time Bachelor of Pharmacy (B.Pharm.) program in Hong Kong, it will be useful for pharmacists and our readers to learn more about the history and the development of the undergraduate pharmacy program offered by the School of Pharmacy (SOP) of the Chinese University of Hong Kong (CUHK).

II BACKGROUND

The establishment of a pharmacy degree course in Hong Kong was first proposed by the pharmacy professional bodies in 1986. Following a feasibility study conducted by the CUHK in 1989 to examine the possibility of offering a pharmacy degree course, the Faculty of Medicine convened a Working Committee to submit a proposal for introducing a pharmacy degree course at CUHK, and received University and Polytechnic Grants Committee's (UPGC's) approval in early 1990. A Working Committee of the Pharmacy Course composed of experts from the Government, pharmaceutical industry, pharmacy professional bodies, hospital and community pharmacists, and various departments in the Faculty of Medicine was formed to draw up the course curriculum. With the assistance of the British Council, the Committee consulted various international pharmacy schools in UK, Australia and USA, and a comprehensive 3-year B.Pharm. curriculum was finalized and approved by the University Senate on 19 December 1991. Prof. Kenneth Raymond from the Victorian College of Pharmacy in Melbourne, Australia was recruited as the founding Chairman of the then Department of Pharmacy, and the first intake of students occurred in September 1992. After three years of full-time studies, the first batch of 31 homegrown B.Pharm. students graduated from CUHK in 1995. They then completed a one-year internship training and became registered pharmacists in July 1996. The Department of Pharmacy was later renamed the 'School of Pharmacy' in August 2000.

The original B.Pharm. curriculum was based on a traditional model with major emphasis on the pharmaceutical sciences and fundamental knowledge in the preparation, distribution, action and uses of drugs and medicines (Table 1).

Because the School of Pharmacy was relatively young, a considerable amount of time and effort in the earlier years had been devoted to the development of courses, staff recruitment, establishment of new research facilities, initiation of postgraduate programs, and establishing links with the local and international pharmacy communities. As a result, the B.Pharm. curriculum originally developed in 1991 had not undergone any significant changes in the first 10 years. However during this time, the pharmacist's role was changing swiftly. The 'new role' of the pharmacist as a 'provider of pharmaceutical care' not only had emerged but also developed quite rapidly in the 1990's. Our profession has embraced the role of the new pharmacist as being patient centered and outcomes oriented. As stated in the ASHP Statement on Pharmaceutical Care, "curricular should be designed to produce graduates with sufficient knowledge and skills to provide pharmaceutical care competently". Thus, the School of Pharmacy took the initiatives to examine whether the present curriculum fulfills the future needs of providing comprehensive health care by the pharmacists in a knowledge-based society.

III INITIATIVES FOR CURRICULUM REVISION

In February 1999, the Curriculum Committee was called upon by Prof. Moses Chow, the new Chairman of the School, to examine the undergraduate pharmacy curriculum and to determine if revisions could be instituted that would increase the course's relevance to modern day pharmacy practice and improve the skills of the pharmacy graduates.

The Curriculum Committee consisted of Prof. Kenneth Raymond (Chair), Dr. Yee Ping Ho and myself as members. Several meetings were held and some deficiencies were identified in the original curriculum:

1. The curriculum had a strong emphasis on pharmaceutical sciences, which would not enable students to develop the necessary knowledge and skill to provide pharmaceutical care.
2. Students entering the pharmacy program had already taken some of the chemistry topics in the A-Level courses.
3. Course material of a distinct subject was included in the syllabi of different disciplines (e.g. biopharmaceuticals and pharmacokinetics were part of the syllabi of Pharmaceutical Formulation and Medicinal Chemistry, respectively).
4. Courses were rigidly divided or compartmentalized by discipline, which would not allow proper integration of knowledge from different but related subjects.
5. There was a lack of systematic training in research methodologies in the undergraduate curriculum.
6. Students were not introduced to the pharmacy profession at an early stage.
7. There was not sufficient emphasis on developing the students' communication and practice skills.

Table 1. Original B.Pharm. Program Developed in 1991

Field of Study	Subjects
Foundation Courses in Bioscience	Anatomy, Physiology, Biochemistry
Pharmaceutical Chemistry	Fundamentals of Organic Chemistry, Functional Group Chemistry, Pharmaceutical Analysis, Medicinal Chemistry
Pharmaceutics	Physical Pharmacy, Data Analysis, Formulation Science, Pharmaceutical Processes (consist of Basic Microbiology, Sterilization and Radiopharmacy)
Pharmacology	Mechanisms of Drug Action, Chemotherapy and Drug Toxicity
Pharmacognosy	Basic Pharmacognosy, Pharmacognosy and Herbal Medicines
Therapeutics	Clinical Pharmacology and Pharmacy
Practice of Pharmacy	Basic Dispensing Techniques, Dispensing Practice, Community Pharmacy Practice, Law Relating to Pharmacy
Graduation Project	A research-based project in pharmaceutical science or pharmacy practice

8. The program lacked flexibility for students to further develop according to their future career preferences (e.g. pharmaceutical scientist vs. practicing pharmacist).

i) Objectives of a Pharmacy Degree Course

A pharmacy degree course should provide students with a sufficiently broad understanding of the scientific/theoretical foundations of the profession to enable them to become competent registered pharmacists after graduation and an appropriate period of pre-registration training. It should be integrated to enable students to develop comprehensive knowledge and expertise in all aspects of the preparation, distribution, action and uses of drugs and medicines. It should instill into the students the highest sense of professional values and ethics. In order to meet the changing social demands and expectations on pharmacists, pharmacy students have to acquire not only communication and patient care skills, but also develop self-directed learning habits for life-long professional development.

Hence, various curriculum changes were proposed by the Committee in late 1999. The teaching staff of the SOP as well as teachers from other departments were consulted on the feasibility and overall impact of the proposed curriculum changes. By August 2000, Prof. Kenneth Raymond had left the CUHK and Prof. Moses Chow assumed the Chairmanship of the Curriculum Committee. The composition of the Committee was also changed, with Dr. Clara Lau replacing Dr. Yee Ping Ho as a new member, and I continued to serve on the Committee.

ii) Graduate Survey

To better understand the graduates' learning experience and their opinion on the pharmacy curriculum, a mail survey was conducted in November 2000. Pharmacy interns who graduated in May 2000 and who had completed 5 to 6 months of internship were asked to provide suggestions for revision of the undergraduate curriculum. Based on the graduates' feedback, further revisions were proposed by the Curriculum Committee.

iii) Proposed Curriculum Changes

The recommendations made by the Curriculum Committee were discussed at various levels within the School, the Faculty and the University. The course revisions received University approval in January 2001 and therefore could be implemented with the September 2001 new intakes. Table 2 illustrates the major areas of curriculum revision.

Since one of the most important changes to the curriculum was the introduction of the 'Pharmacy Clerkship/Project' course, the following discussions will focus on this.

IV THE NEW PHARMACY CLERKSHIP/PROJECT COURSE

This new course provides an opportunity for students to obtain practical experience outside the typical classroom and to understand the role of the pharmacist in various practice environments. During the course, students are exposed to other members of the healthcare team, which will encourage them to carry on a team approach to practice after they graduate. The course consists of two major components, namely pharmacy clerkship experience, and an assigned project in the pharmaceutical science field or in pharmacy practice. A minimum of 3 weeks of clerkship is required for all students in the final year of study. Beyond that, the students have the choice of additional clerkship experience (9 weeks) or conduct a research project according to the individual student's preference.

i) Preparatory Coursework

Prior to the start of clerkships, the students are given a number of preparatory coursework to develop the knowledge and skills required for clerkship activities. The components of the coursework include:

Literature Evaluation
Clinical Application of Statistical Analysis
Journal Club*
Current Treatment Guidelines
Physical Assessment Skill
Clinical Lab Interpretation
Medical Chart Review
Patient Interview Skill
Written Communication Skill
Case Presentation Skill
Drug information Skill*
Management and Pharmaceutical Marketing Short Course#

* Specific for community and clinical clerkship students
\# Specific for industrial clerkship students

ii) Pharmacy Clerkships

a. Clerkship Activities

The required clerkship is scheduled in the hospital, community and industrial pharmacy settings (one week each). During clinical and community clerkships, the emphasis is on selected patient-focused pharmacy practice. Activities may include ward rounding, patient counseling, communication with

Table 2. Major Areas of Curriculum Revision in 2001

Subjects of Revision	Highlights of the Revision
An 'Introduction to Pharmacy' course was added to Year One.	This course introduces the entering pharmacy students to the history and the profession of pharmacy. Various pharmacy practice environments such as community pharmacy, hospital pharmacy, industry, academic research and government are introduced. The role of the pharmacist is discussed through seminars and practice site visits. The course also emphasizes on basic communication skills and the importance of communication between healthcare professionals through seminars, workshops and student presentations.
The Chemistry courses were re-organized and streamlined as necessary.	This change would allow appropriate time to be allocated to other new subject areas.
The subjects of Anatomy, Physiology and Pathophysiology were combined into one course, using an integrated, system-based approach.	This change would allow integration of knowledge from the related disciplines for the student to better understand the structure and function, normal as well as abnormal, of cells, organs and systems.
The subjects of Pharmacology, Clinical Pharmacology & Pharmacy were integrated into one modular-based course entitled 'Pharmacology and Therapeutics I - IV' which extends over four terms.	A modular, disease-based approach is used which provides students with an understanding of the principles of drug action along with the pharmacotherapy of disorders associated with various organ systems.
A new course entitled 'Pharmaceutical Research Methods and Techniques' was introduced.	This course provides students with an understanding of the principles and methods of research in pharmaceutical science and pharmacy practice and the relevant biostatistics. These knowledge and skills are necessary for the pharmacist to be able to read and critically appraise scientific papers published in medical and pharmaceutical journals and to conduct good research.
A new course entitled 'Pharmacy Clerkship/Project I/II' was introduced to the final year of study, which extends over two terms.	This course enables students to practice what they have learned in class in a real-life environment. Each student is placed in a community pharmacy, a hospital ward and a pharmaceutical company under the supervision of a practicing pharmacist serving as the tutor.

other healthcare professionals, provision of drug information to patients and other health care providers, participation in the choice, dosing, and monitoring of drugs for individual patients to optimize efficacy, safety, and cost-effectiveness. During industrial clerkships, students are given an overview of the operation of the industrial sector. Students who have chosen a multinational drug company will learn about regulatory affairs, sales and marketing...etc. where as those who have chosen a local pharmaceutical manufacturer will learn about the manufacturing, quality control and quality assurance of pharmaceutical products. Students who opted for an additional 9-week clerkship experience in their chosen field (either community pharmacy, clinical pharmacy, multinational drug company or local pharmaceutical manufacturer) must also complete a practice-based project during the elective 9-week clerkship period. The project requires the student to prepare a written proposal, implement the project, give an oral presentation and submit a final written report.

b. Appointment of Tutors

A pharmacist tutor is appointed at each clerkship site. The tutors involve and monitor the students in site-specific professional activities. The student will learn the skills and knowledge to achieve a specific competency level of practice at the respective site. The tutors also assess the students' performance during the rotation and provide guidance on the practice-based projects.

c. Checklist of Activities

In order to assure consistency in the delivery of course content across different practice sites, the School of Pharmacy has developed standardized checklists of activities for each type of clerkship. At the end of each rotation, these are checked by the students and co-signed by the tutors to ensure that all the required elements of the rotation have been covered.

d. Assessment of Student Performance

To assess the students' performance, specific assessment criteria as well as standardized scoring system have been developed. They serve as useful guides for the tutors and help to ensure objectiveness in the assessment.

e. Student Evaluation of Clerkship Rotation

At the end of each clerkship rotation, the students complete a standardized evaluation form, which addresses both the clerkship activities (site) and the tutor. This information assists the course coordinators in providing relevant feedback to the teaching staff and pharmacist tutors supporting the activities and in planning for continuous course improvement.

iii) Research Projects

Students who choose the research track must complete a major research project under the supervision of an academic staff. The research project can be in any discipline in pharmaceutical science, e.g. medicinal chemistry, physical pharmacy, pharmacokinetics, pharmacology, pharmacognosy/pharmaceutical analysis, or in pharmacy practice. The research project requires the student to prepare a written proposal, orally present the proposal, submit a progress report and a final written report, and give an oral presentation on the project in the presence of the School's External Examiner.

iv) Tutors' Comments on the Pharmacy Clerkship Program

During the first two years, over 30 practicing pharmacists have participated as tutors in the clerkship program. A survey was conducted in 2004 to obtain feedback on the program from some of the tutors. Not to my surprise, some of the tutors expressed that "CU students are smart and eager to learn but many are shy and passive and in some cases not being proactive". Despite the rote-learning models commonly practiced in Hong Kong secondary schools, university students are encouraged to take an active role in their learning, which is continually being emphasized in the course. As far as the tutors are concerned, a majority of them responded that the experience of becoming a tutor benefit them in their personal and professional development (e.g. "keeping their pharmacy approaches update" and "help strengthen their coaching skills"). These tutors are important role models for the pharmacy students and have made significant contributions towards the education and training of our future pharmacists. We hope that they will continue to be inspired by working with the next generation of pharmacists.

V CONCLUSION

Pharmaceutical education must adequately prepare students to enter into the practice of pharmacy, in whatever areas appropriate to the heath care environment. The pharmacy curriculum must be constantly assessed and evaluated to be in line with and even ahead of professional practice. The School of Pharmacy of CUHK has reviewed and revised its curriculum in Year 2001 with the introduction of experiential learning in the undergraduate program. The new curriculum has more precisely defined the learning outcomes and objectives of our graduates, and is flexible enough to allow students to achieve a broad education in accordance with their interest.

Being the only local university offering a Bachelor of Pharmacy (B.Pharm.) program in Hong Kong, the CUHK is committed towards providing quality pharmacy education. The Pharmacy and Poisons Board of Hong Kong, in it's recent 'Review of the Existing Guidelines for Pharmacy Internship Training and Pharmacist Registration Examination', has stated that it is "satisfied that the Bachelor of Pharmacy programme provided by the School of Pharmacy of the CUHK is of good standard and its standard is on a par with that of the overseas universities". We take pride in this statement and will continue to strive for excellence in pharmacy education.

VI ACKNOWLEDGEMENTS

I would like to acknowledge the following companies and institutions for providing valuable support to our pharmacy clerkship program:

Community Pharmacy
HealthQuest Pharmacy
Mannings (TCM clerkship)
Watson's The Chemist

Hospital Pharmacy
The Prince of Wales Hospital

Pharmaceutical Industry
Abbott Laboratories Ltd.
AstraZeneca Hong Kong Ltd.
Aventis Pharma Ltd.
Bausch & Lomb Hong Kong Ltd.
GlaxoSmithKline Ltd.
Janssen Pharmaceutica
Jean-Marie Pharmacal Co., Ltd.
Merck Sharp & Dohme (Asia) Ltd.
Pfizer Corporation Hong Kong Ltd.
Sanofi Synthelabo Hong Kong Ltd.

Dr. Susan Ho is Associate Director (Education and Professional Development) and Teaching Fellow of the School of Pharmacy, CUHK. She has been a member of the Curriculum Committee of the SOP since 1998 and served as the overall coordinator of the Pharmacy Clerkship/Project course from 2001 to 2004.

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Pharmacy Clerkship Program - The memorable times shared by the students

Leung, Grace; Li, Julianna; Choi, Kwok-Ho; Chan, Queenie; Lam, Sinki; Chiu, Tiffani

Many of our fellow pharmacists have heard about or even been involved in the Pharmacy Clerkship Program of Chinese University of Hong Kong (CUHK). Nevertheless, most of us are not entirely understand the background, rationale and implementation of this program. It is our pleasure to have Prof Susan Ho, CUHK, to explain all these details to us in this issue.

On top of that, six pharmacy students who are participating *(they should have finished the program by the time this issue is published)* in the Clerkship Program 2004/2005 are eager to share their feelings and learning with the readers. From the feedback, one can conclude the clerkship program is valuable indeed to the students for their future career.

Choi Kwok Ho - *Life in Bausch & Lomb*

It's my pleasure to share with you my experience and feeling of clerkship in Bausch & Lomb in the past 9 weeks. I worked in the regulatory department and mainly dealt with the registration of pharmaceutical products. Besides this, I also had chances to participate in other projects relating to the operation of drug registration. The main benefit that I got through this clerkship is the application of knowledge that I have learnt and greatly increase my interest towards them. Take an example, we have studied the pharmacy law during school and should know the legal requirements of drug registration in Hong Kong, However, the actual case is not as simple as the documentary requirements listed in the ordinance. Regulatory staffs need to deal with many duties besides the documentary requirement. Even the documents themselves can have many variations, which makes the whole regulatory process more complex, but more challenging. Moreover, as a regional regulatory office, I have chance to know more about the regulatory requirements in other Asia-Pacific countries. In addition, it is also a valuable experience for us to get a taste of the actual environment in the pharmaceutical industry, and how people work. More importantly I learnt many important skills, such as the importance of planning, no matter for career or any duty, communication skills and interview skills. I think all these are essential for final year students to prepare themselves for the future career and development.

Finally, I would like to give my special thanks to Bausch & Lomb for offering us clerkship program, my tutor, Jack Wong, and other regulatory staff for providing me such a wonderful program. I will never forget this treasurable experience.

Julianna Li - *What a Thrilling Clerkship Program*

This year began in an exciting way. Starting form 3rd January, it came to my last semester in CUHK and I have started an intensive clerkship training program in various sites.

For the first three weeks of the program, I got a chance to rotate between a hospital, a community pharmacy and a local manufacture company. That gave me a valuable chance to explore among different areas and cleared my mind about my future career goal. Then, it was followed by a nine-week attachment in one specific site.

My remaining nine weeks training was in Merck Sharp & Dohme (MSD), a well organized and fantastic multinational pharmaceutical company. My preceptor, Christina Yip, is a really nice person. She has prepared a lot and made me feel like I am a part of the company. Here, I met lots of people and they all taught me many things which can never be learned in the University's lecture theater. I like hearing their working experiences and sharing their point of views from the pharmaceutical industry.

Every minute in MSD is very challenging. I have got a project to do and it was about giving different disease trainings to the colleagues. After several presentations, I found myself more confidence in handling others' questions and learned how to communicate efficiently. I also got a chance to participate in a marketing survey and conducted interviews with some doctors. It was really interesting that through the interviews with the doctors, I realized that different parties have different opinions and thoughts, even upon the same issue! That really impressed me!

The office setting and location of MSD made me became an "Office Lady". It was the first time that I dressed up and worked in such kind of environment. However, things were not just constrained in the office. I got chances to go out with sales representatives and clinical research associates, so as to experience their daily work. The site visit tour to a local distributor and role playcase study in the medical department has further deepened my mind about the operation of a pharmaceutical company. Besides, I also attended their meeting and educational program. What an assorted nine weeks attachment!

I found this clerkship program was very meaningful and I treasured it a lot. It taught me what a pharmacist can contribute in a practical and realistic way. Although working from Monday to Thursday in MSD and having a whole day lecture in CU on Friday made me exhausted, I did gain a lot! Though this program, I have understood my ability and interest more and got a brief idea about my future. I enjoyed my last semester of Pharmacy learning.

Grace Leung and Sinki Lam - *Clerkship in International Pharmaceutical Company*

The clerkship programme not only serves academic purposes but also gives us the chance to actually observe how a company/ pharmacy/ hospital operates in a day-to-day basis. The three-week rotation gave us a taste of working in each field so that we can think about what we like most and what suits us the best. During the one-week rotation to the industrial field, we started to gain an overview of the industry. Afterwards, we entered AstraZeneca for our nine-week clerkship and began to deepen our knowledge and interest in pharmaceutical industry.

Many of us don't have a good understanding of pharmaceutical companies. We could not even know about the role of pharmacists there. This is because the nature of job here does not involve application of much clinical knowledge and, to begin with a medical rep may require some training as not all of us possess the necessary characteristics. However, what we've learnt from these few weeks is far beyond a textbook can tell.

At first, we had a chance to know about the flow and organization of the company through presentations, discussions and field visits. This was a precious chance for us as we could know the function and contribution of different departments in the company. Besides, we could identify the managerial role and advantage of pharmacist in pharmaceutical industry. Generally, we gain knowledge about the environment and the various regulatory forces.

For our project, we could explore new knowledge about marketing in which we already had a general picture through an introductory course in the last semester. We found out new knowledge and incorporated it with our perceived one. Then we applied them when doing our projects. The marketing concepts are very important. All the theories are nothing unless they are applied in real life situation. Many concepts that appear to be simple (e.g. patent, SWOT analysis, etc) are very complicated indeed. Learning by work experience would be more fruitful than memorizing content of a book. It would be much better if we could involve in the company's functions to a greater extend. It's interesting to observe how staffs from different departments cooperate too. Our colleagues were very nice and helpful. They helped us to solve many problems. We could also experience the office and company life there. In addition to marketing, our project also includes our professional knowledge and could establish the role of pharmacists in disease management and outcome improvement. All these were very precious and important.

Above all, we find that working in the industrial sector may provide the greatest job prospect and a greater variety of job types. It seems to be an attractive option for people who want to develop their careers.

We want to thank our school and our tutor, Mr. Allan Chan, for giving us a chance to learn. We hope we can contribute to our profession after the internship.

Queenie Chan - *To expect the unexpected*

I am glad to have this valuable chance to share my feeling about the clerkship programme. I am one of the research track students and I am conducting a research project about the intestinal transport of green tea catechins. I started doing my project in late July last year and am still doing it now. At the beginning, I thought that the project was quite simple and I believed that I could finish all the experimental work within the 1st semester. However, things always go against wishes. In November, I discovered that nearly all the samples I prepared in the past four months degraded. I was frustrated at that moment but what I could do was to prepare the samples once again. Unfortunately, after I had finished analysing all the samples I prepared in the second time, some of the results obtained were surprisingly impossible. Up to now, I have repeated the experiments for four times and every time I discover a new problem that I have not thought of or noticed before. Doing research is really challenging. Unexpected problems may appear for you to solve and unanticipated results may be generated for you to explain. If you ask me whether I regret choosing research track as my 1st choice, my answer is negative. Conducting research is a precious experience and it is unlikely for me to have this chance again in the future. I learnt to be patient, work independently, manage time well and think critically. Also, I received a lot of help and support from my supervisor and the postgraduate student. The knowledge they taught me is invaluable for my future.

Tiffani Chiu - *Clerkship: a good chance to practise*

When it comes to the peak season of job hunting, I'm always asked, "Tiffani, will you really be a pharmacist in the future? It seems to me that pharmacists have to do routine jobs and are boring people, isn't it?"

Since we were admitted to the school of pharmacy, our schedules were filled with lectures at school. I heard about clerkship when I was in year one and was so curious about it. Having waited for 2.5 years, I finally got the chance to have some experience outside school through this clerkship program.

Clerkship is a unique program offered by my school that provides us with exposure to different fields, which include hospital pharmacy, community pharmacy, multinational and local pharmaceutical industry. I'm fortunate that I have been to all of the four fields. One cannot understand what the jobs are like until s/he gets exposed to it. Clerkship surely is meaningful in this way that I can have a brief idea on what the fields are about by experiencing them in person. During my clinical clerkship, we had some ward-rounds with doctors in PWH. There, in my white lab coat, I realized the responsibility that pharmacists have to bear and the importance pharmacists own. This sense was even stronger when I saw how patients suffer in reality. Empathy, which used to be an answer on my examination paper only, is what I really experience during the clerkship.

It was also the first time for me to discuss about patients' cases with doctors with our professional knowledge. Every case is complicated with a different story. We need to consider the whole picture before any judgment. It is not as simple as what I thought in the past. "We are treating the patients but not the disease" is what I learnt from the ward-round physician. This is going to be with me for life during my future practice. Also, the collaboration with doctors gave me a strong sense of responsibility that we are to give our best care to our patients so that they can have healthy lives. These experiences are surely not found in books.

I also experienced my clerkship in Watson's where I knew more about the job a pharmacist does and observed some counseling skill that the pharmacist used, which are all very meaningful to me. For my last week of the 3-week rotation, I, and four other classmates, visited the Jean-Maire Pharmacal Ltd. in Tai Po, which is a GMP pharmaceutical manufacturer in Hong Kong. There, we had lectures and site visits to different departments. It was an abundant 4-day visit to the company, giving a closing of my 3-week rotation.

For the next 9 weeks, I had my clerkship in Merck Sharp & Dohme (Asia) Ltd. (MSD for short), a multinational pharmaceutical company. In the past, we naturally linked pharmacist in pharmaceutical industry with salesperson. Actually, pharmacists there were more than just salesperson. I met some pharmacists in MSD and they are working in different areas, mainly Medical and Sales and Marketing departments. Their jobs are quite diverse and are much different from what other pharmacists do in hospital or community pharmacies. I also came across people with different backgrounds, some are from the science stream and some are from the business sectors. I can see how people with different backgrounds collaborate and the edges pharmacists have in pharmaceutical companies.

Thanks to the arrangement by MSD, I was exposed to both the sales and marketing department and the medical department. We were arranged to work with different colleagues and we had some projects in the two departments. Through accomplishing the tasks, I had a deeper understanding on the jobs they do and found that they are quite interesting indeed. Collaborating with different people allowed me to improve my interpersonal skill as well. Besides working in the office, I also had the opportunity to work outside. We interviewed doctors, visited the distributor, joined meetings with other pharmacists and attended a symposium. These all gave me unforgettable memories and made my 9-week training so fruitful. It is my pleasure to have my 9-week clerkship in MSD.

Last but not least, I'd like to express my gratitude towards my school and all the personnel that contribute to the clerkship, especially my tutor in MSD, Ms. Christina Yip. It gives me a nice finale of my 3-year study as well as a nice prelude of my career as a pharmacist.

Now, besides sharing with my friends how I enjoy being a pharmacist, I'll also say, "Friend, you are always welcomed to come to my pharmacy. We always serve you with the best of our professional knowledge!"

Grace Leung, Julianna Li, Choi Kwok-Ho, Queenie Chan, Sinki Lam and Tiffani Chiu are Year 3 Pharmacy students studying at the Chinese University of Hong Kong. They will start one-year internship in various areas in mid-2005.

NEW PRODUCTS

OLMETEC
(Pfizer)

Active ingredient:
Olmesartan Medoxomil

Presentation:
Available as 10 mg, 20 mg and 40 mg film-coated tablets

Pharmacological Properties:
Olmesartan medoxomil is a selective angiotensin II receptor (type AT1) antagonist. It is expected to block all actions of angiotensin II mediated by the AT1 receptor, regardless of the source or route of synthesis of angiotensin II. The selective antagonism of the angiotensin II (AT1) receptors results in increases in plasma renin levels and angiotensin I and II concentrations, and some decrease in plasma aldosterone concentrations. Angiotensin II is the primary vasoactive hormone of the renin-angiotensin-aldosterone system and plays a significant role in the pathophysiology of hypertension via the type 1 (AT1) receptor.

Indications:
Treatment of essential hypertension.

Dosages and Administration:
Adults - The optimal recommended starting dose of olmesartan medoxomil is 20 mg once daily. If additional blood pressure reduction is required, olmesartan medoxomil dose may be increased to a maximum of 40 mg daily or hydrochlorothiazide therapy may be added. For patients with possible depletion of intravascular volume, particularly those with impaired renal function, Olmetec should be administered under close medical supervision and consideration should be given to a lower starting dose.

Renal impairment - The maximum dose in patients with mild to moderate renal impairment (creatinine clearance of 20-60 mL/min) is 20 mg olmesartan medoxomil once daily, owing to limited experience of higher dosages in this patient group. The use of olmesartan medoxomil in patients with severe renal impairment (creatinine clearance < 20 mL/min) is not recommended, since there is only limited experience in this patient group.

Hepatic impairment - The use of olmesartan medoxomil is not recommended in patients with hepatic impairment, since there is only limited experience in this patient group.

Contraindications:
Hypersensitivity to the active ingredient or any of the other excipients of Olmetec tablets; second and third trimesters of pregnancy Lactation; biliary obstruction.

Precautions:
Intravascular volume depletion - Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions should be corrected before the administration of olmesartan medoxomil.

Renovascular hypertension - There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with medicinal products that affect the renin-angiotensin-aldosterone system.

Renal impairment and kidney transplantation - When olmesartan medoxomil is used in patients with impaired renal function, periodic monitoring of serum potassium and creatinine levels is recommended. Use of olmesartan medoxomil is not recommended in patients with severe renal impairment (creatinine clearance < 20 mL/min). There is no experience of the administration of olmesartan medoxomil in patients with a recent kidney transplant or in patients with endstage renal impairment (ie. creatinine clearance <12 mL/min).

Hyperkalaemia - As with other angiotensin II antagonists and ACE inhibitors, hyperkalaemia may occur during treatment with olmesartan medoxomil, especially in the presence of renal impairment and/or heart failure. Close monitoring of serum potassium levels in at risk patients is recommended.

Aortic or mitral valve stenosis; obstructive hypertrophic cardiomyopathy - As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral valve stenosis, or obstructive hypertrophic cardiomyopathy.

Side effects:
In clinical trials, common side effects (≥1/100, <1/10) reported include dizziness, abdominal pain, diarrhoea, dyspepsia, gastroenteritis, nausea, increased creatine phosphokinase, hypertriglyceridaemia, hyperuricaemia and liver enzyme elevations.

Drug Interactions:
Concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other drugs that may increase serum potassium levels (e.g. heparin) may lead to increases in serum potassium. Such concomitant use is therefore not recommended.

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors and angiotensin II antagonists. Therefore use of olmesartan medoxomil and lithium in combination is not recommended. If use of the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Forensic Classification:
P1S1S3

REYATAZ
(Bristol-Meyer Squibb)

Active ingredient:
Atazanavir

Presentation:
Available as 150mg and 200mg capsules

Pharmacological Properties:
Atazanavir is an azapeptide HIV-1 protease inhibitor. The compound selectively inhibits the virus-specific processing of viral Gag and Gag-Pol polyproteins in HIV-1 infected cells, thus preventing formation of mature virions.

Indications:
REYATAZ is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. In antiretroviral--experienced patients with prior virologic failure, coadministration of REYATAZ/ritonavir is recommended.

Dosages and Administration:
REYATAZ Capsules must be taken with food.

Therapy-Naive Patients - REYATAZ 400 mg (two 200-mg capsules) once daily taken with food.
There are no data regarding the use of REYATAZ/ritonavir in therapy-naive patients.

Therapy-Experienced Patients - REYATAZ 300 mg (two 150-mg capsules) once daily plus ritonavir 100 mg once daily taken with food. REYATAZ without ritonavir is not recommended for treatment-experienced patients with prior virologic failure. Efficacy and safety of REYATAZ with ritonavir in doses greater than 100 mg once daily have not been established. The use of higher ritonavir doses might alter the safety profile of atazanavir (cardiac effects, hyperbilirubinemia) and, therefore, is not recommended.

Contraindications:
REYATAZ is contraindicated in patients with known hypersensitivity to any of its ingredients, including atazanavir.

Coadministration of REYATAZ is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These drugs include benzodiazepines (midazolam,triazolam), ergot derivatives (dihydroergotamine,ergotamine,ergonovine,methylergonovine), GI motility agent (cisapride) and neuroleptic (pimozide).

Precautions:
PR Interval Prolongation - Atazanavir has been shown to prolong the PR interval of the electrocardiogram in some patients. In healthy volunteers and in patients, abnormalities in atrioventricular (AV) conduction were asymptomatic and generally limited to first-degree AV block. There have been rare reports of second-degree AV block and other conduction abnormalities and no reports of third-degree AV block.

Hyperbilirubinemia - Most patients taking REYATAZ experience asymptomatic elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronosyl transferase. This hyperbilirubinemia is reversible upon discontinuation of REYATAZ. Hepatic transaminase elevations that occur with hyperbilirubinemia should be evaluated for alternative etiologies.

Rash - Rash (all grades regardless of causality) occurred in 21% of patients treated with REYATAZ. The median time to onset of rash was 8 weeks after initiation of REYATAZ and the median duration of rash was 1.3 weeks. Rashes were generally mild-to-moderate maculopapular skin eruptions. Dosing with REYATAZ was often continued without interruption in patients who developed rash.

Hepatic Impairment and Toxicity - Atazanavir is principally metabolized by the liver; caution should be exercised when administering this drug to patients with hepatic impairment because atazanavir concentrations may be increased.

Patients with underlying hepatitis B or C viral infections or marked elevations in transaminases prior to treatment may be at increased risk for developing further transaminase elevations or hepatic decompensation. There are no clinical trial data on the use of REYATAZ/ritonavir in patients with any degree of hepatic impairment.

Side effects:
Selected drug-related clinical adverse events of moderate or severe intensity reported in 2% of treatment-naive patients receiving combination therapy including REYATAZ are headache, nausea, jaundice/scleral icterus, vomiting, diarrhea, abdominal pain, dizziness, insomnia, peripheral neurologic symptoms, *and* rash.

Drug Interactions:
Atazanavir is an inhibitor of CYP3A and UGT1A1. Coadministration of REYATAZ and drugs primarily metabolized by CYP3A (eg, calcium channel blockers, HMG-CoA reductase inhibitors, immunosuppressants, and PDE5 inhibitors) or UGT1A1 (eg, irinotecan) may result in increased plasma concentrations of the other drug that could increase or prolong both its therapeutic and adverse effects. Atazanavir is metabolized in the liver by the cytochrome P450 enzyme system. Coadministration of REYATAZ and drugs that induce CYP3A, such as rifampin, may decrease atazanavir plasma concentrations and reduce its therapeutic effect. Coadministration of REYATAZ (atazanavir) and drugs that inhibit CYP3A may increase atazanavir plasma concentrations.

Antimycobacterials (rifampin) - Decreases plasma concentrations and AUC of most protease inhibitors by about 90%. This may result in loss of therapeutic effect and development of resistance.

Antineoplastics (irinotecan) - Atazanavir inhibits UGT and may interfere with the metabolism of irinotecan, resulting in increased irinotecan toxicities.

Benzodiazepines (midazolam, triazolam) - Contradinicated due to potential for serious and/or life-threatening events such as prolonged or increased sedation or respiratory depression.

Ergot Derivatives (dihydroergotamine, ergotamine, ergonovine, methylergonovine) - Contradinicated due to potential for serious and/or life-threatening events such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.

GI Motility Agent (cisapride) - Contradinicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.

HMG-CoA Reductase Inhibitors (lovastatin, simvastatin) - Potential for serious reactions such as myopathy including rhabdomyolysis.

Neuroleptic (pimozide) - Contradinicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.

Protease Inhibitors (indinavir) - Both REYATAZ and indinavir are associated with indirect (unconjugated) hyperbilirubinemia. Combinations of these drugs have not been studied and coadministration of REYATAZ and indinavir is not recommended.

Proton-Pump Inhibitors - Concomitant use of REYATAZ and proton-pump inhibitors is not recommended. Coadministration of REYATAZ with proton-pump inhibitors is expected to substantially decrease REYATAZ plasma concentrations and reduce its therapeutic effect.

Forensic Classification:
P1S1S3

Seeking The Best Chance for a Cure in Chronic Hepatitis

PEGASYS®
peginterferon alfa-2a (40KD)

Breaking News
PEGASYS® **HBV** Indication
Now Approved !

The ONLY
Pegylated Interferon Supplied as a Pre-filled Syringe !

Prescriber-friendly & Patient-friendly

Simple fixed dose, ready-to-inject solution

Unsurpassed Efficacy in Both

– Chronic Hepatitis B

- Statistically significant and superior benefit versus lamivudine.[1,2]

– Chronic Hepatitis C

- Consistent high overall response rates in large, randomized multicentre clinical studies.[3]

Full prescribing information is available upon request

Reference:

1. Marcellin P et al. Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. N Engl J Med 2004;351:1206-17.
2. Lau G et al. 55th Annual Meeting of American Association for the Study of Liver Diseases.
3. Hadziyannis SJ et al, Peginterferon alfa-2a and ribavirin combination therapy in chronic hepatitis C, Ann Intern Med. 2004; 140:346-355.

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