HONG KONG PHARMACEUTICAL JOURNAL

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Pharmacists in Public Health Emergency

Clinical Attachments in the US

Probiotics

Geriatric Drug Therapy (2 CE Units)

Osteoporosis

Genetic Engineering of Recombinant Tissue Plasminogen Activator

Euphrasia officinalis L (小米草)

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

一個既**專業**又**親切**的名字：

善痛眠* NEURONTIN*

gabapentin

- Significantly relieves neuropathic pain of different aetiologies [1]
- Improvement of sleep disturbance due to neuropathic pain [2-6]
- Has a proven safety profile and is well tolerated [7,8]

References:
1. Serpell MG, et al. *Pain* 2002;99:557-566. 2. Block BM, Wu CL. *International Journal of Pain Medicine and Palliative Care* 2001;2:56-61. 3. Rice AS, et al. Pain 2001;94:215-224. 4. Backonja M, et al. *JAMA* 1998;280:1831-1836. 5. Rowbotham M, et al. *JAMA* 1998;280:1837-1842. 6. Cohen MJM, et al. *International Review of Psychiatry* 2000;12:115-126. 7. NEURONTIN. Prescribing information. 8. Braverman DL, et al. *Arch Phys Med Rehabil* 2001;82:691-693.

NEURONTIN ABBREVIATED PRESCRIBING INFORMATION:
INDICATIONS: 1. Neuropathic Pain: Treatment of neuropathic pain in adults. 2. Epilepsy: Monotherapy and adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults and children age 6 years and above. DOSAGE: 1. Neuropathic Pain in Adults: Titration to an effective dose by administering 300mg once a day on day 1, 300mg twice a day on day 2 and 300mg three times a day on day 3. Thereafter, the dose can be increased using increments of 300mg per day given in three equally divided doses to a maximum of 3600mg per day. As an alternative, if the pain intensity requires, 3x daily 1 gabapentin 300mg capsule (corresponding to 900mg gabapentin/day) may be taken starting on Day 1. Then the daily dose may be increased within a week to 1800mg gabapentin and thereafter up to a maximum dose of 3600mg gabapentin, if necessary. The total daily dose should not exceed 3600mg gabapentin. The total daily dose should be administered in three single doses. 2. Epilepsy (Adults and children > 12 years): Titration to an effective dose by administering 300mg once a day on Day 1, 300mg twice a day on Day 2 and 300mg three times a day on Day 3. If necessary, the dose can be increased in three equally divided doses up to a maximum of 3600mg/day. Therapy may be initiated by administering 300mg three times a day (TID) on Day 1. Epilepsy (Children Age 6-12 years): The effective dose is 25 to 35mg/kg/day given in divided doses (3 times a day). Titration to an effective dose can take place over 3 days by giving 10mg/kg/day on Day 1, 20mg/kg/day on Day 2, and 30mg/kg/day on Day 3. The maximum time between doses in the three times a day (TID) schedule should not exceed 12 hours. Refer to full prescribing information on dosing for renal impaired patients. CONTRA-INDICATIONS: Hypersensitive to gabapentin or the product's components. ADVERSE REACTIONS: Somnolence, dizziness, ataxia, fatigue, nystagmus, headache, tremor, diplopia, nausea &/or vomiting, rhinitis, amblyopia. DRUG INTERACTIONS: Antacids. WARNING AND SPECIAL PRECAUTIONS: Elderly, renal impairment, hemodialysis, absence seizures, pregnancy, lactation. Discontinuation of gabapentin &/or addition or substitution of alternative therapy of epilepsy should be gradual, over a minimum of 1 week. May affect ability to drive or operate machinery. PRESENTATION: 100mg, 300mg and 400mg capsule, 600mg and 800mg tablet.

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INSTRUCTIONS FOR AUTHORS

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

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

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

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

Editorial
Editorial *Michael Leung* 114

Pharmacy Practice
A Summary of Development Progress on Involvement of Pharmacists in Public Health Emergency *Chiang, SC* 115

Overseas Attachment Program 2003/04 Experience Sharing *Leung, Suk Man* 118

Exploring the Roles of Pharmacists - My Clinical Attachment in the United States *Choy, Astra Wai-Yee* 119

A Special Journey *Lee, Janet* 121

Over-the-Counter & Health
Probiotics *Tse, Agnes LY* 123

Drug & Therapeutics
Geriatric Drug Therapy *(2 CE Units)* *Wong, Sammas* 127

Osteoporosis *Tam, Vicky* 135

Phamaceutical Technology
Genetic Engineering for the Production of Recombinant Tissue Plasminogen Activator *Cheung, Sau-Ha; Cheung, Hon-Yeung* 139

Herbal Medicines & Nutraceuticals
Topical Uses of *Euphrasia officinalis* L (小米草) for Soothing Tiredness of Eyes and Internal Uses for Curing Coughs or Hoarseness *Cheung, Hon-Yeung; Wong, Kam-Wah; Lai, Wai-Ping* 143

Society Activities
A Great Experience from Hong Kong Pharmacy Conference 2004 *Lee, Vivian WY* 147

Reporting Adverse Drug Reaction in Hong Kong *Helen Wong* 148

New Products
POSTINOR-2 *(Levonorgestrel)* 149
TARKA *(Verapamil HCL / Trandolapril)* 149

Editorial

There is a Hong Kong saying, "Change is everlasting". Year 2004 will be looked back on as a year of change in the history of Hong Kong. Changes shed lights of hope and opportunity. To the pharmacy profession, it is also a year full of changes and opportunities. As the theme of our Pharmacy Conference 2004, "Patients and Pharmacists: In Sickness and in Health", we turn our eye upon our patients. That means, how we act should be based on where the patients' needs are. You can name several initiatives born with this concept during the year. One of them is the Public Private Partnership Program (4P). Building trust and working relationship between the public and private sectors is a long process. It should be rolled out in phases so that we can gain experiences and that we fine tune our services from time to time. The 4P program actually originated from some projects carried out since 2002. It was firstly designed to provide pharmaceutical education to asthma patients via exhibitions and public affairs activities. The Practising Pharmacists Association of Hong Kong (PPA) and the Society of Hospital Pharmacists of Hong Kong (SHPHK) were the key contributors on it. In the second wave, two concrete proposals have been developed aiming to start collaboration among the Kowloon Central Cluster (KCC) and the Hong Kong West Cluster (HKWC) of the Hospital Authority (HA) and the two large chained pharmacy stores. In 2004, the partnership program was further evolved and an Advisory Committee was formed. It is led by Chief Pharmacist of the HA with the support from the three Pharmacists' Societies / Associations. Since then, the direction has focused on the Patients Referral Scheme on drug compliance and counseling services. The Hong Kong Pharmaceutical Journal (HKPJ) has witnessed the development of it and has been publishing articles on this program since 2002.

Another opportunity that our profession captured in 2004 was the pharmacist involvement in public health emergency. For this initiative, the three pharmacists' societies / associations worked with the governmental bodies (the Department of Health and Centre of Health Protection). A plan has been proposed for the pharmacists to take up the roles in performing health surveillance, forming communication network, providing health education and maintaining pharmaceutical services during emergency period (see page 115). If the active roles of a pharmacist in the public health are not limited to crisis situation, then the opportunity is much more attractive. For example, community pharmacies are contracted with the government to work as a counterpart to general practitioners and other allied healthcare professionals. Altogether, the group is accountable to the public health within a pre-specified geographical location. The key roles of pharmacists can be as a pharmaceutical expert, a heath educator, a medicine supplier, and a quality of life champion. It is dream, it is breakthrough and it is our value. However, it will never happen if we do not take action, to participate and to create.

I read a brief note published in The Pharmaceutical Journal reporting that there are 10 key roles in public health practice for community pharmacy in the United Kingdom (PJ 2004;274:37). Here, let me share this piece of information with you. You may find there are some similarities between the thinking of those British pharmacists and our future direction in Hong Kong:

- Conducts a local health needs assessment among regular pharmacy users and residents
- Recognize all the key influences on health, such as income and education, as well as lifestyle issue, such as smoking and diet
- Initiate and design projects that take advantage of the pharmacy's unique position and its contribution to the community
- Try to find dedicated funding that will be sustainable in the longer term
- Build a committed network of participating community pharmacies
- Seek the support of other stakeholders
- Provide training for all staff - preferably in a multidisciplinary environment
- Focus on the needs of the service user
- Evaluate the service
- Provide feedback on the service

For the HKPJ, in 2004, we published various kinds of articles to meet expectation of our readers. To achieve this, lot of hard works have been done behind the scene by our Section Editors and contributors. They prepare useful articles to enrich our knowledge in all aspect of our professional work. The Journal also reported key activities done by different pharmacists so that we can learn from best practices of the others. If you enjoy reading the HKPJ, I believe it is the biggest reward to our group of hidden hero. If you read the sharing from me and the previous Managing Editors, you can feel that the challenge for running a professional journal is not financial sustenance. Instead, it is far more difficult to keep the attention of readers to our journal, especially in this information-mania century. Therefore, we treasure very much your contribution and feedback to us in every way so that we can go ahead with creativity.

In this issue, we carry reports that outline some of the activities and accomplishments that have been conducted in the past 12 months as well as an update on the adverse drug reaction reporting requirements raised by the government recently. Furthermore, we keep our clinical part to be new and practical with articles on probiotics, pharmaceutical care to geriatrics and a product profile on *Euphrasia officinalis* L (小米草). For sure, you will not miss the chance to learn about genetic engineering for the production of thrombolytic agents. Our final issue of the year would not be complete without the traditional Supplements of the bi-lingual Poisons List, Antibiotics List and Dangerous Drug List. We hear a lot of feedbacks from our front-line colleagues that the Supplements are useful and handy helping them to find the Chinese name of medicines registered in Hong Kong. On behalf of the Editorial Committee, we would like to wish all our readers the compliments of the season and look forward to serving you again in 2005.

Special Announcements from the Managing Editor...

I have three special announcements in this issue. The first one is that we are going to change our e-mail addresses so that our staff can be more reachable by our readers. The new addresses can be found in the content page (page 113).

Secondly, I would like to thank two HKPJ colleagues, Ivy Chan and Vivian Ma who will change their roles from active contributors to become our faithful HKPJ readers. Ivy was our previous Business Manager and Vivian supported the Editorial Committee as the Secretary and helped the Journal to get business. Both of these valuable members have served the HKPJ for more than 8 years!

My last announcement in here, probably the most exciting one, is that our "New Products" Section Editor, Lucilla Leung, got married with our "Drug & Therapeutics" Section Editor, Wilson Leung, on 12Dec2004! Please join the Committee to send our best wishes to this new couple and all the blessings to their wonderful marriage.

Michael Leung
Managing Editor

A Summary of Development Progress on Involvement of Pharmacists in Public Health Emergency

Chiang, SC

I INTRODUCTION

During the SARS outbreak last year, pharmacists from various sectors of the health service were seen enthusiastically assuming their roles e.g. the public hospital pharmacists took prompt actions to ensure the continuity in supply on the required drugs, researched and consolidated information on the relevant drug treatment, related dosage regimen and associated adverse drug reactions for the clinicians; conducted training seminars to share with the community pharmacists the latest development on the infection control measures, personal protection and disinfection policies. The community pharmacists also took initiatives to set up telephone hotline to answer the queries from the general public on the proper use of drugs, on how to wear masks, disinfectants, etc., to deliver educational talks to schools, housing estates, etc., to alleviate the fears and misconception about the SARS and to teach the general public how to improve the personal and home hygiene to prevent the spread of the disease. After the outbreak, the three professional societies / associations were mindful of some what their neglected roles by the Government and made active submissions to the Government and the Board of inquiries to emphasize the roles of pharmacists in the promotion of public health, highlighting to the Government the accessibility and the convenience of the community pharmacies network that can be offered to the general public and suggesting that the Government should take strategic advantage of this community network and make full use of the pharmacists' expertise.

In April 2004, the Chief Pharmacist, Department of Health (DoH), on behalf of Centre of Health Protection (CHP), invited the three pharmacy professional societies / associations to a meeting to discuss how pharmacists can participate in public health emergencies. The following is a summary on the development progress and is written in sufficient details for all pharmacists to be kept informed on the matter.

II PROGRESS ON MEETINGS WITH CHP

The first meeting between representatives from CHP, DoH and the three professional societies was held in May. Amongst those present included, from the DoH side, Dr Leung Pak Yin, Dr Regina Ching, Dr Thomas Tsang, Mr Anthony Chan and Mr Thomas Tam; from the societies side were Dr Grace Lau, Mr Billy Chung and Mr Michael Ling, etc. and several others. Another follow up meeting was held in July, with Dr. Emily Leung as the convener. She was joined by Mr. Anthony Chan, Mr. Thomas Tam, Ms. Marian Ma and Ms. Lucy Mak from Department of Health. The representatives from the societies included Mr. Benjamin Kwong, Mr. Billy Chung, Mr. Ng Kim Wah and et al.

III SUGGESTIONS FROM CHP ON THE EXPECTED ROLES OF THE PHARMACISTS

Dr Leung Pak Yin suggested that there were three possible roles for the pharmacists i.e. surveillance, response and communication. DoH would consider, involving the community pharmacists, in the set up of the surveillance system, as they are in a good position to detect unusual upsurge in sales of certain drugs e.g. cold medicines and anti-diarrheas to prompt early responses, to ascertain and control disease outbreak. Then, as part of the response actions, pharmacists can be involved as volunteers in public health emergencies so that they can be provided with fact sheets, posters pamphlets on infectious disease, medical referral mechanisms and to disseminate such information to the patients and the public. In addition, pharmacists can also take part in manning hotlines and dispensing medicines. In this regard, it was agreed that training on matters such as infectious diseases, emergency response and how to man telephone hotline service should be provided to the volunteers.

It was also recognized that an effective communication channel between CHP and the professional societies, using e.g. emails, fax and telephones, should be established in order to follow up on the outstanding matters discussed and to facilitate the exchange of information between CHP and the pharmacists on infectious disease outbreak and public health emergencies. The issue of legal liability and insurance coverage for the volunteers during their of course work with CHP was brought up at the first meeting and was subsequently clarified that the government would not have such arrangement on insurance coverage for the volunteers. Plans are being made for regular tests/drills on the emergency response mechanism and the next territory wide exercise would be in October 2004.

IV ACTIONS TAKEN BY THE THREE PROFESSIONAL SOCIETIES / ASSOCIATIONS

Basing on the understanding on the suggested roles and expectations from CHP concerning the involvement of pharmacists during public health emergencies, the three professional societies / associations have worked out several things together in the months between May and August.

i) Suggestion to form the PCG

To avoid the CHP having to communicate separately and directly with each pharmacist (this was considered inefficient resulting in miscommunication), it was suggested that a Pharmacy Core Group (PCG) can be formed. As the name suggest, this PCG is a core group of pharmacists, from the three societies /

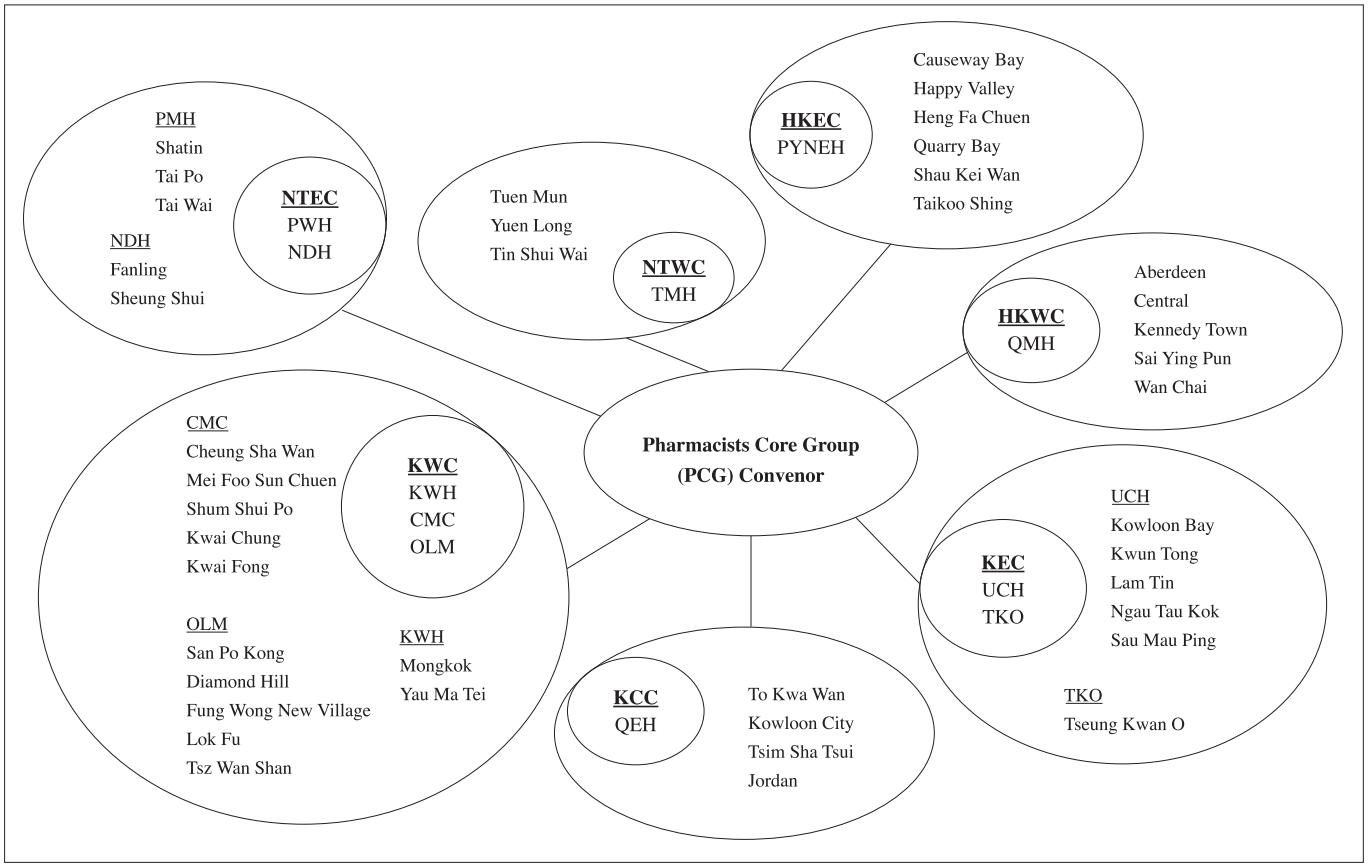

Figure 1. Seven Hospital Clusters / Community Districts Communication Network

associations but practicing in various pharmacy sectors, who have volunteered to come together. At the centre of the PCG, there could be a Head or Director who would be responsible for bridging the communication between CHP and the Core Group members who have been distributed into seven geographical clusters (see Figure 1).

At normal times, the PCG through the Head or Director will maintain and update the network of communications amongst pharmacists, share and disseminate any relevant information received from CHP e.g. notification on disease alerts, outbreak or spread of communicable diseases, etc. During urgent situations, the Head or Director will activate the PCG to support the request from CHP in the areas of surveillance, response and communication. With this PCG mechanism in place, some of the initial work within the group can include the setting up of communication network, identification and building up the pool of expertise for activation during emergencies, attending relevant training courses e.g. offered by CHP, working out the activation mechanism, etc. This proposed framework of communication network has been presented to Dr Emily Leung, DoH at the second meeting and it was recognised at the meeting that this was an organized approach that should be pursued.

ii) Invitation for signing up as pharmacist volunteers

At the same time, the three societies / associations have separately sent out letters to its members inviting them to sign up as volunteers to meet the purposes as suggested by CHP. There was an overwhelming response and each society/association was able to have about twelve to fifteen members coming forward. To enable pharmacists to gain a better understanding of what the possible roles of pharmacists in public health emergencies were, two articles from the ASHP on emergency response network and role of pharmacists in US during state of emergency were sent to the three societies / associations for reference. From these articles, a discussion paper "the draft document on the preparedness for the pharmacists in the CHP" was drafted by SHPHK and was sent to all the volunteers through the respective societies / associations.

iii) Discussion meeting amongst pharmacist volunteers

On 8th September, all volunteers met and the progress on the entire issue was summarized and all attendants were made fully aware of the reasons for calling the pharmacists together as volunteers, the possible roles and functions, duties and responsibilities, and the implications by participating as volunteers, etc. as outlined in the 'preparedness' draft discussion paper. In particular, the following suggested roles of the pharmacist volunteers were highlighted:

1. Logisticians
   a. Working out how medications and necessary supplies can be made between the concerned parties
   b. Distribute medications, provide preventive medical services

2. Safety Officer
   a. Provide immediate assistance and consultation with patients and other health care professionals
   b. Communicate necessary information about the prevention, treatment and support measures

3. Liaison Officer
   a. Collect and report significant findings in the community to the concerned officials using established channels
   b. Co-ordinate the actions

necessary between the concerned groups and those in the community

4. Hotline Service Provider
   a. Report to duty at the hotline service
   b. Get to know the latest information
   c. Answer telephone queries
   d. Provide solutions/patient counseling/information
   e. Collect & feedback

Also, the volunteers were reminded the following implications and they needed to consider carefully when they signed up for the volunteers:

1. Need to be aware of the levels of duties and responsibility
   a. Know what to do at all times
   b. Aware of the latest development at all times
   c. Bear risks and liability (no insurance coverage)
   d. Suffer financial loss (cannot go to work, travel cost, equipment cost)
   e. Bear blames and finger pointing

2. Need commitment
   a. Commit resources for communication (e.g. fax, mobile, pager, computer, emails, printer, etc.)

3. Need communication skills
   a. Communicate clearly, precisely, patiently

4. Need professionalism
   a. Handle crisis in a professional manner
   b. Cooperate with others
   c. Give / follow instructions
   d. Team work

iv) Attending training provided by DoH

On Sept 15th, forty five pharmacist volunteers attended the first 2-hour training session provided by CHP. The attendants became better aware of the technical skills for manning telephone hotlines, the operation of the hotline service and the experience gained by the nurses who were responsible for providing this service during the SARS outbreak.

V THE WAY FORWARD

The three societies / associations need to agree on how to proceed. Forming the PCG might be viewed by some as unnecessary and served only to subdivide the pharmacists. As explained, this PCG is a joint effort by the three societies / associations and is designed to be an effective means of maintaining the communication network. It would not duplicate any existing functions of the three societies / associations. With this PCG, it is hoped that in case of emergencies, the pharmacist network can be activated to respond promptly. We never know when this time is but we must be kept prepared at all times, remember we have already paid the price and even once is already too much. We can't afford to wait and see.

References

- Invitation letter dated 20th April 2004 from Chief Pharmacist DoH to 3 professional societies to participate in public health emergencies.
- Notes of meeting with DoH on 5th May 2004.The Proposal on formation of PCG written by SHPHK
- Notes of meeting with DoH on 27th July 2004
- Letters of invitation from three societies / associations for pharmacist volunteers
- "Bioterrorism preparedness and response: Emerging role for health-system pharmacists" AJHP Vol 61 Jun 1 2004
- "Illinois affiliate uses grant to improve emergency-response network" AJHP Vol 61 June 1 2004
- The draft document "The preparedness for the pharmacists in the CHP" written by SHPHK

Ms. S.C. Chiang is a Senior Pharmacist working in the H.A. Chief Pharmacist's Office. She wrote this article on behalf of the three professional societies/ associations (PSHK, PPAHK, SHPHK).

Overseas Attachment Program 2003/04 Experience Sharing

Leung, Suk Man

The clinical attachment program was established by Chief Pharmacist's Office of Hospital Authority with the College of Pharmacy, University of Illinois at Chicago since September 2001 with the aim to enhance the level of clinical practice of pharmacy practitioners in Hong Kong and to explore opportunities to improve the local pharmacy practice, teaching and research programs. The program was composed of 6 weeks of clinical practice training at the University of Illinois Medical Center Hospital and Clinics (Fig.1), adjacent to the College of Pharmacy. During the period, the participants were arranged to work as integral members in the numerous training sites for clinical pharmacy practice in accordance to our own interests and inclinations. The following is some of my experience sharing during the 6 weeks (February to March 2004) studying and learning at University of Illinois Medical center at Chicago.

Figure 1. University of Illinois Medical center at Chicago

The patient record system

The University of Illinois Medical Center Hospital has a total information system, the Cerner Gemini Millennium (Fig. 2) for Computerized Physician Order Entry (CPOE). The orders flow directly from the physician's electronic orders into an electronic version of the patient's pharmacy profile in the computer system. Not only it helps avoid order misinterpretation but provides alerts when prescribed therapy may be unsafe. This computerized system also takes care of all the admission & progress notes, lab results, medication ordering and administration records. There are some 10-15 stationed or mobile Gemini terminals in each ward, and all staff has our own assess login and password to the system. Clinical Pharmacist can review the medication administration record (patient profile) and obtain the necessary monitoring parameters (e.g. vital signs, laboratory test results) readily in this computerized system.

Figure 2. Cerner Gemini Millennium for CPOE

Intensive Care Unit

The medical Intensive Care Unit on the sixth floor (Fig.3) cares for patients who are suffering from severe medical illnesses, and very often they are respiratory collapse. The patient census for this unit is about 14, being cared by the critical care medical team, which includes physicians and clinical pharmacists. The clinical pharmacists make recommendations on drug selection, the dose, and duration of therapy; and monitor the drug administration and effects of the drug.

Figure 3. Medical Intensive Care Unit

The clinical pharmacy resident usually begins his day at about seven in the morning, preparing for the work round started at eight. During the wok round, medical residents and interns will discuss what happened to the patient during the night, the progress of the patient's evaluation or therapy or both, the laboratory and radiologic tests to be ordered for the patient, and talking with and evaluating the patient. The clinical pharmacy resident will advise on the use and dosage of drugs for these patients. He also identifies drug-related problems and provides evidence-based recommendations.

In the afternoon, the clinical pharmacist (faculty members of the UIC College of Pharmacy) will go over cases presented in the morning with the clinical pharmacy resident. This is a time for discussing the pathophysiology, the common and serious side effects of medication, defining factors to modify medication and outlining the monitoring parameters to evaluate response to therapy. It is very impressive to find out that pharmacists have such a prominent role in taking care of the intense drug therapy of patients in critical condition.

Infectious Disease Consults service

The clinical pharmacist is working with physicians in the Infectious Diseases Consults service, which take care of a list of patients with infectious diseases. They gather in a meeting in the afternoon at Room 7104E for discussing the care of the patient. During the round, they systemically evaluate each patient's response to therapeutic intervention, review the results of diagnostic or therapeutic procedures, and establish and communicate future treatment plans to the patient and the team.

Figure 4. Room 7104E - Infectious Disease Consults service

The clinical pharmacist is responsible for providing information of antibiotics, dosing and monitoring individual patients on narrow therapeutic spectrum antibiotics (aminoglycosides, vancomycin) according to their clinical conditions, renal functions and laboratory results. She also does all the troubleshooting

and providing proactive drug therapy recommendations. It is obvious that her role is highly appreciated and recognized by her teammates.

Ambulatory Care Practice Attachment at Rockford

The one-week Ambulatory Care Practice Attachment Program at Rockford is inspiring and meaningful. We observed and participated in clinical activities in two ambulatory care pharmacy practice settings, UIC University Family Health Center at Rockford and the UIC University Primary Care Clinic at Mt. Morris. The clinics are the home of the Family Practice residency program for medical and pharmacy students.

Clinical pharmacists working in the clinics reviewed patient charts and shared with us their expertise in clinical management of these patients. In addition, they will supervise pharmacy students to see patients with medical students together to assess overall status of patients and their response to therapy.

Meanwhile, we had a chance to join the educational noon conferences for asthma and pain control at clinics and attend a lecture for smoking cessation at the UIC College of Medicine at Rockford. The clinical pharmacist also taught us to perform evidence-based medicine by pulling out useful information from the medical literature, clinical trials, reviews and guidelines. We learned a lot from her and we are grateful for her professionalism, kindness and patience with us.

Conclusion

After the six week clinical attachment at University of Illinois Medical center at Chicago. I am refreshed with new insights of the practice of clinical pharmacy and the role of clinical pharmacists. I am also inspired of how a pharmacist could practice pharmaceutical care to patients. The rotation to different settings allows me to experience different modes of serve delivery and expertise emphasis.

In attending activities such as journal club and topics presentation, I realize my limitation in knowledge and the need of continuous improvement. "It is important to nurture the habit of reading regularly the profession's current periodicals. Here you will find information that will expand your knowledge of pharmacy. You will learn how pharmacists interrelate with other health professionals."

During the attachment, I have learnt to develop the skills of self-learning, critical thinking and decision-making. The focus of attention should be on learning the process of solving drug-related problems, rather than simply finding the scientific answer to the problem themselves.

"Changes in the profession are occurring all the time. Prepare yourself for being an active participant in those. Pharmacy will be more fulfilling of you if you go into it feeling that you are part of a movement that is committed to finding better ways to improve its service to the public."

I hope that the knowledge and experience I acquired from the US is immediately applicable and beneficial to our pharmacy practice. And I wish the attachment program continued to allow more pharmacists to share the joy and excitement.

Acknowledgement

I would like to express my sincere thanks to several parties. Firstly, I would like to acknowledge Prof. Alan Lau of the UIC College of Pharmacy for his work and time in coordinating program schedule, and for his kind hospitality during our stay in Chicago. I also appreciate for the preceptors of UIC for their time and eagerness in sharing their expertise with me. Especially to Lingtak, Isaac Cha and Linda Feng who inspired me a lot. Furthermore, I would like to thank the Chief Pharmacist's Office for organizing this program and the financial support. Finally, I would like to express my gratitude to Mr. William Chui, Associate Professor, Chief of Pharmacy Service, HKWC, for his support all along.

Leung Suk Man is currently working as a resident pharmacist at Queen Mary Hospital.

Exploring the Roles of Pharmacists - My Clinical Attachment in the United States

Choy, Astra Wai-Yee

The Exciting Trip

Even since I was studying Pharmacy at the university, I have always been eager to know what a pharmacist can do. Dispensing drugs? Counseling patients? Answering drug enquiries? There should be more, more for us to explore and contribute. Luckily, I had the opportunity to join the 6-week clinical attachment at the University of Illinois at Chicago (UIC) from Feb to March. I can't deny that it was a very valuable experience to widen my horizons on the well- developed clinical pharmacy practice in the USA. I was also very pleased to have Karen Leung from the Queen Mary Hospital to be my partner of this trip.

Arriving at UIC Medical Centre

On the third day of arrival at Chicago, while I was still adapting to the cold weather and the horrible jet lag, Professor Alan Lau from the College of Pharmacy, kindly introduced me to the training site - UIC Medical Center. The Medical Center provides a variety of services, including tertiary hospital care and ambulatory services at dozens of outpatient clinics. It also serves as an excellent training site for medical residents, pharmacy residents and PharmD students. I was excited to know that there are full-time clinical pharmacists working hand in hand with doctors at about eighteen different clinical areas. These areas include inpatient medical wards, surgical wards, ICUs, and a multitude of outpatient clinics like transplant clinic, diabetes clinic, etc.

Experiencing Clinical Pharmacy Practice

My rotation began at the Renal Dialysis Centre where patients had hemodialysis three times a week. The

clinical pharmacist, Dr. Cheryl Gilmartin has rounds with nephrologists every day to provide recommendations on drug therapy and solve drug related problems. I was glad to see that nephrologist and clinical pharmacist respect one another and cooperate for the benefits of the patients. Another role of the clinical pharmacist is to monitor therapeutic outcomes and drug side effects. Cheryl taught me the monitoring parameters useful for renal failure patients and the corresponding drug dosage adjustments using real patient cases.

Figure 1. Inside the UIC College of Pharmacy

The clinical pharmacist also acts as a good bridge between patients and doctors. She interviews new patients or their relatives to gain more information about patients' drug history, drug compliance and encountered side effects. It is very important because in the USA many patients see several doctors at the same time and the problem of polypharmacy is common. In addition, the concomitant consumption of herbal products and western drugs is arousing greater and greater concern about drug-herb interactions. Cheryl shared with me that in the USA, like in Hong Kong, the unregistered herbal products and health food pose a big challenge to pharmacists and other health care professionals.

My next rotation was at the Antithrombotic Clinic. There are three full-time clinical pharmacists managing patients on warfarin. The pharmacists get paid for their service, and they can prescribe warfarin on behalf of the referral doctors. A handy machine is used to measure the International Normalized Ratios (INRs) of warfarin patients at the clinic. The INR result comes out almost instantly and this saves a lot of patient waiting time. From every new patient to the clinic, the clinical pharmacist would first obtain detailed histories about their medical problems, drugs, lifestyle and diet. Then patients are given thorough education on warfarin management.

I feel like that each pharmacist acts like a detective to find the culprit(s) for any undesirable INR result. This task requires good knowledge, good communication skills and a meticulous mind. Based on her clinical experience, the pharmacist would then prescribe an appropriate warfarin dose and arrange a follow-up date for the patient. I was also impressed by the concise and systematic documentation done by the clinical pharmacists.

Figure 2. A clinic at Rockford

Apart from these, I also learned more about the management of warfarin therapy when patients plan to have dental checkup or surgical procedures. The pharmacist would design a detailed management plan for the patient, specifying when the warfarin should be held, when and how to give low molecular weight heparin shots on their own, as well as possibly when the warfarin is restarted.

Besides the ambulatory care settings, I also had a quick look at what clinical pharmacists do on ward levels. I rotated to the internal medicine wards with Dr. Ann Kuchta as my preceptor. On the first day we met, Dr. Kuchta gave me a very good demonstration on her approach to identify drug-related problems and to make recommendations to doctors. Her enthusiasm for providing pharmaceutical care for her patients was very impressive.

In addition to joining the medical rounds with physicians, I also had the opportunity to join the discussion among clinical pharmacist, pharmacy resident and PharmD candidates about individual patient drug plans. The discussion was very rewarding and it was a very good learning experience. What is more, I was very glad to learn from Dr. Kuchta the skills in presenting patient cases and formulating pharmaceutical care plans. These skills are very useful and essential to the work of a clinical pharmacist.

In this rotation, I had more opportunity to use the Gemini computer system to read patients' laboratory results, physician's care notes as well as drug orders. This system facilitates pharmacist to monitor the efficacy and side effects of drug therapy. There was too much to learn on the internal medicine wards and I regretted I didn't have the time.

In the last week of the attachment period, Karen and I went to Rockford and met two friendly pharmacists, Linda Chang and Isaac Cha. They shared their experience and knowledge with us, giving us a nice and fruitful end to the trip.

Pharmacists all over the world are expanding their roles. We, Hong Kong pharmacists, can work together to overcome obstacles ahead and strive for better pharmacy services.

Giving thanks

I should take this opportunity to express my gratitude to those people who made my attachment a wonderful trip. To begin with, I appreciate the Chief Pharmacist's Office for the organizing the overseas attachment program. Also, I would like to give special thanks to Professor Alan Lau and the College of Pharmacy for giving so much effort in arranging the attachment rotations. Besides, I thank Professor Lau, Mrs. Lau (Shirley), Priscilla and Kwanta for their care and support given to me during my stay at Chicago.

What is more, I am most grateful to my preceptors and other pharmacists that I met at UIC, including Dr. Cheryl Gilmartin, Dr. Aimee Chevalier, Dr. Ann Kuchta, Dr. Christina Mactal Haaf, Dr. Linda Chang and Dr. Isaac Cha for their patience and valuable time in coaching my rotations. Last but not least, I appreciate Ms. Rosa Yao for granting me the chance to widen my horizons and my colleagues who shared my work during the study leave.

Astra Choy Wai Yee, is currenty a resident pharmacist at the Princess Margaret Hospital.

A Special Journey

Lee, Janet

My tough days

January 10, 2004 was a tough day for me. This was the day I left my newly wedded husband and started my trip to the United States. After over 10-hour flight, I arrived at Chicago, Illinois, local temperature was roughly 20F. After settling, I started my six-week clinical attachment in the University of Illinois Medical center, Chicago.

I belonged to the third batch of this overseas clinical attachment program. I started my rotation in January; while Ms. Astra Choy (Princess Margaret Hospital) & Ms. Karen Leung (Queen Mary Hospital) started in late February. I envy them of having a chance to work in pair in such a challenging training.

My exposure in the University of Illinois (UIC)

University of Illinois Medical Centre located at about 40 minutes ride of CTA subway from my downtown apartment, is one of the renowned teaching institutes in the United States.

Thanks to the arrangement of Prof. Alan Lau, the co-ordinator of the clinical attachment program, on my first day there, I was given an orientation of the medical center & college of pharmacy, including all the underground routes, connecting all the buildings together at the UIC. Even though I have chosen critical care as my main area of interest and spent five weeks in Medical Intensive care unit (MICU), with Prof. Lau's arrangement, I was able to visit internal medicine service, warfarin clinic and dialysis clinic. I observed pharmacotherapists providing clinical services in these specialties. Before I started my rotation at MICU, I was introduced to the "Gemini", the computerized patient care system. The advance in in-patient electronic medication order and clinical data system had enlightened me that we still have a lot of IT development ahead locally.

MICU rotation

In UIC, there are two intensive care units, one for surgical, the other for medical. There are nine beds in the medical intensive care unit; however, patient population is highly variable, from 4 to over 20. If all beds were fully

Figure 1. (left to right) Ms. Astra Choy, Ms. Karen Leung, Prof. Alan Lau, Mr. William Cheung (Princess Margaret Hospital), myself and Dr. Todd S. Ing (author of Handbook of Dialysis) at the UIC College of Pharmacy.

occupied in MICU, patients may be colonized in the emergency department, medical and surgical wards. The MICU has one attending physician, one clinical pharmacist (Dr. Lingtak Chan, my preceptor for the rotation), a medical resident, three medical students, a pharmacy resident and two final year Pharm D. students. Normally, Dr Chan only took pharmacy students for a two 4-week slot per year. Fortunately, I had such a chance of working with them.

My daily schedule at MICU

A typical day started usually before 7am at MICU, our work involved updating patients' progresses & checking if any new patient admitted overnight. If new cases have arrived, I would assess their admission notes, evaluate their medication regimen, medical history, major complaint, checking if there was any drug-drug interaction. Pharmacy students and myself then divided up the number of patients so that each one of us would be managing roughly three patients at a time. At around 8a.m., medical students would report each patient's condition, or any progresses to the medical resident. The medical resident

Figure 2. (left to right) Ms. Astra Choy, Dr John Garofalo (Associate director of clinical services), Ms. Karen Leung and myself at UIC hospital pharmacy.

will advise for any additional tests and orders that were required. Our pharmacy team would join their discussions and made clinical decisions together.

At 9 a.m., the attending physician would lead the "attendant round" at the conference room. Most of the medical students would be so excited since they may face questions that they may not know the answer. Dr Lingtak Chan and the pharmacy resident, acted as a drug consultant in the team, who recommended appropriate drug regimens for patients.

Common questions were: "How would you taper the steroid dose for Mrs. Charles?", "What empiric antibiotic would you suggest for Ms. Jones?"

Everyone would then gather around the X-ray/ CT computer interpreting the radiograms of each patient. The attendant would lead the team to patients' bedside, "eyeballing" the patient and perform necessary interventions. After the round, medical members were usually busy with patient monitoring procedures; while the pharmacy team, with Dr Lingtak Chan's instruction, would be busy entering prescribing orders into Gemini and communicate such information to nurses. The attendant round usually took till lunch time to finish.

The pharmacy team usually performed case reviews in the afternoon; members would be responsible for presenting their cases. It would be our turn to face challenges since Dr Chan would throw difficult questions to us. Through such question and answer forum, we could learn a lot from him. He also shared his view with us areas involving disease conditions, medication regimens, laboratory data interpretation, ventilator setting, etc. Dr Chan is renowned of keeping students till 8 to 9 pm but we all enjoyed learning from him through the lectures.

Sometimes I picked up the role of "ambassador" as staff in UIC approached me regarding the practice in Hong Kong. MICU in Chicago and ICU in Kwong Wah Hospital, where I worked, both employed the same computer system, "Care vue" to record vital signs and relevant medical information for each patient. I am proud to say we utilized "Care vue" even more extensively in Hong Kong.

Doctors and nurses employed "Care vue" for documenting physician notes, nurses' notes, medication orders, laboratory results, etc. However, in UIC, they had the luxury to having two computer systems for recording and monitoring patients' care. For vital signs, they referred to "Care Vue"; they used "Gemini" for medication orders, laboratory results, and physician notes entry.

Also, unlike MICU at Chicago, not only doctors participated at ICU ward round, nurses also gathered at each patient's bedside discussing patents' medical progresses and treatment regime in Kwong Wah Hospital. I consider our treatment discussion with nurses involved is quite useful, since we could grasp a more complete status of the patient. Also, our treatment meeting with nurses enable us to change the treatment regime in real-time through our communication with nurses. We could provide the most appropriate treatment for patients in a more efficient manner.

Figure 3. Dr Lingtak Chan, Dr. Joanne Witsil, pharmacy resident, Jason & Darlene, pharmacy students, and myself at MICU.

A golden opportunity

During my five week rotation in MICU, I had attended an autopsy round of a patient who passed away in the critical care unit. He was a 30 plus year old male with pheochromocytoma. His adrenal gland was one and half-times over the normal size. The patient died of toxic megacolon due to Clostridium difficile infection. The pathologist also showed us the yellowish pseudomembrane attached to the colon. Medical members who had previous attended that patient participated the autopsy round. We had an interactive discussion of the disease condition, medication regimen, infection control measures, and any possible measures to cure him from any critical condition.

In MICU, most patients were in critical conditions and you could imagine there are always unpredictable events to happen everyday. I had witnessed a patient developed ventricular tachycardia, the scene was quite similar with the popular hospital drama "ER", where everyone gathered to perform cardiopulmonary resuscitation. The doctor ordered epinephrine, sodium bicarbonate and Joanne, the pharmacy resident, quickly cracked the E-kit and prepared medications for administration. Unfortunately, the patient could not survive after the team paying the best effort. I also had an opportunity to witness some complicated procedures such as, the placement of Swan Ganz catheter and bronchoscopy. I counted these as my valuable experience, since every procedure did carry a complication with it. Without actual experiences, one may not be aware all the potential complication could involved. All these experiences taught me a good lesson on how to apply the multidisciplinary approach in the provision of best care for patients.

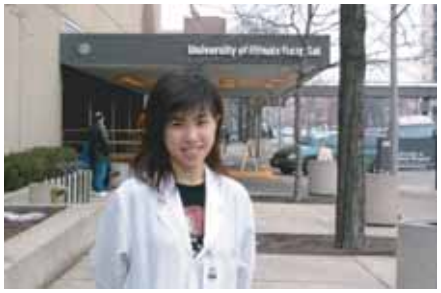

Figure 4. The UIC Medical Centre (I was freezing with only wearing lab coat)

Conclusion

Quoted from a letter for my friend during the first week of my attachment program, *" it is a long way before I can become a clinical pharmacist"*. I agreed with Mr. Simon Leung, Pharmacist at Pamela Youde Nethersole Eastern Hospital, *"it is impossible to become any specialist in six weeks' training."* quoted from his UIC experience sharing in the HKPJ. In order to become a clinical pharmacist, I understand that I should train my competency in particular areas, particularly critical care. Even after training with the pharmacotherapists, I may not have acquired all the clinical knowledge, but the training has shown me the route of how to learn continuously to prepare for the challenge ahead. Even though clinical skills are essential, I consider patients' care is more crucial. Throughout this rotation, with the inspiration of pharmacotherapists, especially Dr Lingtak Chan and Dr. Ann Kuchta, I appreciated how we should treat patient as a whole, not just on one or two organ system. As Lingtak always said, *"we do not treat the numbers (laboratory values), we are here to treat the patient"*. The six-week clinical experiences has shed light for me and led me to a route, may be a long, winding road to the destination of becoming a clinical pharmacist.

Acknowledgement

I appreciate support that had facilitated my valuable six-week training. Thanks to Mr Winham Lok & the Chief Pharmacist's Office, for their effort to organize this program. Being assigned as the third batch of this clinical attachment program, I also appreciate advices from colleagues of previous batches, Mr Simon Leung, Ms Josephine Yung, Ms. Dora Chan & Mr. Stanley Wu.

Thanks to Prof. Alan Lau for organizing such a marvelous training program. This has given me an opportunity to experience different aspects of clinical pharmacy services in the United States. Again, thank him, his wife (Shirley) & Mrs. Lau for the hospitality they provided. Despite the time I stayed in Chicago was in the coldest month of the year, I felt the warmth due to the hospitality provided by them.

Thanks to Dr. Andrew Donnelly (UIC hospital pharmacy director) & his colleagues for arranging us a hospital pharmacy tour. This tour provided us with an overview of the hospital pharmacy services and their roles coping with clinical pharmacists aiming to provide better patients' care.

I express my appreciation for Dr Lingtak Chan to take me as his student, despite his busy schedule. He spent time with me sharing his view of clinical pharmacy and possible ways to provide clinical pharmacy service in our setting. I also appreciate Dr Ann M. Kuchta, Dr Aimee Chevalier & Dr Cherly Gilmartin providing me a valuable shadowing experience in showing me the clinical pharmacists' work in the internal medicine, warfarin clinic and dialysis clinic services.

Above all, I want to extend my gratitude for my boss, Mr. Michael Ling, Kwong Wah Hospital Department Manager, for allowing me to be out of my normal duty from Kwong Wah Hospital for 6 weeks and explore such a precious exposure/training at the UIC in Chicago. This experience has definitely broaden my view on the clinical pharmacy and being so fortunate as to have had such a great first-hand introductory experience, I am keen to further my training in the areas of clinical pharmacy so as to be of use in helping the Hospital Authority serve the wider community.

Figure. 5 Navy Pier- Popular tourist destination.

Janet Lee is a pharmacist working in the Kwong Wah Hospital and she graduated from a pharmacy school in Canada.

Probiotics

Tse, Agnes LY

I INTRODUCTION

The word "probiotic" is derived from the Greek meaning "for life". This concept was established early in the last century, when Metchnikoff postulated that lactic acid bacteria in fermented milk products provided health and longevity benefits to Bulgarian peasants.[1] In the 70's, Parker defined the term as "Animal feed supplements that have a beneficial effect on the host animal by affecting its gut microflora." At that time, the term was applied specifically to animals.[2] As the role of microorganisms in human health and disease became better known, several definitions evolved over the past few decades. Recently, a much broader definition has been developed: "Live microorganisms, which when administered in adequate amounts, confer a health benefit on the host".[3] The application has been expanding from the limited use in fermented milk industry to the fast-growing development of functional foods in the form of powder, tablet or capsule. This definition, however, confines that the microorganisms must be viable. Some researches are now focusing on inactivated organisms, bacterial components or DNA. The upcoming findings may change the perspective in the future.

II WHAT ARE PROBIOTICS?

Various criteria were used for isolating and defining probiotics.[4] Microorganisms of human origin seem important as some effects rely on species specificity. They must arrive at the site of action by resistance to acidity, bile and digestive enzymes in the gastrointestinal tract or by providing large numbers of live organisms to compensate for loss during passage. Adherence to intestinal epithelial cells and colonization are probably other prerequisites to give the microorganisms' advantages. Safety for human consumption together with scientifically proven health effects would be important from the regulatory and market point of view.

Microorganisms from many genera are being used as probiotics (table 1). The most commonly used strains are members of lactic acid bacteria; *Lactobacilli* and *Bifidobacteria*. *Lactobacilli* are gram-positive rods, primarily facultative or strict anaerobes that produce a major amount of lactic acid when they ferment glucose. Despite the intense interest in probiotics, *Lactobacilli* make up no more than one per cent of the total bacterial count of human faeces. In general, *Lactobacilli* have not been associated with any disease. They have been regarded as nonpathogenic members of the intestinal and urogenital floras.[5,6] *Bifidobacteria* are also gram positive rods, obligate anaerobic bacteria that produce acetic and lactic acid from the fermentation of glucose. They represent up to 91% of the faecal microflora in breast-fed infants, but no more than 1-3% of those in adults.[5] It should be noted that experimental data suggest the potential use of yeast strains as probiotics, though there are rare attention on its use and safety.[7]

III MECHANISMS OF ACTION

The concept of microbiologic balance in the intestine has been well established in the literature. Previous researches focused on intestinal colonization and probiotic-induced suppression of pathogen growth and/or invasion.[9] Two strains of probitoics, *Streptococcus thermophilus* and *Lactobacillus acidophilus*, were demonstrated to inhibit the adhesion and invasion of Escherichia coli into human intestinal epithelial cells by enhancing phosphorylation of actinin and occlusion in the tight junction region.[10] Another proposed barrier function of *Lactobacillus* rhamnosus GG was shown in intestinal cell models through preventing cytokine-induced apoptosis.[11] Some other proposed mechanisms of probiotics include lowering intestinal pH by stimulating lactic acid, production of bacteriocins, hydrogen peroxide and biosurfactants.[12]

Recent research has focused on probiotics and their secreted products in modulating immune responses and epithelial function in the host by different mechanisms. Without altering the bacterial number and colonization in the intestine, strains of *Bifidobacterium* and *Lactobacillus* used in treating or preventing eczema/dermatitis in infants and children appeared promising.[13-15] It was also well documented that epithelial and immune cells can discriminate between different microbial species and respond differently to whole bacteria, bacterial components or DNA.[16-19]

IV PREBIOTIC AND SYNBIOTIC

A closely related concept is prebiotic.

Table 1. Microorganisms used as probiotics [8]

Genus	Species	Example strains
Lactobacillus	*acidophilus*	La5
	casei	Shirota
	fermentum	KLD
	johnsonii	La1
	paracasei	F19
	plantarum	299v
	rhamnosus	GG
	brevis	
Bifidobacterium	*bifidum*	
	breve	
	longum	BB536
	infantis	
	adolescentis	
Propionibacterium	*freudenreichii*	JS
Escherichia	*coli*	Nissle 1917
Enterococcus	*faecium*	SF68
Pediococcus	*acidilactici*	
Saccharomyces	*cerevisiae*	boulardii

A prebiotic substance has been defined as "a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon".[20] Therefore, prebiotics should escape digestion in the upper gastrointestinal tract by pancreatic and brush-border enzymes, reach the large bowel, and be utilized as fuel by a selective group of microbes that have clear health promoting properties, i.e. probiotics.[21] Commonly used and studied prebiotics include lactulose, fructo-oligosaccharides, galacto-olisaccharides, xylo-oligosaccharides and inulin.[22] Gibson and Roberfroid introduced a new concept, the synbiotic, or combination of probiotics and prebiotics. They defined a synbiotic as a "mixture of probiotics and prebiotics that beneficially affects the host by improving the survival and implantation of live microbial dietary supplements in the gastrointestinal tract, by selectively stimulating the growth and/or activating the metabolism of one or a limited number of health-promoting bacteria, and thus improving welfare".[20] Despite the increasing popularity and the number of researches in prebiotics, for the purposes of discussion, this article will focus on probiotics.

V CLINICAL EFFECTS OF PROBIOTICS

i) Constipation

Constipated individuals have been observed to have a modified faecal microflora with reduced levels of *Bifidobacteria, Bacteroides* and *Clostridia.* Probiotics have been suggested to relieve the condition.[23] However, review of the literature does not support this claim. This may be explained by the diverse causes of constipation, including lack of physical activity, fiber intake, fluid intake and medications. The altered microflora appears to be more of a consequence than a cause of constipation.[8]

ii) Lactose intolerance

Lactose intolerance is a common condition in human except the decent in northwestern Europe. The condition is caused by a reduced production of the intestinal enzyme, lactase. Lactase degrades lactose to glucose and galactose. Upon ingestion of lactose, the undigested load exerts an osmotic effect in the small intestine with subsequent secretion of fluids which leads to loose stools accompanied by abdominal pain of unknown origin.[24] Most of the studies on lactose intolerance involved fermented milk products rather than isolated probiotic strains. The positive effects were explained by the presence of lactase in the bacteria fermenting the milk. In addition, the higher viscosity of fermented milk compared to plain milk allows a longer transit time and thus further aids lactose digestion.[25]

iii) Childhood diarrhea

Rotavirus is one of the most common causes of acute childhood diarrhea.[26] The probiotics *L. rhamnosus* GG, *L. reuteri, L. casei,* and *B. lactis* have been shown to shorten the duration of acute rotavirus diarrhea in well-designed trials.[27-29] A meta-analysis of 18 clinical trials by Huang *et al.* demonstrated that coadministration of probiotics with standard rehydration therapy in children reduced the duration of diarrhea by about 1 day. Similar results using *L. rhamnosus* and *L. reuteri* for 5 days were obtained in two studies carried out in outpatient and inpatient settings.[30,31] However, evidence for the role of probiotics in prevention or treatment of diarrhea caused by other viral or bacterial pathogens was less well documented.

iv) Traveler's diarrhea

The prevention of travelers' diarrhea by probiotics in several studies has been inconsistent. In a study involving more than 200 travelers to developing countries, *L.* GG decreased the risk of diarrhea to 3.9 per cent compared to 7.4 per cent in the control group.[32] Black *et al.* demonstrated a reduced incidence of diarrhea in travelers to Egypt given capsules of *S. thermophilus, L. bulgaricus, L. acidophilus* and *B. bifidum.*[33] However, the same result was not obtained in another group of Austrian tourists.[34] The effect of probiotics on travelers' diarrhea appears to differ between strains and destinations of the traveler.[35]

v) Antibiotic-associated diarrhea

Recently, metaanalyses on randomized, double-masked, controlled trials of probiotics in the prevention of antibiotic-associated diarrhea have been published. The results confirmed the preventive role of probiotics, including *Lactobacillus, Saccharomyces boulardii, Enterococcus faecium* SF68, alone or in specific combination, over placebo.[36,37] Ahuja *et al.* investigated the effect of *Lactobacillus* in 740 patients receiving ampicillin/cloxacillin for pre-cataract surgery treatment.[38] The incidence of diarrhea in patients receiving antibiotic alone was 13% compared with 0% in patients receiving both antibiotic and probiotic. The probiotic *Clostridium butyricum* was also found effective in reducing diarrhea in children on antibiotics for upper respiratory tract infections.[39] Overgrowth of *Candida* in the gastrointestinal tract is another common consequence of antibiotic therapy. Animal studies using the probiotic *Saccharomyces boulardii* suppressed the colonization of *Candida albicans.*[40] Further studies are needed to explore whether a similar response occurs in human.

The use of probiotics in *C. difficile* diarrhea has also been investigated. *Saccharomyces boulardii* was found to prevent disease recurrence in patients with more than one sequential infection.[41] Wullt *et al.* demonstrated the ability of *L. plantarum* 299v plus metronidazole in reducing the incidence of recurrent *C. difficile* diarrhea compared with metronidazole with placebo.[42] The ability of *Lactobacillus* GG to eradicate *C. difficile* in subjects with relapsing colitis was shown in a study of small number of subjects.[43] Another probiotic strategy was proposed by Sambol *et al.*, using nontoxigenic *C. Difficile* strains in hamsters to prevent diarrheal disease upon challenge with toxigenic *C. difficile.*[44] This novel concept, together with the eradication of *C. difficile*, needs to be further explored for confirmation of the benefit.

vi) Irritable bowel syndrome (IBS)

Lactobacillus plantarum 299v was shown to reduce flatulence and abdominal pain but not bloating in IBS.[45] Quigley and colleagues studied 77 patients with IBS who were randomized to receive either *Lactobacillus spp* or *Bifidobacterium spp* in milk or control milk, for 8 weeks. Subjects who received *Bifidobacterium* had a significant improvement in pain, bloating, and stools. However, any benefit of *Lactobacillus* was limited to fluctuating improvement in pain. Probiotic strain specificity appears to be important in determining the outcome in IBS.[46] The study results of probiotics have been scant and inconsistent.

vii) Inflammatory bowel disease (IBD)

Inflammatory bowel disease is clinically divided into two types, Crohn's disease (CD) and ulcerative colitis (UC). The aetiology of the disease is not fully understood, yet the disturbance in gut flora is thought to play an important role. Manipulating the composition and activity of the gut flora may improve the disease.[8] Animal models of IBD suggested that probiotics can prevent or treat established intestinal inflammation. *L.* GG, *L. salivarius, B. longum, B. infantis* and a proprietary

probiotic brand VSL#3 were shown to be effective in preventing or ameliorating colitis in different animal models.[47-49] Yet, probiotics exert different effects on different experimental models.[50]

Clinical trials have demonstrated the efficacy of probiotics in the maintenance or remission of UC, as well as the treatment of active UC and CD.[50]

Borody *et al*. used human fecal rectal infusions from health individuals for 5 days in patients with UC. Full clinical remission, cessation of UC medication and normalized endoscopic and histologic features were attained in all patients.[51] While *L. casei* or *L. bulgaricus* reduced release of TNF-α from intestinal mucosa of patients with CD, *L. crispatus* or *E. coli* did not demonstrate the same effect.[52] The effect of *Lactobacillus* GG in CD was inconsistent among studies.[53]

viii) *Helicobacter pylori* infection

The role of probiotics in the prevention or treatment of *Helicobacter pylori* infection was reported. The effect was attributed to an inhibition of *H. pylori* growth and its adhesion to epithelial cells, as well as effects on the host immune system. *In vitro* study demonstrated the inhibition effect of *Lactobacillus gasseri* on the growth of clarithromycin-resistant *H. pylori*.[54] The probiotic strain also significantly decreased *H. pylori* colonization. In a study by Cruchet *et al*., *Lactobacillus johnsonii* significantly decreased *H. pylori* colonization in school children while another strain, *Lactobacillus paracasei*, did not influence colonization.[55] In a study of *H. pylori* eradication using triple therapy, Cremonini *et al*. demonstrated the effect of different probiotics on anti-*H. pylori* therapy-related side effects. *L. rhamnosus, S. boulardii, L. acidophilus* plus *B. lactis* lowered incidence of antibiotic associated diarrhea but did not alter eradication rate or compliance compared with placebo.[56]

ix) Urogenital disease

Despite the increasing incidence of antimicrobial resistance, increasing numbers of urinary tract/vaginal infections and secondary complications (e.g. increased risk for preterm delivery) arising from persistent vaginal infections, the prevention and treatment of urogenital infections have relied mainly on antibiotics and antifungals.[57] Studies showed that depletion of *Lactobacillus* in the vagina associated with overgrowth of anaerobic pathogens causing bacterial vaginosis resulted in significantly increased risk for HIV, gonorrhea, Chlamydia, and herpes simplex infections.[58-60] The concept of a protective role of the commensal vaginal microflora sets the basis for the research on application of probiotics to various urogenital diseases.

Different routes have been adopted for probiotic administration in urogenital care. These include incorporation in skimmed milk-based preparations, dried microorganisms in form of oral capsules, vaginal pessaries or capsules.[57] Studies using daily oral intake of *L. rhamnosus* GR-1 and *L. fermentum* RC-14 can modify the vaginal flora, resulting in less yeast and fewer coliforms.[61] Shalev *et al*. demonstrated yogurt enriched with live *L. acidophilus* was associated with an increased prevalence of colonization of the rectum and vagina by the probiotic, and suggested that ingestion of yogurt may have reduced episodes of BV.[62] Hilton *et al*. also demonstrated the ability of *L. acidophilus* enriched yogurt in reducing both candidal colonization and infection.[63] Previous studies are providing encouraging results, but well-designed, large scale studies are required to define a clear role of probiotics in urogenital diseases.

x) Immunity and allergy

The systemic effect of probiotics on the immune system was demonstrated in studies targeting different conditions. One of the studies applied *L.* GG to adults receiving typhoid vaccine; another one applied the same strain to children in Finland receiving rotavirus vaccine.[64,65] Both studies suggested an enhanced antibody response in the probiotic-treated group. In a double-blind, randomized, long-term study, milk containing *L.* GG reduced the incidence of respiratory infections and antibiotic treatment in children at day-care centers.[66]

Preliminary results on atopic eczema were published. Perinatal administration of the probiotic *L. rhamnosus* GG (ATCC 53103) reduced incidence of atopic eczema in at-risk children during the first 2 years of life. The follow up data at four years showed a possible extension of the reduced risk. Additional studies to address the role of probiotics in the prevention of atopic diseases are warranted.[67]

xi) Cholesterol

Two controlled studies examined the effect of probiotic-enriched yogurt in subjects with normal to borderline serum cholesterol levels. *L. acidophilus* taken 200ml daily[68] or yogurt containing the same strain of probiotic together with the prebiotic, fructo-oligosaccharides, taken 375ml daily[69], reduced serum cholesterol by 2.9 and 4.4 per cent respectively. The consumption of yogurt enriched with *L. acidophilus* in a placebo-controlled study of 78 healthy men and women showed no effect on serum lipids.[70] The effects of *L. acidophilus* on serum cholesterol are inconclusive.

xii) Cancer

A double-blind trial was conducted in 138 patients with superficial transitional cell carcinoma of the bladder following transurethral resection to evaluate the prophylaxis of recurrence by an oral *Lactobacillus* casei Shirota preparation. The probiotic showed a prophylactic effect in subgroups with primary multiple tumors or recurrent single tumors.[71]

The effects of probiotics on cancer, with emphasis on colon cancer, have been based largely on *in vitro* and animal studies. Some of the probiotic strains used include *Streptococcus faecalis, Clostridium butyricum,* and *Bacillus mesentericus*. Different mechanisms involved may include alteration of the metabolic activities of gut flora, alteration of physicochemical conditions in the colon, binding and degradation of potential carcinogens, quantitative and/or qualitative alterations in the intestinal flora incriminated in the production of carcinogens, production of antitumorigenic or antimutagenic compounds, enhancing the host's immune response, and effects on the physiology of the host.[50]

A European Union funded project, namely SYNCAN, which involves 8 research centers in Europe, is underway to examine the effect of probiotics on colon cancer. The core of the project is a human dietary intervention study for 12 weeks. The research utilizes a synbiotic that consists of two probiotics, *Lactobacillus* GG/*Bifidobacterium* lactis, and the proprietary prebiotic, Raftilose® Synergy1 containing inulin and oligofructose. (SYNCAN) The upcoming results will provide lights for future investigations into the relationship between probiotic, synbiotic and colorectal cancer.[72]

VI SAFETY

Probiotics have been consumed without the observation of major side effects. Extremely rare cases of infective endocarditis and bacteremia have been described for *Lactobacillus* and *Bifidobacterium* with underlying diseases. Case reports also documented fungemia in immunocompromised patients and

exacerbation of diarrhea patients with ulcerative colitis consuming *S. boulardii*.[50] Although the risk of adverse effects is thought to be very low, caution should be taken in the use of probiotics in premature infants and immunocompromised individuals. It is important to watch out for theoretically side effects including deleterious metabolic activities and gene transfer.

There is currently no consensus worldwide on the doses of probiotics. Consumers are therefore advised to follow the instructions provide by the manufacturers.

VII CONCLUSION

Well-designed studies suggest that consumption of probiotics have various health benefits, in particular, therapeutic effects in rotavirus diarrhea and recurrent *Clostridium difficile* infections. Other promising areas of application include inflammatory bowel disease, irritable bowel syndrome, urogenital diseases and atopic diseases. Additional investigations will better identify the potential subgroup of patients, specific strains, duration of treatment, in support of their mainstream use.

In view of the accumulating evidence and growing consumption of probiotics, regulatory authorities are planning the implementation of clear guidelines for evaluation and minimum requirements needed for probiotic status. We are expecting products with well-defined strain identity, advanced manufacturing technologies, clear storage instructions, as well as proof of clinical safety and efficacy. With the support of scientific evidence, specific health claims on product labels would be more informative to the public to avoid misinterpretation.

Agnes Tse graduated from the CUHK and is now working as a pharmacist in a local pharmacy chain.

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Geriatric Drug Therapy

Wong, Sammas

2 CE Units

I INTRODUCTION

i) Aging population

According to the Census and Statistics Department, the proportion of the population in Hong Kong aged 65 or over is expected to rise substantially, from 11.7% in 2003 to 27% in 2033. It is also anticipated that the median age of the population will increase from 38 in 2003 to 49 in 2033. Over the past two decades, Hong Kong has experienced a decline in mortality rate and a corresponding increase in life expectancy. The same trend is projected to continue in the next 30 years. With the continuous advancement of medical technology, the life expectancy for males will be expected to be 82.5 years and 88 years for female by 2033. [1]

Due to the changes in the physiological functions and increase in the number of medical conditions, aged people are naturally taking more medications than the young. In Canada, the elderly represent 12% of the population but account for nearly 40% of total prescriptions. [2] Consequently the elderly will be more susceptible to drug-related problem such as adverse drug reactions, inappropriate drug prescribing, polypharmacy and drug-drug interactions.

ii) Prevalence of drug use among the elderly in Hong Kong

In Hong Kong, local data showed that around 75% of those aged 65 or above suffer from one or more chronic diseases, [3] and 71% of people aged 70 years or over took drugs, [4] 20% of whom were taking five or more. [5]

II PHYSIOLOGICAL CHANGES ASSOCIATED WITH AGING

To understand how drug handling is altered in elderly patients, we have to look into the pharmacokinetic and pharmacodynamic changes upon normal aging. Table 1 shows the age-related physiological changes which can affect pharmacotherapy.

i) Pharmacokinetics changes [6,7,8]

Old people have decreased gastrointestinal motility, reduced blood flow by 40% and increased gastric pH. The extent of drug absorption was not affected in clinical studies. However, when a rapid achievement of therapeutic concentration is required (e.g. for antibiotics), alternative routes of administration (such as intravenous, intramuscular) may be considered.

Elderly people have a net increase in adipose tissue which increases the volume of distribution and half-life of lipid soluble drugs such as diazepam, amiodarone, haloperidol and desipramine, etc. Meanwhile, the reduced lean body mass and total body water results in reduced volume of distribution and increased plasma concentration of water soluble drugs. Examples include cimetidine, digoxin and ethanol. On the other hand, acidic drugs are bound by serum albumin. The total serum albumin level decreases approximately by 12% in the elderly, and even more for malnourished individuals. Thus, the resultant increase in the fraction of free drug in serum may necessitate extra caution if the drug is highly protein bound (e.g. warfarin, phenytoin, diazepam, indomethacin and frusemide, etc.). Other medical conditions leading to a fall in serum albumin level include heart failure, renal disease, rheumatoid arthritis,

Table 1. Normal physiological changes associated with aging [8]

Organs	Manifestation
Overall body condition	↓ Height (secondary to kyphosis) ↓ Total body water ↑ Fat-to-lean body weight ratio ↑ Wrinkling of skin Change in skin pigmentation; atrophy of sweat glands
Cardiovascular system	↓ Sensitivity to beta-adrenergic stimulation ↓ Baroreceptor activity ↓ Cardiac output ↑ Total peripheral resistance
Central nervous system	↓ Weight and volume of brain ↓ Hours of sleep and REM (rapid eye movement) sleep Alternations in cognitive behaviour
Endocrine system	Atrophies of thyroid function Menopause; ↑ incidence of diabetes mellitus
Oral changes	↓ Sensation to taste sweetness, sourness, bitterness
Gastrointestinal system	↑ Gastric pH; delayed gastric emptying ↓ Blood flow and saliva flow
Genitourinary system	Postmenopausal vaginal atrophy Prostatic hypertrophy Age-related incontinence
Immune system	↓ Cell-mediated immunity
Liver	↓ Liver size and blood flow
Pulmonary system	↓ Respiratory muscle strength ↓ Chest wall compliance ↓ Total alveolar surface ↓ Vital capacity and maximal breathing volume
Renal system	↓ Glomerular filtration rate ↓ Renal blood flow ↓ Tubular secretary function ↓ Renal mass
Sensory changes	↓ Accommodation of eye lens, ↓ perception of high frequency and pitch discrimination
Skeletal system	Osteopenia and osteoporosis

Note: ↓ = Reduction in; ↑ = Increase in

hepatic cirrhosis and some malignancies. Basic drugs tend to bind to alpha$_1$-acid glycoprotein but its level remains virtually unchanged in elderly people.

Upon oral drug absorption, drugs will go through the liver via portal circulation. Liver size, blood flow and hepatic extraction ratio decrease upon normal aging. Drugs that undergo extensive liver metabolism or having a high hepatic extraction ratio will have increased half-life and reduced clearance. Propranolol, nifedipine, verapamil, amitriptyline and nitrates, etc. are some examples. Thus, the use of short-acting nifedipine in elderly may manifest as excessive hypotension. For renal drug excretion, glomerular filtration rate, renal plasma flow and renal tubules function are generally declined in the senior. Dosage adjustment may be required for drugs such as digoxin, metformin, atenolol, salicyate, procainamide, methotrexate and many antibiotics.

ii) Pharmacodynamics changes [6,7,8]

Elderly population often demonstrates clinical response to a lower dose of warfarin and narcotic analgesics. They are also more susceptible to the central nervous system (CNS) effects of benzodiazepines. Moreover, an increased risk of orthostatic hypotension with anti-hypertensive drugs (especially alpha blocker and angiotensin converting enzyme inhibitor (ACEI)) suggests functional changes of autonomic nervous system. Dampened reflex tachycardia and reduced sensitivity to beta adrenergic blockade indicate decreased baroreceptor and parasympathetic function, respectively. Such altered drug response observed may be attributed to the change in receptor number and affinity and impaired homeostatic mechanisms.

III ASPECTS OF CONCERN IN GERIATRIC DRUG THERAPY

i) Polypharmacy and inappropriate medications

Polypharmacy, commonly defined as the concomitant use of five or more medications, is common in the elderly population. It happens in one-fifth of patients aged over 70 years in the United Kingdom and 60% of nursing home residents in Singapore. [9,10] Classes of drugs most commonly prescribed for elderly patients include analgesics and anti-inflammatory agents, sedatives and hypnotics, cardiovascular drugs, diuretics, anti-depressants and anti-psychotics, and laxatives. [11] Older people are also likely to self medicate with over-the-counter (OTC) medications. Previous success of using OTC drugs in treating certain symptoms, convenience of obtaining them, recommendation from friends and reluctance to consult doctors all contribute to the use of OTC drugs and hence polypharmacy in the elderly.

Both healthcare providers and patients can contribute to polypharmacy. The lack of complete and updated medication history may result in treating an adverse drug reaction as a new illness. Moreover, the patients' expectation for a prescription, multiple diseases, self-medication and their behaviour of borrowing drugs from others can all lead to the high prevalence of polypharmacy. Undesirable outcomes of polypharmacy include non-adherence to drug therapy; adverse drug reactions; drug-drug interactions; increased risk of hospitalization, medication error and increased healthcare expenditures. [12]

On the other hand, as drug handling is altered in the elderly, medications that are safe and effective for the younger population can be inappropriate for them. Drug toxicity can have a profound effect on old people in terms of clinical and economical outcomes since as much as 30% of hospital admissions in elderly patients were associated with drug-related problems or drug toxicity. [13]

A number of previous studies on inappropriate drug prescribing for older adults used the explicit Beers criteria developed by a panel of experts, [10,14,15] led by Marks H Beers, MD. The panel members reviewed published literatures regarding the ineffectiveness of particular drugs and their risk of adverse effects for elderly persons. The drugs listed in the criteria are those considered to carry risks that outweigh their benefits. Medications included in the explicit criteria have severity ratings of high or low and are subdivided into those which are independent or dependent of diagnosis. Table 2a and Table 2b list the selected drugs and summarize the prescribing concern for drugs graded with a high severity rating according to the updated Beers criteria in the year 2003. [17]

Table 2a. Selected drugs and their prescribing concern (independent of diagnoses or medical conditions) with high severity ratings according to the Beers criteria 2003

Drug	Prescribing concern for elderly
Indomethacin	This drug produces the most CNS adverse effects among all available NSAIDs
Muscle relaxants (methocarbamol; chlorzoxazone)	Poorly tolerated in elderly due to anti-cholinergic side effects, sedation and weakness
Long-acting benzodiazepines (Chlordiazepoxide; diazepam; chlorazepate; flurazepam)	The long half-life causes prolonged sedation and increases the risk of fall and fractures
High doses of short-acting benzodiazepines (lorazepam > 3mg; alprazolam> 2mg; triazolam > 0.25mg)	Increased sensitivity in elderly, smaller doses should be effective and safer. Total daily doses should rarely exceed the suggested maximum
Disopyramide	Its potent negative inotropic effect may induce heart failure; consider other anti-arrhythmics.
Methyldopa	May cause bradycardia and depression in elderly
Chlorpropamide	The long half-life causes prolonged hypoglycaemia; the only sulphonylurea causing Syndrome of Inappropriate Antidiuretic Hormone (SIADH)
Gastrointestinal anti-spasmodics (dicyclomine; hyoscyamine; propantheline; clidinium)	Should be avoided since these drugs are highly anti-cholinergic and their effectiveness are uncertain
Diphenhydramine	Should not be used as hypnotic since it causes confusion
Ticlopidine	Should be avoided since it is more toxic than aspirin but no better in preventing clotting
Long-term use of the longer half-life non-COX-selective NSAIDs at full dosage (naproxen; piroxicam)	High potential to cause GI bleed, renal failure, high blood pressure and exacerbate heart failure
Daily fluoxetine	Long half-life and increased risk of causing excessive CNS stimulation, sleep disturbance; alternatives should be sought
Amiodarone	Associated with QT prolongation and torsade pointes. Efficacy not proven in elderly
Nitrofurantoin	Potential to cause renal impairment; alternatives should be sought
Thioridazine	Greater CNS and extra-pyramidal adverse effects in elderly; alternatives should be sought
Short-acting nifedipine	Potential to cause hypotension and constipation

Table 2b. Selected drugs and their prescribing concern (Considering diagnoses / conditions) with high severity ratings according to the Beers criteria 2003

Disease / Condition	*Drug*	*Prescribing Concern for elderly*
Heart failure	♦ Disopyramide; ♦ Drugs with salts of high sodium contents (alginate; bicarbonate; citrate; phosphate; salicylate; sulphate)	Negative inotrope Fluid retention and exacerbation of heart failure
Hypertension	♦ Pseudoephedrine; ♦ Amphetamine ♦ Sibutramine ♦ Phentermine	Elevation of blood pressure
Seizure / epilepsy	♦ Clozapine ♦ Chlorpromazine ♦ Thioridazine ♦ Thiothixene ♦ Bupropion	Lowering of seizure threshold
Bladder outflow obstruction	♦ Anti-cholinergics ♦ Anti-histamines ♦ Anti-spasmodics ♦ Muscle relaxants ♦ Decongestants	Reduced urinary flow and resultant urinary retention
Stress incontinence	♦ Alpha blockers ♦ Anti-cholinergics ♦ Tricyclic anti-depressants ♦ Long-acting benzodiazepines	Polyuria and worsening of incontinence
Arrhythmias	♦ Tricyclic anti-depressants	Risk of QT prolongation and proarrhythmic effects
Insomnia	♦ Decongestants ♦ Theophylline ♦ MAOIs,	CNS stimulants
Parkinson's disease	♦ Metoclopramide ♦ Typical anti-psychotics ♦ Tacrine	Concern about anti-dopaminergic and cholinergic effects
Depression	♦ Long-term benzodiazepines ♦ Methyldopa	Induction or exacerbation of depression
Syncope and falls	♦ Short-to-medium acting benzodiazepines ♦ Tricyclic anti-depressants	Ataxia and impairment of psychomotor function
Chronic Obstructive Pulmonary Disease	♦ Long-acting benzodiazepines (see above) ♦ Beta blockers	CNS adverse effect; induction or exacerbation of respiratory depression
Chronic constipation	♦ Calcium channel blockers ♦ Anti-cholinergics ♦ Tricyclic anti-depressants	Worsening of constipation

Situation in Hong Kong - Local studies on polypharmacy or inappropriate medications prescribing in the older adults have been conducted in different settings, namely nursing home, outpatient and inpatient environments. Sun XL has reviewed the pattern of drug use at a nursing home in the year 2001. Polypharmacy occurred in 42.5% (n=83) of all residents; cardiovascular and psychotropic agents were most commonly used. [18]

A survey conducted by Felix HW Chan and his colleagues at geriatric wards of a local hospital indicated 30.7% (n=55) of subjects had polypharmacy, 18% (n=32) of whom had inappropriate medications with reference to the British National Formulary. Drugs for gastrointestinal system were the most frequent class of inappropriate medications (33%), followed by drugs for the respiratory system (24%) and cardiovascular system (13%). [16] Another local survey in a geriatric outpatient clinic of Hospital Authority showed that 31.6% (n=115) of attendants had polypharmacy and 7.7% (n=28) of them were given inappropriate medications as defined by the 1994 version of Beers criteria and British National Formulary. The risk factors for polypharmacy identified in this survey were chronic obstructive pulmonary disease (COPD), congestive heart failure, coronary heart disease, gout and increasing number of medical conditions. [14]

ii) Adverse drug reactions in seniors

The World Health Organization defines Adverse Drug Reaction (ADR) as a noxious or unwanted response that occurs with a dose that usually would be therapeutic. The frequency of ADR-related hospital admissions in elderly people aged 65 years or over ranged from 10.5% to 18.9%. [19]

Epidemiological studies showed that anticoagulants, cardiovascular drugs (mainly digoxin & diuretics), hypoglycemic agents, non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics and anti-neoplastic agents are responsible for 60% of ADRs leading to hospital admissions and 70% of ADRs occurring in hospital. [6,20] In Hong Kong, severe hyponatremia with indapamide and unexpected hepatotoxicity with enalapril had been previously reported in elderly Chinese. These two commonly prescribed drugs in primary care setting implied that drug toxicity in older adults can be totally different from younger adults. [21]

Illustrating examples [22] - Older patients are more sensitive to the anticoagulant effect of warfarin and very often require smaller dose to achieve the desirable therapeutic effect than in younger individuals. The risk of bleeding is approximately doubled in the elderly. Altered drug metabolism, reduced protein binding as well as increased vascular endothelial fragility may make them more susceptible to anticoagulant-related bleeding.

For hypoglycemic agents, including sulphonylureas and insulin, epidemiological studies indicated that recent hospitalization was the strongest predictor of serious hypoglycemia. Polypharmacy also increases the risk of such adverse reactions. Although sulphonylureas are less effective than insulin in normalizing blood glucose level in Type 2 diabetic patients, they carry a lower risk of serious hypoglycemia (1/2 relative risk than using insulin) and are more convenient to use.

NSAIDs are the most commonly prescribed medications in the industrialized world. It can increase the risk of peptic ulcer by around four-fold in patients aged above 65 years. A prospective study of elderly in a long-term care facility who were newly prescribed NSAIDs revealed that 13% developed azotemia over a short course of therapy. The adverse effect was strongly associated with higher dose and concurrent use of loop diuretics.

iii) Compliance and medication history taking

Non-compliance can be a major problem in older patients and more than half of them do not comply with their medication regimens. [23] Polypharmacy, inappropriate drug use, occurrence of adverse drug events, traditional health belief, asymptomatic disease (e.g. moderate essential hypertension), deteriorated physical (e.g. visual acuity / manual dexterity) and cognitive functions all increase the likelihood of non-compliance in the elderly individuals.

Discrepancies among recorded and reported medications were common in elderly patients attending ambulatory care, with nearly 30% of patients not taking recorded medication and 20% reporting difference in dosage. [24] Patients and physicians often omit OTC medicines when giving or taking

An Open Letter from Merck & Co.,Inc.
Whitehouse Station, N.J. USA

BY RAYMOND V. GILMARTIN

CHAIRMAN, PRESIDENT AND CEO

In the weeks since Merck & Co., Inc., Whitehouse Station, N.J. USA,* announced our decision to voluntarily withdraw VIOXX® (rofecoxib) on September 30, questions have been raised about events and business practices surrounding VIOXX. We have tried to answer those questions in a straight forward way.

However, incomplete and sometimes inaccurate information has been presented by others about our scientific integrity and our commitment to ensuring patient safety. I want to take this opportunity to set the record straight.

Our consistent and rigorous adherence to scientific investigation, transparency and integrity is borne out by the fact that:

We extensively studied VIOXX before seeking regulatory approval to market it.

We promptly disclosed the clinical data about VIOXX.

When questions arose, **we took additional steps, including conducting further prospective, controlled studies** to gain more clinical information about the medicine.

When information from these additional prospective, controlled trials became available **we acted promptly** and made the decision to voluntarily withdraw VIOXX.

We believe that a complete review of the facts will demonstrate that our conduct with respect to VIOXX shows both an ongoing commitment to study VIOXX and prompt and decisive action in response to data from prospective, controlled clinical studies.

These actions are consistent with putting the interests of patients first, as well as with faithful adherence to the best principles of scientific discipline and transparency.

Throughout our history it is those fundamental priorities that have enabled us to bring new medicines to patients who need them.

We will continue to address the facts through letters like this one in the days ahead.

MSD

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12-2005-VOX-2004-HK-4052-L-(HK)

For 100 years, patients first.

BY RAYMOND V. GILMARTIN
CHAIRMAN, PRESIDENT AND CEO

At Merck & Co., Inc., Whitehouse Station, N.J. USA,* we know that the challenging mission of discovering, developing, and manufacturing new medicines and vaccines brings with it the responsibility to conduct rigorous scientific investigation and maintain high standards of corporate behavior.

We extensively study our medicines both before and after the medicines are approved by regulatory authorities. When we obtain data from our clinical studies, we promptly disclose them. When questions arise about our medicines, we quickly analyze the available data, explore their meaning within the company and in scientific forums, and conduct further studies as warranted.

We strive to ensure that our product communications are properly balanced with benefits and risks.

Our ethical standards are the foundation of our company. We strive to ensure that every employee knows that meeting high ethical standards is at the heart of how we do business. We have clear policies and formal training programs to reinforce these standards.

The value we place on business and scientific ethics is among the reasons why we have consistently been recognized as one of the world's most ethical companies.

For more than 100 years, our adherence to these high standards has produced life-saving benefits for countless patients in numerous therapeutic areas. And that long-standing record of achievement continues as our scientists conduct research in areas such as diabetes, obesity, Alzheimer's disease, and cancer.

We believe that our actions surrounding VIOXX® (rofecoxib) are consistent with putting the interests of patients first, as well as a faithful adherence to the principles of scientific discipline and disclosure.

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medication history. Older patients may also obtain medications from multiple physicians and pharmacies. [25] Thus constant medication history taking and review is necessary if ADR and drug-drug interaction are to be avoided.

IV SOME COMMONLY ENCOUNTERED PROBLEMS IN THE ELDERLY [11, 26]

The following medical conditions are frequently encountered in older adults. Many of them are associated with pharmacological agents being used which be potentially prevented with appropriate choice of medications. Other relevant information regarding the health problems of elderly can be found from the webpage of the Elderly Health Services, Department of Health: http://www.info.gov.hk/elderly/english/health_information.htm

i) Urinary incontinence

Nearly 30% of male and 40% of female aged 75 or above in Hong Kong suffer from urinary incontinence according to the Hong Kong Continence Society. Urge incontinence due to instability of the detrusor muscle is the most common cause of the problem; other possible reasons include aged-related changes of genitourinary system, neurological disorders, and last but not the least - drugs. Alcohol, caffeine, diuretics, alpha-blockers, anti-cholinergics, tricyclic anti-depressants and calcium channel blockers may exacerbate urinary incontinence and should be avoided whenever possible. [11]

ii) Fall

Local study showed that in elderly Chinese aged 70 or over, the rate of fall over the past 12 months was 32%. Two simple balance and gait tests provide good correlation with falls. The "One-leg balance test" predicts injurious fall. It is performed by asking the patient to stand unassisted on either leg for five seconds. The "Get up and go" test predicts the risk of falling: the patient is asked to rise from a sitting position, walk 10 feet, and turn and sit on the same chair. Patient taking more than 16 seconds are at increased risk of falling. Drugs that increase the risk of fall include short-to-medium acting benzodiazepines, tricyclic anti-depressant, sulphonylureas, diuretics, alpha blockers, ACEIs and nitrates. Unfortunately, drugs such as prochlorperazine are commonly mis-prescribed for dizziness due to drug-induced postural instability and therefore review of medication use is crucial in minimizing drug-related fall and polypharmacy.

iii) Dementia

Dementia has been defined as acquired global impairment of memory, intellect and personality, without impairment of consciousness. The prevalence of dementia roughly doubled every five year in the older adults. The most commonly employed tool for screening dementia is the Mini-Mental State Examination (MMSE) which has 90% sensitivity and 80% specificity. Apart from Alzheimer's disease that accounts for most of the irreversible dementia cases, alcohol intoxication, depression and metabolic disorders are associated with reversible dementia. Anti-cholinergics, tricyclic anti-depressants, digoxin, opioid analgesics, corticosteroids, beta-blockers, hypoglycaemic drugs, theophylline and various sedatives may all precipitate confusional states.

iv) Constipation

Constipation is a common complaint in the elderly due to immobility, neurological disorders, inadequate fibre and fluids, laxative abuses and other drugs. Non-pharmacological treatment such as increased physical activities, adequate intake of fibre and fluid are effective in alleviating constipation. Anti-cholinergics, tricyclic anti-depressants, codeine and other opioid analgesics, iron supplements, aluminium-containing antacids and verapamil can all produce constipation. Bulk forming agents (psyllium plus adequate fluid), fecal softener (docusate sodium) with or without stimulant (senna) are laxatives of choice for older people. Hyperosmotics (lactulose) may also be used while phosphate enema or suppositories are suitable for acute constipation and fecal impaction. Nevertheless, attention should be paid to those drugs that may exacerbate constipation and laxatives abuse must be avoided.

V ROLES OF PHARMACIST

As part of the healthcare team pharmacist has a major role in providing pharmaceutical care to patients. We can help to optimize drug therapy in older individuals that ultimately enhances their quality of life. Regular review of medication history; assessment of medication inappropriateness and patient drug adherence; documentation of drug-related problems, intervention and monitoring patient progress are essential for achieving positive outcomes.

i) Pharmaceutical care: Advisory role for patients

To improve the drug compliance of old patients, we could help them to choose easy-to-open container and easy-to-swallow dosage forms, provide information regarding the appropriate use of compliance aids (e.g. Dosett box, drug calendar, special drug packaging, spacer for inhaler). Review of studies showed that drug counseling and patient education together with reminder chart / medication calendars / information leaflets significantly improved the rate of patient compliance. [23] Discharge counseling for geriatric patients with polypharmacy also contributes to better drug knowledge, drug compliance and reduces unscheduled doctor visit or re-admission. [27]

Hospital and community pharmacists are becoming more involved in providing patient education and monitoring patient compliance. Public-private partnership approach can help maximizing the beneficial outcomes within available resources. In Hong Kong, the Drug Compliance and Counseling Service (DCCS) is an example which aims at developing a collaborative relationship between hospital and community pharmacists in order to optimize drug therapy and improve the health outcomes of patients.

Pharmacists are also in the best position in compiling complete medication list since we are regarded as the most knowledgeable profession on drugs. The list should include all prescription drugs, OTC medicine, herbs and other alternative medicines. Such medication history has to be updated, especially upon hospital admission, after discharge and ideally during each follow up or when drug-related problems are suspected.

Making home visits to housebound patients with suspected medication problems by community pharmacists was shown to be beneficial. [28] Previous outreach services by both hospital and community pharmacists in local nursing facilities significantly improved various drug management standard including drug storage, administration and documentation as well as the caregivers' knowledge on drugs. [29] The use of multiple drugs, and hence the risk of inappropriate drug therapies, is particularly commonplace in nursing home residents and warrants greater pharmacist input.

ii) Clinical pharmacy services: Advisory role for clinicians

Hospital pharmacists could initiate various drug rationalization programmes. For example, pharmacists may be involved in clinical audit on polypharmacy and the appropriateness of medication use in geriatric wards using established criteria to help care providers to avoid unnecessary or inappropriate medications and rationalize drug therapy. We could assume an advisory role in drug & therapeutic committees for establishing prescribing guidelines and as information provider regarding geriatric pharmacotherapy. Local experiences have demonstrated the economical benefit of involving pharmacist at ward level. A randomized controlled trial indicated that provision of pharmaceutical care by clinical pharmacists resulted in a significant reduction in inappropriate drug prescribing without compromising health-related quality of life in elderly patients. [30] The positive impacts of pharmacist on resolving drug-related problems, eliminating unnecessary drugs and reducing drug expenditures have been demonstrated in geriatric ambulatory clinics. [31] These examples of pharmacy services can potentially be implemented in the primary and secondary settings of Hong Kong.

VI CONCLUDING HIGHLIGHTS

Within the limited resources and our goal of improving the quality of life of older patients, our primary concern could be targeted on high-risk elderly who have significant polypharmacy (e.g., > 8 medications); those who are taking inappropriate medications or drugs with narrow therapeutic window (e.g. warfarin, digoxin, lithium), those with a history of ADR and multiple chronic diseases. Collaboration with physicians and nurse is essential for promoting safe prescribing.

Sammas Wong graduated from CUHK and is now working in KWC of Hospital Authority.

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Questions for Pharmacy Central Continuing Education Committee Program

2 CE Units

Geriatric Drug Therapy

1. ***Which of the following drugs has increased plasma concentration in elderly as a result of reduction in total body water?***

A. Diazepam
B. Digoxin
C. Amiodarone
D. Haloperidol
E. Desipramine

2. ***All of the followings are the normal physiological changes associated with aging except:***

A. Increased perception of high frequency and pitch discrimination
B. Increased total peripheral resistance
C. Decreased hours of sleep and rapid eye movement sleep
D. Delayed gastric emptying
E. Reduction in glomerular filtration rate

3. ***Which of the following statements is incorrect according to the article?***

A. Total serum albumin level decreases in elderly due to malnutrition and other concomitant diseases such as heart failure, renal disease, rheumatoid arthritis, hepatic cirrhosis
B. Basic drugs are likely to bind to alpha1-acid glycoprotein
C. Elderly patients have increased adipose tissues and reduced lean body mass
D. The use of short-acting nifedipine in elderly may produce excessive hypotension due to reduced renal excretion of the drug.
E. Functional changes of autonomic nervous system in elderly enhance the risk of orthostatic hypotension with antihypertensive medications

4. ***TC, 70 years female, had her medication reviewed by clinical pharmacist during her outpatient clinic visit. During the visit TC complained of dysuria and insomnia. She was then prescribed with nitrofurantoin 50mg qid and lorazepam 1mg nocte for 3 days.***

The list of her concurrent medications is as follow:

(I) Chlorpropamide 250mg qd po
(II) Metformin 250mg bd po
(III) Methyldopa 500mg bd po

How many potentially inappropriate medication(s) is/are now being taken by TC with respect to the Beers Criteria?

A. 1
B. 2
C. 3
D. 4
E. 5

5. ***Which class of drugs was most frequently associated with polypharmacy problem of old people in Hong Kong as mentioned in the article?***

A. Respiratory system agents
B. Gastrointestinal system agents
C. Psychotropic system agents
D. Musculoskeletal system agents
E. Cardiovascular system agents

6. ***In the "Get up and go" test, the patient is at risk of falling if he/she takes more than how many seconds to complete this test?***

A. 14
B. 15
C. 16
D. 17
E. 18

7. ***Which of the following statement(s) is /are correct?***

(I) Prochlorperazine is appropriate to treat drug-induced dizziness and prevent drug related fall.
(II) Tricyclic anti-depressants should be used with caution in elderly with dementia, constipation and those with the result of the "One-leg balance test" being less than five seconds
(III) Sulphonylureas carry a higher risk of serious hypoglycaemia than insulin therapy but is associated with reduced risk of dementia in elderly
(IV) Severe hyponatremia with indapamide and liver toxicity with enalapril had been reported locally in elderly Chinese

A. II only
B. II and IV
C. II, III and IV
D. I, II and IV
E. I, III and IV

8. ***TY is 70-year-old male with a history of post-cerebrovascular accident epilepsy. He is later diagnosed with schizophrenia and the psychiatrist would like to initiate anti-psychotic for him. According to the Beer's criteria, which of the following agents will you recommend provided there are no other factors to contraindicate their use?***

A. Olanzapine
B. Clozapine
C. Thioridazine
D. Chlorpromazine
E. Thiothixene

9. ***WC, a 75-year-old female with good past health, is diagnosed with rheumatoid arthritis. She has mild swelling and pain on both knees and her family doctor would like to initiate a non-COX selective non-steroidal anti-inflammatory drug (NSAID), which of the following drugs may be most appropriate for her?***

A. Naproxen
B. Celecoxib
C. Indomethacin
D. Piroxicam
E. Ibuprofen

10. ***WS is a 75-year-old male with normal renal and hepatic functions and with no known drug allergy. His BP is 155/95mmHg. He has a history of COPD and urinary incontinence. His family doctor would like to initiate monotherapy with antihypertensive medication to improve his blood pressure. Taking into account the disease conditions in WS and the factors discussed in the article, which of the following agents will you initially recommend?***

A. Metoprolol
B. Indapamide
C. Lisinopril
D. Verapamil
E. Methyldopa

Answers will be released in the next issue of HKPJ.

Answers for the past issue (Jul-Sep2004)

Vol 13 No 3 - Japanese Encephalitis and Vaccines
1)A 2)C 3)D 4)D 5)C 6)A 7)C 8)D 9)C 10)D

Osteoporosis

Tam, Vicky

I INTRODUCTION

Osteoporosis is an insidious disease often only coming to light in later life following a low trauma fracture of the wrist, hip or spine (figure 1). It is associated with increased mortality, increased disability and reduced quality of life. It has become increasingly recognised as a major healthcare problem, which will affect the lives of a considerable number of individuals. In the United Kingdom the annual incidence of osteoporosis-related fractures is 200,000. The annual cost to the NHS has been estimated at £942 million pounds. [1]

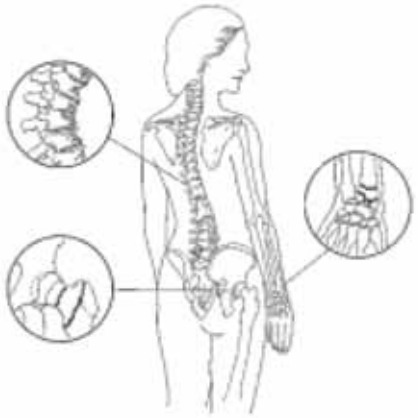

Figure 1. Picture indicated the common fracture sites due to osteoporosis [2]

II PREVALENCE IN HONG KONG

In Hong Kong one in three women and one in eight men over aged 50 will have an osteoporosis-related fracture in her/his remaining lifetime. At least 250,000 people have osteoporosis and it is estimated that ten people aged 65 or above are hospitalised everyday due to osteoporosis-related fractures[3]. It is estimated that 15% of postmenopausal women are unaware that they have the disease[4].

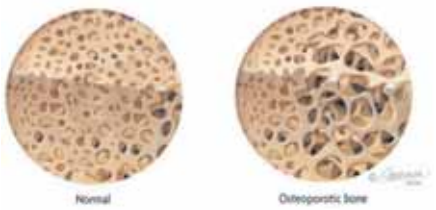

Figure 2. Osteoporosis is a condition of weak bone caused by a loss of bone mass as well as a change in bone structure. The first picture is normal bone and the second shows osteoporotic bone.[5]

III WHAT IS OSTEOPOROSIS?

Bone in skeleton is made of a thick outer shell and a strong inner mesh filled with collagen, calcium salts and other minerals. The inside looks like a honeycomb, with blood vessels and bone marrow in the spaces between struts of bone. Bone is a living tissue and is continuously undergoing a renewal process, with old bone removed (bone resorption) and subsequently replaced by new bone (bone reformation). This cyclical process is mediated by a complex interaction between bone resorbing cells (osteoclasts) and bone forming cells (osteoblasts). By mid-30s, the peak bone mass is established and from this age onwards, bone mass follows a age-related decline. As a result, bones become thinner and structurally weaker. The decline is accelerated in women after their menopause. This partly explains the higher incidence of osteoporosis in women than in men.[5]

Figure 3. Dual Energy X-ray Absorptiometry [8]

According to the World Health Organisation (WHO), osteoporosis is defined as "a progressive systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture" (figure 2). In order to categorise the state of the bone, the individual bone mineral density is compared with the peak bone mass of a healthy young adult. The difference is then referred to as a standard deviation (SD) unit (T scores). Table 1 categorises the state of the bone according to the T-scores.[6]

IV DETECTION

Bone mineral density (BMD) is the single most important determinant of liability to fractures in the general population. At present the technique employed in the measurement of BMD is dual energy X-ray absorptiometry (DXA) (figure 3).[7] This uses low doses of ionising radiation and enables accurate and reproducible measurements of BMD. The test is painless, noninvasive, and safe. Other methods used to predict fracture include ultrasonic-based techniques and computed tomography.

BMD measurement is usually performed at the most common fracture sites due to osteoporosis such as spine, wrist, and/or hip, but bone in the heel or hand may also be measured. In several prospective studies, it has been indicated that the risk of fracture increases by two to three folds for every standard deviation decrease in BMD. Sequential BMD measurements can be used as a means to monitor the efficacy of treatment and may improve drug compliance.

V RISK FACTORS [1]

Table 1. Bone mass definition

Measurement of BMC or BMD	Definition
T score value greater than -1 SD	Normal
T score value -1 to -2.5 SD	Osteopenia (low bone mass)
T score value more than -2.5 SD	Osteoporosis
Osteoporosis (as defined above) and a fragility fracture	Established osteoporosis

Note: BMC = Bone mineral content, BMD = Bone mineral density
Adapted from the WHO definition 1994

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Table 2. Risk factors for osteoporosis

Pre-existing Diseases	Lifestyle	Others
☒ previous fragility fracture ☒ women with premature menopause, whether natural, surgical or related to the effects of chemotherapy ☒ long-term corticosteriod use ☒ anorexia nervosa ☒ hyperparathyroidism, ☒ thyrotoxicosis, ☒ malabsorption syndromes (including coeliac disease) ☒ myeloma ☒ hypogonadism in men	☒ smoking ☒ high alcohol, tea and coffee intake ☒ low lifetime calcium intake ☒ vitamin D deficiency ☒ physical inactivity	☒ family history of osteoporosis (especially maternal hip fracture) ☒ height loss ☒ kyphosis (figure 4) ☒ being Caucasian or Asian ☒ low body mass index (less than 19kg/m^2).

It is well known that lifestyle factors, such as low calcium intake, long- term bedridden (as a result in limited sun exposure and causing vitamin D deficiency) are the key contributing factors to the osteoporosis. The disease can also be developed secondarily from some other metabolic diseases and from chronic use of certain types of medication. Other factors including family history and small body size are considered as non-modifiable. These risk factors are summarized in Table 2.

VI TREATMENT

Until now there is still no cure for osteoporosis, treatment is aimed to slow or stop its progress. The medications used for prophylaxis and/or treatment of osteoporosis includes bisphosphonates, hormone replacement therapy, selective estrogen receptor modulators and calcitonin.

i) Bisphosphonates

Bisphosphonates are structural analogues of pyrophosphate which bind strongly to the hydroxyapatite crystal in bone. They have the effect of inhibiting bone resorption. There are two products licensed in Hong Kong for the prevention and treatment of post-menopausal osteoporosis: alendronate *(Fosamax® - 10 mg per day or 70 mg once a week)* and risedronate *(Actonel® - 5 mg per day or 35 mg once a week).* Risedronate is also approved for prevention and/or treatment of glucocorticoid-induced osteoporosis.

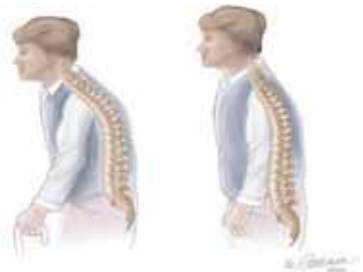

Figure 4. Picture of woman with kyphosis [5]

Panel 1. Management of missing a dose of bisphosphonate medication

Once Daily regimen — skip the missed dose and follow the remaining tablets as scheduled. Do not take 2 tablets on the same day.

Once-Weekly regimen — take the dose in the next morning, then continue to take the remaining doses as scheduled on the chosen day. Do not take 2 tablets on the same day.

Both drugs are poorly absorbed from the gastro-intestinal tract, thus they should be taken on an empty stomach, first thing in the morning, with eight ounces of water (no other liquid), at least 30 minutes before eating or drinking. Patients must remain upright during this 30-minute period. Side effects for alendronate and risedronate are uncommon but may include abdominal or musculoskeletal pain, nausea, heartburn, or irritation of the esophagus. The use of bisphosphonates should be avoided or cautioned in patients with a high risk of oesophageal ulceration, hypocalcaemia, inability to stand or sit upright for at least 30 minutes and severe renal impairment.[9,10 & 11]

Etidronate *(Didronel PMO® - not available in HK)* is licensed for the prevention of postmenopausal osteoporosis, as well as the prevention of corticosteroid-induced osteoporosis in the UK. It is available in a combination pack based on 14 days treatment followed by 76 days of calcium. This cycle is then repeated continuously.[12]

ii) Hormone Replacement Therapy

Hormone replacement therapy (HRT) has been available for a long time and is available in various forms. HRT was thought to be the first choice therapy for the prevention of osteoporosis in postmenopausal women, through its effect on alternation in bone mineral density as a surrogate for fracture reduction.

Oestrogens and progesterone as well as the synthetic variants of these hormones are used for HRT. Due to the presence of cellular oestrogen receptors present in bone, by binding to these receptors, oestrogens increase bone mass via increasing bone formation and reducing bone resorption. Oestrogens also increase calcium absorption and decrease renal calcium loss.

It has been shown that oestrogen deficiency is associated with subsequent bone loss. HRT may be offered to all women with a premature menopause, regardless of age, provided that oestradiol levels are low and gonadotrophin levels are high. In contrast, in women with an intact uterus, a combination of oestrogen with progestogen should be given to minimize the risk of endometrial cancer. Such combinations may be cyclic, sequential, long cycle or continuous-combined.

Adverse effects of HRT include nausea, cramps, bloating, return of menstruation, weight changes and changes in libido. More serious side effects include the increase in risk of thrombosis, breast and endometrial cancer after prolonged use of HRT. The current advice is that short-term use of HRT is not associated with a detectable increase in breast cancer but longer-term use, possibly for five years but most probably for above 10 years, may be associated with an increased risk of breast cancer.[1 & 12] Thus, HRT is now reserved as alternative therapies when other therapies are contra-indicated, cannot be tolerated, or if there is a lack of response. The UK Committee on Safety of Medicines recommended that HRT should not be considered as first-line therapy for long-term prevention of osteoporosis in women over 50 years of age. It is known that HRT needs to be given for at least seven years to realise the maximum benefits. Once the treatment is stopped, these advantages are soon lost.[13 & 14] Therefore, prior to prescribing long-term HRT to patients with osteoporosis, doctors are advised to provide a detailed discussion with the patients and assess the major benefits and risks of treatment.

iii) Selective Estrogen Receptor Modulators

Selective oestrogen receptor modulators (SERMs) have selective agonist or antagonist activity on tissue which responds to oestrogen. The first licensed product to be made available is raloxifene (Evista®), which has a high affinity to bind to oestrogen receptors. Raloxifene is used to

prevent and/or treat osteoporosis in post-menopausal women. It can provide the beneficial effects of estrogens without their potential disadvantages. Raloxifene increases bone mass and reduces the risk of spine fractures; it can also lower total and low density lipoprotein cholesterol in blood without changing the level of high density lipoproteins cholesterol. Studies have shown that raloxifene reduces the rate of fracture and the incidence of breast carcinomas; but like HRT it may increase the risk of venous thrombosis especially during the first four months of treatment. [15 & 16]

iv) Parathyroid Hormone

Calcitonin (Miacalcic®) is a polypeptide hormone secreted by parathyroid to regulate calcium and bone metabolism. It has been reserved as a second line treatment for women with a postmenopausal osteoporosis who have low bone mass, and who cannot or refuse to take other treatments, or for whom other therapies are not an option. Studies have demonstrated a reduction in the risk of spinal fractures but have no effect on the reduction of non-spine fractures.[17]

Because calcitonin is a protein, it cannot be taken orally as it is digested before it works. Calcitonin is available as an injection (50-100 IU per ml) or nasal spray (200 IU x 14 actuations). As injectable calcitonin may cause an allergic reaction, patients with a history of allergy should be subject to skin test before treatment is started. Other adverse effects include flushing of the face and hands, urinary frequency, nausea and skin rash. Side effects for nasal calcitonin are uncommon but may include nasal irritation, backache, bloody nose, and headaches.[12]

Teriparatide, (Fortéo®) is another recently approved parathyroid hormone for the treatment of osteoporosis in postmenopausal women and men who are at high risk for a fracture. Like calcitonin, teriparatide is only available as a pre-filled injection.

VII PREVENTION

On panel 2, there are some dietary tips that pharmacists can advise patients to follow. For those who have been diagnosed with osteoporosis, on top of dietary advice, methods to reduce the risk of fractures should be adopted, e.g. avoidance of fall. Patients should be reminded to have regular eyesight test. Use of sedative drugs should be regularly reviewed and, where possible, these drugs should be discontinued.[18] For older patients, their living environment may need to be assessed and modified where necessary. Hip protector pads may be used to minimise injury from falls.[19]

VIII CONCLUSION

Osteoporosis is the gradual decline in bone mass with age, leading to increased bone fragility and fractures. As the overall population ages, the prevalence of osteoporosis is also expected to increase. Furthermore the incidences of fractures due to osteoporosis increase in an exponential fashion. Apart from its impact on the morbidity and mortality of individual patients, osteoporosis poses a significant drain on health care resources.[20]

Prevention of osteoporosis appears logical but the evidence for effectiveness is pending. People at risk of developing osteoporosis should be targeted and provided the appropriate preventative treatments. Once diagnosed with osteoporosis, therapeutic interventions should be given together with other measures to reduce the risk of further fracture. As many of the treatments have adverse effects that may jeopardise compliance, it is essential to have a full discussion with patients to outline the benefits and side effects. Patients should be allowed to make an informed choice based on the acceptability of the medications.

Panel 2. Preventive measures against osteoporosis

- √ Stop smoking
- √ Avoid tea, coffee, alcohol and salt
- √ Improve calcium and vitamin D levels in diet, e.g. milk, yoghurt, cheese, soy products or supplements
- √ Encourage to have healthy diet, i.e. plenty of fruit and vegetables, bread, cereals, lean meat or fish, legumes and dairy products, in order to gain nutrients for maintaining bone health.
- √ Perform regular weight bearing exercise

Vicky Tam is currently working in a chain pharmacy.

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Genetic Engineering for the Production of Recombinant Tissue Plasminogen Activator

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The present article reviews techniques for the production of a recombinant thrombolytically active protein (rt-PA) which is used for the treatment of myocardial infarction. It is about the cloning and expression of a DNA sequence, which codes for the protein, in Escherichia coli. The protein was isolated as inactive inclusion bodies from chromatographic separation. rt-PA is a non-glycosylated protein expressed as a deleted mutant of the wild-type. This human tissue plasminogen activator contains only the kringle 2 and the protease domain but lacks the kringle 1, the finger and the growth factor domains. It contains 355 of the 527 amino acids of native t-PA (amino acids 1-3 and 176-527). Thus, it is a truncated protein with a molecular weight of about 39.57 Kd. These structural changes in rt-PA were translated into a decreased fibrin binding, a lower affinity to endothelial and liver cells but resulted in an extended half-life. Conditions for reconstitute the active protein was also described.

I INTRODUCTION

Tissue-type plasminogen activator (t-PA), which catalyzes the rate-limiting step in fibrinolysis, plays an important role in the removal of fibrin from the vascular vessels[(1)]. It is a serine protease consisting of several domains and is synthesized by vascular endothelial cells as a protein of 562 amino acids. Mature protein, i.e.,"wild type", is released into the plasma after intracellular cleavage of the amino terminal "pro" and "signal" sequences[(2,3)]. It consists of a single polypeptide chain of 527 amino acids (Figure 1A) and binds to the fibrin component of blood clots to activate plasminogen specifically to plasmin on the thrombus surface (Figure 2). The protease-sensitive peptide bond Arg^{275}-Ile^{276} of t-PA is cleaved by plasmin during fibrinolysis, resulting in two chain moieties which are originally held together via a disulfide bridge. The 275-residue A chain (also referred to as the heavy chain) consists of four structural domains; i.e. (1) the finger domain (amino acids 1-49) displays certain similarities to the finger structure in fibronectin, (2) the growth factor domain (amino acids 50-86; a modular protein that can stimulate cell proliferation), is to a certain extent, homologous to murine and human epidermal growth factors and (3) the two kringle domains (amino acids 87-175 and 176-262) are to a large extent homologous to the fourth and fifth kringle domain of plasminogen. The finger domain and the kringle 2 domains of t-PA are especially involved in fibrin binding and in the stimulation of proteolytic activity by fibrin. The carboxyl terminal B chain of t-PA (amino acids 276-527) comprises a serine protease domain that includes the active-site residues His^{322}, Asp^{371}, and Ser^{478}. It specifically cleaves the substrate plasminogen and is largely homologous to the B chains of urokinase and plasmin.

rt-PA (e.g. Reteplase®, Retavase®) is a single chain non-glycosylated mutant of native human tissue plasminogen activator (t-PA). It contains only kringle 2 and the protease domain of human t-PA but lacks the kringle 1, the finger and the growth factor domains (Figure 1B). It is a recombinant product containing amino acid 1-3 and 176-527 of the wild-type t-PA (deletion of Val4-Glu175). The Arg275-I1e275 plasmin cleave site is maintained. These structural differences between rt-PA and native t-PA (proprietary name: Alteplase) explain why it was translated into a decreased fibrin binding but preferential activation of fibrin bound plasminogen and an extended half-life of the former compared to the later.

The embodiment of the present process is a recombinant tissue-type plasminogen activator which is not glycosylated and consists of the amino acid sequence which is extended by methionine at the amino end, i.e. at the amino acid No. 1=S (Figure 3).

Except kringle 2, deletion of other domains which are present in native t-PA

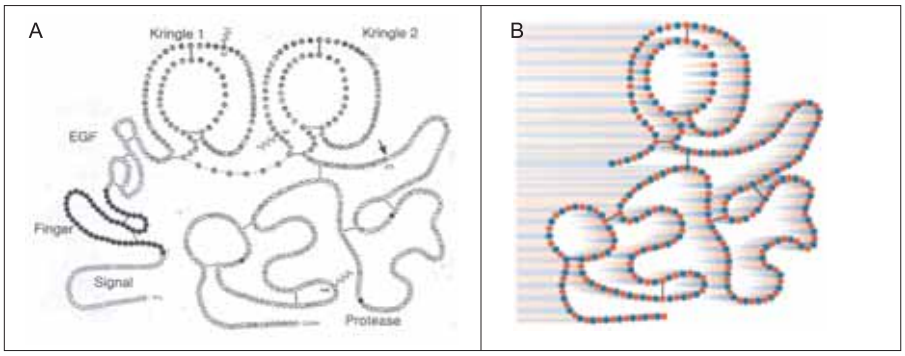

Figure 1. Molecular structure of human t-PA. Frame A = "wild type" t-PA; B = rt-PA.

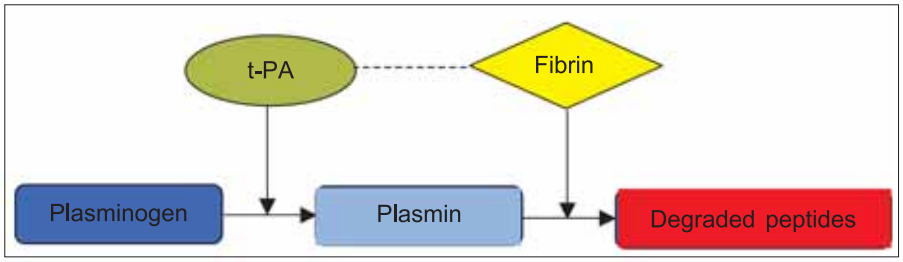

Figure 2. Action of t-PA in the process of clot-specific thrombolysis.

was reported no effect on the thrombolytic efficacy of the protein and that the fibrin-dependent stimulatability of the mutein was comparable to that of native t-PA. Although the thrombolytically active protein lacked the property to bind to fibrin, it however exhibited a thrombolytic efficacy in vivo which was even much improved compared to that of native t-PA. When a dose of rt-PA is administered which is sufficient for an effective thrombolysis the systemic fibrinolysis remains almost unaffected. It has therefore been demonstrated that under physiological conditions the thrombolytically active protein shows the typical t-PA property of fibrin specificity. In addition, the protein has a very high specific activity. By using a renaturation procedure described below activities of 500 to 800 kU/mg of t-PA have already been measured.

II DNA SEQUENCES CODING FOR t-PA

The DNA sequences which code for the thrombolytically active protein consist of the sequences shown in Figure 4.

The DNA sequences shown above serve to express the thrombolytically active protein when it is inserted into an expression vector.

III CONSTRUCTION OF EXPRESSION VECTOR

Besides the sequences coding for the protein, the expression vector should preferably contains a promotor structure which can be regulated (e.g. tac), an efficient terminator (e.g. fd), selection markers (e.g. β-lactamase and antibiotic genes) and an origin of replication. The construction of an expression vector (pA27.3) is described in Figure 5. It contains a DNA sequence which codes for the thrombolytically protein region with incorporation of further regions of the t-PA protein, the kringle 2 and the protease domains. Deletion of those domains coding for amino acids not required for the thrombolytically activity was achieved by site-directed mutagenesis.

The choice of a vector into which the DNA sequences coding for the thrombolytically active protein to be inserted, is dependent on the host cells which are subsequently used to express the derived product. Suitable plasmids, as well as the minimum requirements for such a plasmid (e.g. origin of replication, restriction site) are known to the expert. Within the scope of invention of a cosmid, replicative double-stranded form of phages (lambda M13) and other existing vectors known to the expert were used instead of a plasmid.

Construction of a vector, pA27.3, is shown schematically in Figure 5. The starting plasmid pREM7685, which had been described in EP-A 0 242 836 contains the following components: a tac-promotor, a lac-operator region with an ATG-start codon, the region coding for the t-PA derivative FK2P, the transcription terminator

	(M)					
1	SYQGNSDCYF	GNGSAYRGTH	SLTESGASCL	PWNSWILZGK	VYTAQNPSAQ
51	ALOLGKHNYC	RNPDCDAKPW	CHVLKNRRLT	WEYCDVPSCS	TCGLRQYSQP
101	QIRIKGGIA	DIASHPWQAA	IJAKHRRSPG	ERPLCGGJLI	SSCWILSAAH
151	CFQERFPPHH	LTVILGRTYR	VVPGEEEQKF	EVEKYIVHKE	FDDDTYDNDI
201	ALLQLKSDSS	RCAESSVVR	TVCLPPADLQ	LPDWTECELS	GYGKHEALSP
251	PYSLKLKLAH	VRLYPSSRCT	SQHILNRTVT	DNMLCAGDTR	SGGPQANLHD
301	ACQGDSGGPL	VCLNDGRMTL	VGHSWGLGC	GQKDVPGVYT	KVTNYLDWTR
351	DNWRP				

Figure 3. Amino acid sequences of t-PA.

1	ATGTCTTACCAAGGAAACAGTGACTCCTACTTTGGGAATGGGTCAGCCTACCGTGGCACG	60
61	CACAGCCTCACCGAGTCGGGTGCCTCCTGCCTCCCGTGGAATTCCATGATCCTGATAGGC	120
121	AAGGTTTACACAGCACAGAACCCCAGTGCCCAGGCACTGGGCCTGGGCAAACATAATAC	180
181	TGCCGGAATCCTGATGGGGATGCCAAGCCCTGGTGCCACGTGCTGAAGAACCGCAGGCTG	240
241	ACGTGGGAGTACTGTGATGTGCCCTCCTGGTCCACCTGCGGCCTGAGACAGTACAGCCAG	300
301	CCTCAGTTTCGCATCAAAGGAGGGCTCTTCGCCGACATCGCCTCCCACCCCTGGCAGGCT	360
361	GCCATCTTTGCCAAGCACAGGAGGTCGCCCGGAGAGCGGTTCCTGTGCGGGGGCATACTC	420
421	ATCAGCTCCTGCTGGATTCTCTCTGCCGCCCACTGCTTCCAGGAGAGGTTTCCGCCCCAC	480
481	CACCTGACGGTGATCTTGGGCAGAATATACCGGGTGGTCCCTGGCGAGGAGGAGCAGAAA	540
541	TTTGAAGTCGAAAAATACATTGTCCATAAGGAATTCGATGATGACACTTACGACAATGAC	600
601	ATTGCGCTGCTGCAGCTGAAATCGGATTCGTCCCGCTGTGCCCAGGAGAGCAGCGTGGTC	660
661	CGCACTGTGTGCCTTCCCCCGGCGGACCTGCAGCTGCCGGACTGGACGGAGTGTAGCTC	720
721	TCCGGCTACGGCAAGCATGAGGCCTTGTCTCCTTTCTATTCGGAGCGGCTGAAGGAGGCT	780
781	CATGTCAGACTGTACCCATCCAGCCGCTGCACATCACAACATTTACTTAACAGAACAGTC	840
841	ACCGACAACATGCTGTGTGCTGGAGACACTCGGAGCGGCCGGCCCCAGGCAAACTTGCAC	900
901	GACGCCTGCCAGGGCCATTCGGGAGGCCCCCTGGTGTGTCTGAACGATGGCCGCATGACT	960
961	TTGGTGGGCATCATCAGCTGGGGCCTGGGCTGTGGACAGAAGGATGTCCCGGGTGTGTAC	1020
1021	ACAAAGGTTACCAACTACCTAGACTGGATTCGTGACAACATGCGACCG	1068

Figure 4. DNA sequences coding for the rt-PA.

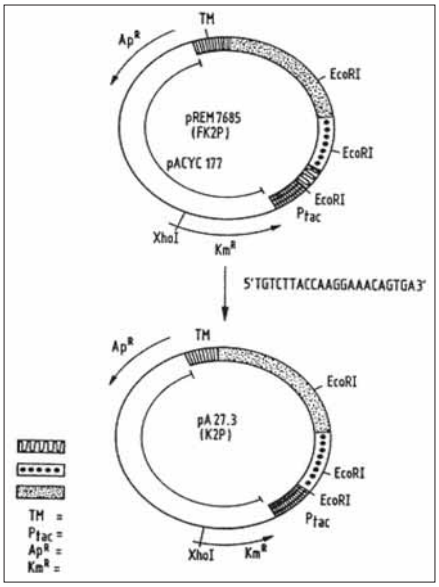

Figure 5. Construction of an expression vector harboring the plasminogen activated gene.

from pKK223-3, a β-lactamase gene, a kanamycin-resistance gene and the origin of the plasmid pACYC177, a plasmid which is present in the cell in a small copy number. The sequence of the t-PA derivative FK2P is composed of the nucleotides 190-336 (F-domain), 715-1809 (K2-domain, protease, small portion of 3'UT) and an ATG-start codon. The nucleotide positions are quoted according to the sequence described by Pennica *et al* [2].

For the deletion of the F-domain from the FK2P-construction in plasmid pREM7685 the method of Morinaga *et al.* [Biotechnology 21 (1984), 634] was essentially used. Two fragments were isolated from pREM7685 for heteroduplex formation. Fragment A: pREM7685 was cleaved with the restriction enzyme EcoRI. The cleavage products were separated by gel electrophoresis and the largest EcoRI fragment was eluted from the gel. Fragment B was isolated from plasmid pREM7685 after linearized with the restriction enzyme XhoI. The linearized plasmid was also obtained preparatively by gel electrophoresis. The following oligonucleotide was prepared synthetically for probing.

5' TG TCT TAC CAA GGA AAC AGT GA 3'

In order to form the heteroduplex, fragment A, fragment B (450 pmol of each) and the oligonucleotide (75 pmol) were mixed and incubated initially for 3 minutes at 100°C in the presence of 50 mmol/L NaCl, 10 mmol/L Tris-HCl, pH 7.5 and 10 mmol/L $MgSO_4$ and then transferred immediately onto ice. Renaturation of the DNA was carried out for 30 minutes at 60°C. The following were added to the heteroduplex for repair synthesis: Deoxynucleotide triphosphate (0.25 mmol/L), ATP (1 mmol/L), NaCl (100 mmol/L), Tris-HCl, pH 7.5 (6.5 mmol/L), $MgCl_2$ (8 mmol/L), β-mercaptoethanol (1 mmol/L), Klenow-fragment of the DNA-polymerase from *E. coli* (0.125 U/ml reaction mixture) and T4-ligase (0.1 U/ml reaction mixture). The repair synthesis was carried out for 4 hours at 16°C. Subsequently, this preparation was transformed into *E. coli* cells (RM82, DSM 3689) with a lac-I_q-plasmid and the transformed cells were selected by the addition of kanamycin (25 μg/ml) to the culture medium. Clones which contain the plasmid pA27.3 were selected by colony hybridisation technique using the synthetic oligonucleotide described above as a probe.

IV EXPRESSION OF rt-PA IN *Escherichia coli*

Large scale production of the thrombolytically active protein was achieved by cultivating the transformed *E.coli* strain C600+ in selective rich medium. The product was separated from the culture after lysis the host cells. Prokaryotic cells were preferably used as the host cells for protein expression because products could be over expressed and easily separated as "inclusion bodies" (insoluble protein aggregates) from the soluble cellular materials. Solubilization of the inclusion bodies containing t-PA could be achieved by treatment with guanidine hydrochloride under reducing conditions, then to derivatise with GSSG and finally to renature the t-PA derivative by addition

of L-arginine and GSH. Exact instructions for the activation of t-PA from "inclusion bodies" are for example described in EP-A 0 219 874 and EP-A 0 241 022.

1. Lysis of Cells and Preparation of the Inclusion Bodies (IB's)

1.6 kg cell wet-weight (*E. coli* DSM 3689, transformed with plasmid pA27.3) was suspended in 10 L 0.1 mol/L Tris-HCl, 20 mmol/L EDTA, pH 6.5, 4°C. 2.5 g lysozyme was added to this and incubated for 30 minutes at 4°C; afterwards complete cell lysis was carried out by high pressure dispersion. 5 L 0.1 mol/L Tris-HCl, 20 mmol/L EDTA, 6% Triton X100 and 1.5 mol/L NaCl, pH 6.5 was mixed with the lysate solution and incubated for a further 30 minutes at 4°C. Following this, the inclusion bodies (IB's) were separated by centrifugation in a Padberg centrifuge. The pellet was suspended in 10 L 0.1 mol/L Tris-HCl, 20 mmol/L EDTA, pH 6.5, incubated for 30 minutes at 4°C and the IB-preparation was isolated by subsequent centrifugation.

2. Solubilization of the IB's

100 g IB's (wet-weight) were suspended in 450 ml 0.1 mol/L Tris-HCl, 6 mol/L guanidine.multidot.HCl, 0.2 mol/L DTE (1,4 dithioerythritol), 1 mmol/L EDTA, pH 8.6 and stirred for 2.5 hours at 25°C. After adjustment of the pH to 3 with HCl (25%), the solution was dialyzed against 10 mmol/L HCl (3 x.50 L, 24 hours, 4°C).

3. Derivatization

Guanidine.multidot.HCl (solid) was added in such a quantity that after final dilution of the above dialysate with 10 mmol/L HCl the guanidine-HCl concentration was 6 mol/L. The preparation was preincubated for 1.5 hours at 25°C, afterwards the oxidized glutathione (GSSG) concentration was adjusted to 0.1 mol/L and the Tris-HCl concentration to 0.05 mol/L and the pH was titrated with 5 mol/L NaOH to pH 9.3. The preparation was stirred for 3.5 hours at 25°C. After adjustment of pH to 3 with HCl (25%) the solution was dialyzed against 10 mmol/L HCl (3 x.100 L, 48 hours, 4°C). After dialysis, the preparation was centrifuged and the clear supernatant was processed further.

4. Renaturation

A 10 L reaction vessel was filled with 0.1 mol/L Tris-HCl, 0.8 mol/L L-arginine, 2 mmol/L GSH (glutathione, reduced form), 1 mmol/L EDTA, pH 8.5. The renaturation was carried out at 20°C by a three-fold addition of 100 ml derivative (mixed disulphide, see above) at 24 hour intervals. After the renaturation, a preparation was obtained with a specific activity of 1500 to 10000 IU/mg (determination cf Example 4b). The unit IU is a unit of the activity according to the definition of the WHO, National Institute for Biological Standards and Control.

5. Concentration of the Renaturation Preparation

The renatured preparation can, if required, be concentrated on a haemodialyzer.

V PURIFICATION OF rt-PA FROM *E. coli*

In the purification process, it is preferably to work in the presence of L-arginine, in particular in a concentration of 10 to 1,000 mmol/L. Removal of foreign proteins by affinity chromatography was carried out in a preferred embodiment of the invention over an ETI (Eritrina Trypsin Inhibitor) adsorber column. In this connection, ETI is fixed on a carrier material (adsorber) such as e.g. sepharose. The purification over an ETI adsorber column has the advantage that the ETI adsorber column material could be loaded directly with the concentrated renaturation preparation even in the presence of such high concentrations of arginine as 0.8 mol/L arginine. In this way, an aggregation of rt-PA, which can occur at low arginine concentrations under 10 mmol/L, is avoided. Thus, it is especially preferred to carry out the purification of rt-PA over an ETI adsorber column in the presence of 0.6 to 0.8 mol/L arginine. In this process the solution containing the rt-PA has preferably a pH of over 7, particularly preferably of 7.5 to 8.6.

The elution from the ETI column is effected by lowering the pH in the presence as well as absence of arginine under conditions which allow a good solubility of rt-PA. Preferably the pH value is in the acid range during the elution, particularly preferably in the range of 3 to 5.5.

Rt-PA produced according to the present invention had a specific t-PA activity of 550,000.+-.200,000 IU/mg with a purity of more than 95%, preferably of more than 99%.

1. Purification of rt-PA from E. coli by Affinity Chromatography on ETI-Sepharose After Previous Concentration

a) Elution with citric acid

The renaturation preparation was concentrated 1:23 on a haemodialyzer (Asahi AM 300) and supplemented with 0.5 mol/L NaCl. 550 ml concentrate of the reoxidation preparation was applied (10 column volumes per hour, 10 CV/h) to an ETI (Erythrina-Trypsin-Inhibitor)-Sepharose column (V=50 ml) which was equilibrated with 0.1 mol/L Tris-HCl, pH 7.5, 0.8 mol/L arginine, 0.5 mol/L NaCl and washed with the equilibration buffer until the absorbance of the eluate at 280 nm reached the blank value for the buffer. The bound material was eluted with 20 mmol/L citric acid, pH 3.2.

	Concentrate	ETI-eluate
Volume *(ml)*	550	90
Activity *(IU/ml)*	57162	330000
C*prot.* *(mg/ml)*	14	0.71
SA[1] *(IU/mg)*	4083	465000

[1] *SA = Specific Activity which is the activity in chromogen test (cf Example 4b) divided by protein content of the sample*

b) Elution with 0.3 mol/L arginine, pH 4.5

The renatured preparation was concentrated as described in Example 3.1.a). 800 ml of the concentrate was applied to an ETI-Sepharose column (25 ml; 12 CV/h) which was equilibrated with 0.1 mol/L Tris-HCl, pH 7.5, 0.8 mol/L arginine, 0.5 mol/L NaCl and washed with the equilibration buffer until the absorbance of the eluate at 280 nm reached the blank value for the buffer. The bound material was eluted with 0.3 mol/L arginine, pH 4.5.

	Concentrate	ETI-eluate
Volume *(ml)*	800	55
Activity *(IU/ml)*	20000	280000
C*prot.* *(mg/ml)*	11.3	0.6
SA *(IU/mg)*	1770	55000

2. Purification of rt-PA from E. coli by Affinity Chromatography on ETI-Sepharose Without Previous Concentration

12 L of the re-oxidation preparation was applied to an ETI-Sepharose column (V=10 ml) which was equilibrated with 0.1 mol/L Tris-HCl, pH 7.5, 0.8 mol/L arginine, 0.5 mol/L NaCl and washed with the equilibration buffer until the absorbance of the eluate reached the absorbance of the buffer. The bound material was eluted with 0.8 mol/L arginine, pH 5.

	reoxidation-preparation	ETI-eluate
Volume *(ml)*	12000	42
Activity *(IU/ml)*	615	105000
C*prot.* *(mg/ml)*	0.135	0.185
SA[1] *(IU/mg)*	4556	568000
F[1]	25	35

[1] *F: stimulation by fibrin = activity in the presence of fibrin divided by activity without fibrin*

VI CHARACTERIZATION OF THE PURIFIED rt-PA

The homogeneity of the preparation purified by affinity chromatography on ETI-Sepharose was demonstrated by SDS-PAGE and reversed-phase HPLC (RP-HPLC). From the relative mobilities the molecular weight of rt-PA from prokaryotes was calculated at 38,500+2,000 Da. The densitometric analysis showed a purity of the preparation of >95%.

RP-HPLC is based on the different interactions of proteins with hydrophobic matrices. This property was used as an analytical method to quantify the degree of purity.

The analysis of the purified rt-PA from E. coli was carried out on a Nucleosil 300 separation column (Knauer) using a trifluoroacetic acid/acetonitrile gradient

(buffer A: 1.2 ml trifluoroacetic acid in 1,000 ml H2O; buffer B: 300 ml H_2O, 700 ml acetonitrile, 1 ml trifluoroacetic acid; 0 - 100%). Integration of the chromatographic analysis yielded a purity of >95%.

a) N-terminal amino acid sequence

The N-terminal amino acid sequence was determined using an ABI 470 sequencer with a standard programme and on-line PTH detection. The determined sequence SI-Y2-Q3-G4-N5-S6-D7-C8-Y9 agreed with the expected sequence deduced from the DNA-sequence.

b) Activity Determination

The *in vitro* activity of rt-PA from *E. coli* was determined according to the test instructions in the "Zeitschrift fur die gesamte innere Medizin" [ZGIMAL, 42 (17):478-486 (1987)]. The specific activity was 550,000 IU/mg.+-.200,000 IU/mg. The stimulatability of rt-PA from *E.coli* in this test system by BrCN-fibrinogen fragments (activity in the presence of fibrinogen fragments divided by activity in the absence of fibrinogen fragments) was >25.

c) *In Vitro* Binding to Fibrin

The *in vitro* binding of rt-PA from *E. coli* to fibrin was determined according to the method described by Higgins and Vehar[4].

To increase the yield of expression product, the sequence encoding the t-PA gene was subcloned in a plasmid with a high copy number. Plasmid pePa 126.1 described in the patent application DE 38 38 378.0 was used for this. This plasmid is composed mainly of the vector pKK223-3 and the t-PA coding sequence as described in EP-A 0 242 835. An fd-terminator sequence was first integrated into this plasmid. For this, the plasmid pePa 126.1 was linearized with the restriction enzyme Hind III. The plasmid cleaved in this manner was separated by gel electrophoresis and isolated preparatively. The plasmid pLBUI was cleaved with Hind III and a Hind III fragment of about 360 bp which contained the fd-terminator was isolated preparatively by gel electrophoresis and gel elution[5,6]. The linearized plasmid pePA 126.1 and the 360 bp Hind III fragment from pLBUI were ligated. The ligation preparation was cotransformed with the plasmid pUBS 500, described in the application DE 38 38 378.0, in *E. coli*, DSM 2102 . From the clones, those were selected that contained the desired plasmid pePA 126 fd which differs from the starting plasmid pePA 126.1 in that it contains a second Hind III cleavage site.

Two fragments were isolated from the plasmid pePA 126 fd: a BamHI/PvuI-fragment of 3.4 kb size and a PvuI/XmaI fragment of 1.3 kb size. Both these fragments were ligated with a BamHI/XmaI fragment of about 1.3 kb from plasmid pA27.3 and transformed with the plasmid pUBS 500 into *E. coli*. The resultant plasmid was named pA27 fd and can be distinguished from pePA 126 fd in that in a restriction digest with EcoRI the second smallest EcoRI fragment from pePA 126 fd of about 610 bp length is about 515 bp shorter in pA27 fd.

VII THE FINISHED PRODUCT

rt-PA produced according to the present approach has a specific t-PA activity of 550,000.+-.200,000 IU/mg with a purity of more than 95%, preferably of more than 99%. The molecular weight of rt-PA is 39,571 daltons. Thus, a thrombolytically active protein is provided which has a significantly longer plasma half-life due to the reduced clearance rate. The protein does not, however, lose any of its properties which appear to make it suitable as a therapeutic agent for thrombolysis of arterial and venous thrombi. On the contrary, the dose necessary for a thrombolytic therapy with rt-PA can be reduced to at least a quarter of the usual dose for native t-PA. With equipotent doses of rt-PA and native t-PA, the coagulation system is affected less by rt-PA than by native t-PA and the bleeding time is significantly extended in contrast to native t-PA so that complications of bleeding which occur in the therapy with rt-PA can possibly be reduced. With rt-PA, it is only necessary to administer a significantly smaller dose than is the case for native t-PA produced in CHO.

VIII CONCLUSION

Human t-PA is an effective and specific thrombolytic agent for clinical use[7]. Thrombolytic therapy has been recognized as an important treatment in the management of acute myocardial infarction[8]. Thrombolytic agents, however, have been limited by short half-lives that necessitate complex administration protocols and by the potential for bleeding complications. The enzymatic activity of natural t-PA or t-PA obtained from eukaryotes by genetic engineering, i.e. the catalytic activation of plasminogen to plasmin, is also very low in the absence of fibrin or fibrinogen cleavage products. The native t-PA molecule has since been modified in an attempt to achieve improved lytic characteristics with less risk of bleeding. The rt-PA described above is a third-generation recombinant mutant of tissue-type plasminogen activator (t-PA) that is expressed in *Escherichia coli* cells and consists of the kringle 2 and the protease domains of t-PA. Compared with t-PA, rt-PA has a lower fibrin binding, which may translate to improved dot penetration. As well as a longer half-life and a more rapid initiation of thrombolysis, preclinical pharmacology studies have indicated that it has potent *in vivo* thrombolytic activity and leads to rapid reperfusion; these findings have been confirmed by promising results obtained in large-scale clinical trials. Other new agents developed by modifying the native t-PA molecule include the n-PA and the TNK mutants of t-PA. These novel, genetically modified thrombolytic agents all lyse clots better than the native t-PA; however, they differ with respect to their half-lives and fibrin-binding activity. Although all the third-generation thrombolytic agents have shown considerable potential in improving the efficacy of thrombolytic therapy, their risk of intracranial bleeding remains problematic and is still somewhat uncertain.

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Other Useful Information

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2. New Thromolytic agents, Dr. M.Verstraete, Annals of Academy of Medicine, Singerpore. Vol 28 (3) p424-433, 1999.
3. Product Monograph : Retavase, Boehringer Mannheim GmbH

Topical Uses of *Euphrasia officinalis* L (小米草) for Soothing Tiredness of Eyes and Internal Uses for Curing Coughs or Hoarseness

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Botanical Name: *Euphrasia officinalis* L. (小米草), *Euphrasia rostkoviana* Hayne, *Euphrasia stricta* J.P. Wolff ex J.F. Lehm.
Plant Family: Scrophulariaceae (Figwort family)
Pharmacopoeia Name: Euphrasiae, *Euphrasia stricta* D. Wolff ex F.J. Loam (Fr); *Euphraise officinale* (Fr)
Other Names: Eyebright, Eyewort, Euphrasia, Euphrasiae herba, Euphrasy
Names in other languages & countries:
Germany: Augentrostkraut
Italy : Eufrasia
France : Casse-lunettes
Poland: Swietlik lakowy
Brand Names: *Euphrasia officinalis,* eyebright, Euphrasiae herba, Eyebright herb

I ABSTRACT

Eyebright is a group of herbs used to refer to a vast genus of over 450 flowering species of *Euphrasia, Lobelia* and *Sabbatia*. Amongst these, *Euphrasia officinalis* L. is the most common species and has been used by European as folk medicine for over 600 years. Preparations of eyebright are used externally as lotions, poultices, and eye-baths for eye problems associated with conjunctivitis, blepharitis and as preventive measure against mucus and catarrh. It is also used internally as an anti-inflammatory and astringent agent. The pharmacological benefits of the herb are thought to lie in the high contents of iridoid glycosides, flavonoids and tannins.

II BACKGROUND AND DESCRIPTION

Euphrasia officinalis L., commonly known as eyebright, belongs to the genus of *Euphrasia* while *Euphrasia* is a genus of the Scrophulariaceae (figwort) family[1] which is often referred as the Snapdragon Family. Euphrasia is widespread in temperate regions of both the southern and northern hemispheres[1,2]. The family consists of 80 genera and 1285 accepted taxa overall [3]. Currently the number of identified *Euphrasia* species is 170 and 40 of them ocurr in Europe [4]. Plants of the genus *Euphrasia* consist of semi-parasitic annual and perennial terrestrial herbs as well as undershrubs. Although *Euphrasia* are semi-parasitic, they can survive in the absence of host plants. This semi-parasitic characteristic accounts for their advantage over other plants in the crowded meadow [2].

Eyebright is the common name which actually refers to more than one species including Euphorbia, Lobelia, and Sabbatia, as well as the *Euphrasia officinalis* L.[4]. In addition, the taxonomy of the genus (*Euphrasia*) is very unclear[5], the reason may be the frequent hybridization in nature [1]. Since Linnaeus classified a mixture of a number of species as *Euphrasia officinalis* L, therefore the *E. officinalis* L. is a very ambiguous name with no standing [6].

Figure 1. Photo of Euphrasia officinalis L (小米草). Insert photo is the flower of eyebright.

Contraindications

Eyebright is generally thought to be safe when taken internally in the recommended doses, but precaution is required during pregnancy and lactation. Patients with ophthalmic disease such as glaucoma should avoid use.

Undesirable Effects

Intense pressure in the eyes with tearing, itching, redness, swelling, photophobia and changes in vision may happen following its' application.

Interaction with Conventional Drugs

A disulfiram-like reaction between disulfiram or metronidazole and eyebright preparations containing high alcohol content may happen. Consequently, precipitation occurs.

Table 1. Herbal substances listed as eyebright under Genus of Euphrasia[3]

Scientific Name	Common Name
Ayenia euphrasiifolia Griseb.	Eyebright ayenia
Euphrasia officinalis L.	Eyebright
Euphrasia disjuncta Fern. & Wieg.	Polar eyebright
Euphrasia hudsoniana Fern. & Wieg.	Hudson Bay eyebright
Euphrasia hudsoniana Fern. & Wieg. var. contracta Sell & Yeo	Hudson Bay eyebright
Euphrasia hudsoniana Fern. & Wieg. var. ramosior Sell & Yeo	Hudson Bay eyebright
Euphrasia micrantha Reichenb.	Northern eyebright
Euphrasia mollis (Ledeb.) Wettst.	Subalpine eyebright
Euphrasia nemorosa (Pers.) Wallr.	Common eyebright
Euphrasia oakesii Wettst.	Oakes' eyebright
Euphrasia randii B.L. Robins.	Small eyebright
Euphrasia rostkoviana Hayne	Eyebright
Euphrasia stricta D. Wolff ex J.F. Lehm.	Drug eyebright
Euphrasia subarctica Raup	Arctic eyebright
Euphrasia tetraquetra (Bréb) Arrondeau	Maritime eyebright

According to the United States Department of Agriculture, a list of herbs has been listed as Eyebright [3]. Among the 15 Euphrasia species as listed in Table 1, *Euphraise officinale* has been officially listed in French Pharmacopeia, 10th edition. At the same time, it is substituted by *Euphrasia stricta* D. Wolff ex F.J. Loam. , *Euphrasia rostkoviana* Hayne and hybrids of their mixture[7]. Many botanists, especially those of continental Europe, believe that *E. officinalis* L. merely represents a group of plants used medicinally. Hence it includes other Euphrasia species, such as E. *rostkoviana* Hayne[4,5,6,8,9,10], *E. stricta* J.P. Wolff ex J.F. Lehm as well as their hybrids[4,8]. Although these closely related plants are slightly different in their botanical features, nevertheless the chemical contents of them are quite similar [4].

Therefore, the term *Euphrasia officinalis* L. is not entirely accurate but seems to be useful as a collecting term referring to *E. rostkoviana* Hayne and *E. stricta* D. Wolff ex F.J. Loam as well as their hybrids. Nevertheless, name, such as Euphraise officinale (Fr) and *Euphrasia stricta* D. Wolff ex F.J. Loam (Fr) is used in Pharmacopoeia[7].

Euphrasia officinalis L. (eyebright) is a small, green, attractive, annual herb which grows to approximately 15 cm in height. It is characterized by odorless, bitter in taste[11] and semi-parasitic[9]. It is indigenous to the European continent, Britain, subarctic regions of North America[4] and naturalised locally in parts of the USA[3]. This European wild plant thrives in the sunny sites such as meadows, heaths and pastures. In addition, it is often found in mountains and places near the sea wherever it is sandy or chalky. One particular characteristic of this plant is its ability to obtain nourishment by attaching nodules (root sucker) to roots of neighboring host plants[9]. Nevertheless, it is difficult to cultivate this plant and in fact the entire supply is harvested from the wild when the plant is in the flowering period[4,12].

The stem of this herb is erect, thin, wiry, square or round-shaped with slightly hairy fragments. It is either unbranched or with many opposite branches. It can grow from 5 to 30 cm in height. The leaves of the eyebright are small-sized, about 0.5 cm - 1 cm long and 0.6 cm broad. In addition, the shape of the leaf is ovate, strongly ribbed, furrowed, downy, serrate (pointed teeth) along the margin that often occur in tight clumps and the leaf is light to dark green in color. Furthermore, they are opposite to one another on the lower portion of the stem.

The flower of this plant is zygomorphic and usually appears from around mid-summer to late autumn. It usually produces numerous, grooved, oblong seeds in oblong flattened seed pods [10]. The corolla part of this plant varies with a brilliant variety of colour usually a solitary white and violet-veined flower with a prominent bright yellow spot on the lower lip. The upper lip of the corolla is galeate, emarginated, having 2 large spreading lobes whereas the lower lip is broad, larger with 3-cleft and the lobes are obtuse. The calyx is bell-shaped with 4-cleft. The flower has 4 stamens and fertilises under the upper lip. It is small sized (up to 1 cm long), numerous and inodorous. Furthermore, calyx and leaves close to the inflorescence bear glandular hair[6].

The medical part of the eyebright is the aerial part of the plant. Stuart mentioned that the eyebright species which have medical value are those with glandular hairs on its calyx[6]. It has been identified the trichomes and their distribution pattern on the aerial parts of the plant of the genera of *Euphrasia* and all trichomes belong to the multi-cellular, uniseriate category, as well as glandular or non-glandular type[13]. Furthermore, the presence of the glandular trichomes has been dentified in eyebright drug powder. These glandular trichomes are 2-3 celled unicellular stalk present as a unicellular round head[8]. Little is known about the medical value of hair. However, one of the adaptive values of the glandular hairs seems to protect the plant from water loss[14]. Nevertheless, the aerial part of the plant (without roots) is the only part used for medical purposes. It has been used exclusively in folk medicine for eye diseases since the 14th century [9,10,15,16]. In addition, it was listed as a specific treatment for conjunctivitis in the British Herbal Pharmacopoeia[17] and it was one of the components of the British Herb Tobacco that was used to relieve pulmonary congestion and coughs[6,15].

III BIOACTIVE CONSTITUNETS

Various phytochemical analyses of *E. officinalis* have been carried out and a number of chemical compounds were discovered. All bioactive constitutes were found in the aerial part of the eyebright. These include iridoid monoterpenes, tannins, flavonoids and phenolic acids; all of them are suitable for medicinal applications[18]. The bioactive compounds, found in the *E. officinalis*, are derivatives of iridoid glycosides (e.g. aucubin, catalpol and geniposide), flavonoids (e.g. quercetin, rutin and kaempherol), phenolic acids (caffeic acid, ferulic acid and gallic acid) (Table 2).

Table 2. Important bioactive constituents in *Euphrasia officinalis* L.

Category	Constituent
Iridoid glycosides	Aucubin Catalpol Geniposide
Flavonoids	Quercetin Rutin Kaempherol
Phenolic acids	Caffeic acid Ferulic acid p-Coumaric acid Gallic acid

i) Iridoid glycosides

Iridoids are monoterpene compounds with cyclopentane pyran rings. They are classified into four distinct subgroups: iridoid glycosides, non-glycosides, seco-iridoids and bis-iridoids[19]. Among the four distinct groups, iridoid glycosides are the most abundant substances found in eyebright (Figure 2).

Scrophulariaceae are plant families well known for their high contents of iridoid glycosides[20]. These glycosides are reported to have diverse biological activities.

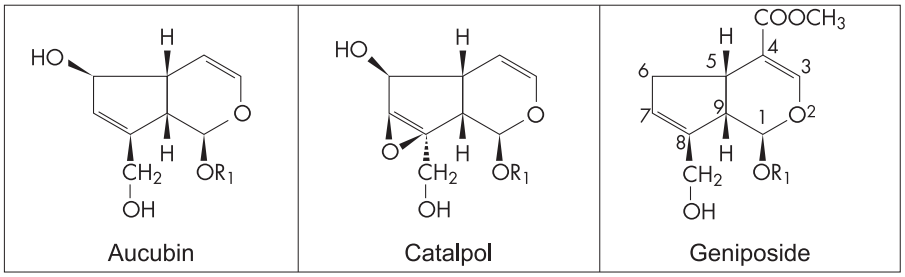

*Figure 2. Chemical structures of some iridoid glycosides present in E. officinalis L. (**R_1**=Glycosidic residue, which is usually β-D-glucose)*

ii) Flavonoids

Flavonoids are naturally occurring in many fruits and vegetables. They are a large class of polyphenolic compound including several subgroups such as the flavones, flavonones, flavonols, isoflavonoid, chalcone and anthocyanins[21]. Among all flavonoids, the most common and important subgroups in eyebright are flavonols (e.g. quercetin, kaempherol and rutin). This subgroup of flavonoid (Figure 3) exhibits a notable antioxidant activity[22]. In addition, quercetin and kaempherol are indicated as a most abundant dietary flavonols [21].

iii) Phenolic acids

A range of free and combined phenol-carboxylic acids, such as caffeic acid, ferulic acid, gallic acid, p-coumaric acid and *p*-hydroxyphenylpurvate have been identified and isolated. These phenol-carboxylic compounds are accounted for the herb's antibacterial properties.

IV CONTEMPORARY USES

The use of eyebright was probably originating from its shape that looked like a bloodshot eye because those ancient herbalists, especially those believed in the Doctrine of Signatures, would regard its shape as a sign to combat ailments of the eye[4]. The traditional view of this herb was said to cure all evils of eye. In addition, it was considered slightly tonic and astringent that could be used specifically to treat all increase discharge of mucous-related diseases in nasal membrane and lachrymal apparatus as well as the catarrhal diseases of the digestive tract[10].

The traditional therapeutic uses of eyebright preparations are mostly restricted to external as lotions, poultices and eye-baths for aliments of eye such as blepharitis (inflammation of the eyelids and eyelash follicles), conjunctivitis (inflammation of the mucous membrane lining in eye), style (inflammation of eyelid gland) as well as a series of preventive measures for respiratory infections such as coughs, colds, hoarseness and catarrh[8,23,24]. In addition, it is used for combating allergic rhinitis with mucus (including hay fever) and prevention of nosebleeds (tradition use), sinusitis[16,25]. In homoeopathic practices, it is used to treat catarrh, cold, conjunctivitis, hay fever, keratitis, mucositis and scrofula[15].

Despite the lack of concert scientific evidence to substantiate the efficacy of eyebright, modern herbalists still maintain great faith in it. The fresh herb is commonly used to prepare either compresses or water baths for the eye, often in combination with goldenseal. Most preparations recommend taking 15 gm of the dried herb boiled in 500 ml of water for 10 min and applying the undiluted liquid to the eye via a compress. Eyebright tea prepared in exactly the same manner is also taken internally at same time. Some synergies between the simultaneous internal and external application of the herb are thought to exist. In addition, the dried herb is also an ingredient in British Herbal Tobacco, a substance smoked most usefully for chronic bronchial colds.

Modern preparations of the herb are now available in the market as eye-drop, capsule, tablet and tincture forms, again often in combination with goldenseal. A recent clinical trial by Stoss *et al*. investigated the effectiveness of Euphrasia eye-drops in treating inflammatory or catarrhal conjunctivitis. Of the volunteers for the study, a full recovery was noted in over 80% within tow weeks and a clear improvement in around 17%. No adverse events were reported throughout the trial[26].

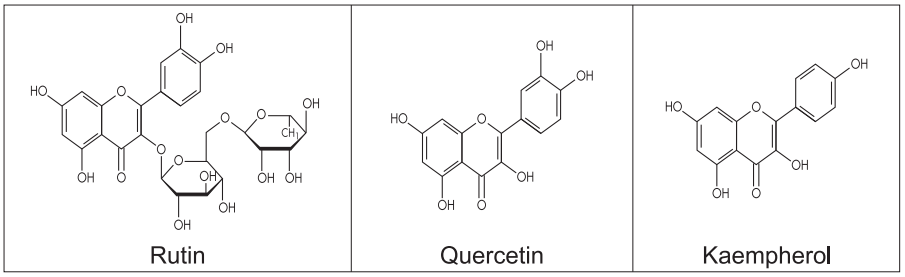

Figure 3. Chemical structures of some flavonoids identified in E. officinalis L.

V MODE OF ACTION

i) Antimicrobial and anti-inflammatory activities

Aucubin has been shown to have antimicrobial activity, hepatic protective effect, anti-tumoral and virus properties and anti-inflammatory as well as beneficial effect in the treatment of chronic allergic inflammatory disease[27]. It is the aglycone of aucubin that exhibits the antibacterial activity against organisms such as *Bacillus subtilis, Escherichia coli, Micrococcus aureus, Mycobacterium phlei* and fungi such as *Penicillum italicum*[10].

Aucubin was also found to stimulate removal of uric acid from tissue to the blood and excretion of uric acid from the kidney[28]. Quercetin is known to have anti-inflammatory, antiulcerative, antihepatotoxic and anti-oxidant[29]. Its antioxidant ability is more superior to synthetic butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT)[22]. Furthermore, Quercetin and its metabolites has been reported to effectively inhibit the oxidative damage in rat lens; thus prevents the cataract formation[30]. Both quercetin and kaempherol have been shown to have antibacterial activity while rutin itself has not. However rutin has been shown to have synergistic effects on the antibacterial activities of quercetin and kaempherol, thus enhance the power of antibacterial [31].

Aucubin alone has no antiviral activity *in vitro*. However, when it at concentration above 100 μM is mixed with β-glucosidase it has significant antiviral activity against hepatitis B[10].

ii) Hepatoprotective and antitumour activities

Aucubin and geniposide have been shown to have hepatic protective effect such as activity against hepatic damage induced by aflatoxin B_1, carbon tetrachloride (CCl_4) and alpha-naphthylisothiocyanate. Growth of C-6 glioma cells was inhibited following addition of geniposide manifesting that it is a potential chemotherapeutic agent against tumor[32].

Catalpol is commonly known to have active diuretic properties[33]. It has been reported to suppress H_2O_2-induced apoptosis (activated by caspase cascade) by inhibiting (i) the down regulation of Bcl-2(B cell lymphoma 2) family protein, (ii) the up-regulation of Bax or Bak (pro-apoptotic protein) and (iii) the mitochondrial cytochrome c release resulted in attenuating caspase cascade activation and cleavage of PARP (poly-ADP-ribose polymerase)[34].

iii) Antispasmodic activity

Geniposide is a potent anti-inflammatory substance and has been recommended for use as an anti-asthma bioactive substance[35]. Peracetylated aucubin was reported to exert a non-specific antispasmodic effect on contractions of rat uterus induced by acetylcholine and calcium chloride. *In vitro* antispasmodic activity was also found for rat vas deferens which as depolarized by potassium. The degree of activity was similar to papaverine[10].

iv) Antihyperglycemic activity

Leaf of *Euphrasia officinale* has been reported to have antihyperglycemic activity. Aqueous extract of the leaf (600 mg/kg for oral administration) was found to demonstrate hypoglycemic activity in alloxan-diabetic rats but not significant in normal rats[36].

VI CONTRAINDICTIONS

Due to the need for sterility when dealing with substance that are directly applied to the eyes, topical preparations of the herb cannot be recommended without professional support as there is limited information available. Eyebright is generally though to be safe when taken internally in the recommended amounts, but safety during pregnancy and lactation is as yet unproven so should be avoided.

VII UNDESIRABLE EFFECTS AND TOXICITY

No adverse side effects following the proper administration of designated therapeutic dosages have been recorded but intense pressure in the eyes with tearing, itching, redness, swelling, photophobia and changes in vision may happen following application of eyebright.

VIII INTERACTION WITH CONVENTIONAL DRUGS

No detail of any drug interaction with eyebright was found in literature. But a disulfiram-like reaction between disulfiram or metronidazole and eyebright preparations containing high alcohol content may happen. Consequently, precipitation occurs.

IX MODE OF ADMINISTRATION

Only the dried or fresh herb should be used for external applications in the amount specified previously. Also available are eye-drop formulations as well as tablets, tinctures and capsules for internal usage.

X DOSAGE

Compresses should be applied to the eyes for between fifteen and twenty minutes, several times a day. When taking tablet or capsule forms of the herb, amounts equivalent to between 2 and 4 grams should be taken three times a day. The tincture is usually taken in 2 to 6 ml doses three times a day.

XI DURATION OF APPLICATION

As per the manufacturer's recommendations, topical preparations should not be used without prior consultation with a professional.

XII REGULATORY STATUS

Germany: Commission E Monograph recommends that preparations of eyebright can be used externally as, poultices, lotions or drops for eye complaints, inflammation of the blood vessels, conjunctivitis, inflammation of the eyelid, and various skin conditions.
United Kingdom: Freely available on sale list.
Australia: Eyebright is not included in Part 4 of schedule 4 of the Therapeutic Goods Act.
USA: Does not have GRAS status. However, it is freely available as a "dietary supplement" in the USA under DSHEA legislation.
AHPA Botanical Safety Rating: Class 1, which means it is safe with appropriate use.

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A Great Experience from Hong Kong Pharmacy Conference 2004

Lee, Vivian WY, Chairperson, Hong Kong Pharmacy Conference 2004

Although the 17th Hong Kong Pharmacy Conference was over, it left me with great memories. I am sure that whoever attended the conference would have the same feelings. It was especially meaningful to me because this was my first time chairing the organizing committee although I had been one of the organizing committee members for the past 3 years. This year, the conference was concluded with great success. We had a record-breaking of over 400 including both local and overseas participants attended the conference. We had received positive comments about the 2-day programs and the dinner program. It was a very rewarding experience to me.

The theme of the conference this year was "Patients and Pharmacists: In Sickness and In Health" which was adopted from the wedding vows. Certainly, I felt like organizing my own wedding for this conference with long preparation. Fortunately, I had a great group of people to help. The organizing committee had been preparing for this conference since December 2003. There were numerous meetings, countless phone calls, and email exchanges. The student helpers and interns who participated in the dinner subcommittee, the publication and registration subcommittees had been vital to the entire program. The entire crew for the dinner program this year---"PharmaMia" had impressed us by their great performance during the opening and the dinner program. "Bravo" to them!

During my chairmanship of the conference, I treasured the unity of our pharmacy profession. I was impressed by the support from the entire profession. We could all put aside our difference backgrounds, our interests, and our different opinions in joining hands to promote our profession through the conference. The Hong Kong Pharmacy Conference has become one of the yearly highlights of our profession. Not only we could have extensive academic exchanges but also networking within our profession both locally and internationally. I was impressed by our participants especially those who attended our newly introduced early clinical case presentations. You could certainly sense the enthusiasm among all participants. Everyone was so eager to learn.

When I looked back one year ago after I accepted to be the chairperson of the conference, I was so afraid that I was not good enough to be the chairperson. I was afraid that the conference program could not meet the expectations of the audiences. I was afraid that the dinner program would not be as good as previous years. There were so many worries; however, everything turned out to be fine at last. I am in no position to take the credit for the success of this year conference. In order to make this year conference a successful one, it was because of all those who participated, supported and contributed. I am grateful to have a wonderful group of organizing committee members especially those experienced members who gave me good advices and suggestions. I am thankful that they trusted me in chairing the committee. The experience that I gained from this event was very valuable to me.

The future of pharmacy profession in Hong Kong is in our hands. It is not one person's responsibility but each of you in the profession. It requires team effort and unity to make our profession better. The healthcare system in Hong Kong is changing and so are the roles of pharmacists. We could certainly provide better pharmaceutical care to our patients through proper education, more initiative actions, and multidisciplinary approaches. As I mentioned in my opening speech at the conference, recognition needs to be earned. It does not happen overnight. It will still be a long journey. Are you ready to be part of it? I am ready. Let us join hands to work for a bright future of our profession.





Reporting Adverse Drug Reaction in Hong Kong

Helen Wong

Department of Health (DH) will implement a voluntary reporting program of adverse drug reaction (ADR) in January 2005. This ADR monitoring program, with an aim to safeguard the use of medicine in Hong Kong, is important in drug safety monitoring. The program will help to promote rational use of medicine. A reporting system of ADR bears a crucial role in public health. Indeed, health authorities worldwide have similar systems to evaluate drug safety monitoring.

As part of the healthcare team, we pharmacists need to understand more about the rationale and implementation plan of the system, so as to contribute to the monitoring of drug safety.

Details of the program have been announced at the DH's website, http://www.info.gov.hk/pharmser/adrform.htm. The information is also available at the Public Health & Epidemiology Bulletin, Vol 13, No. 5, http://www.info.gov.hk/dh/diseases/. For your convenience, some of the information is abstracted from the website as below:

"The World Health Organization defines Adverse Drug Reaction (ADR) as "a reaction to drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.....

From 1 January 2005, doctors, Chinese medicine practitioners and dentists are encouraged to report suspected ADR of their patients to the ADR Monitoring Unit voluntarily. ADR reports can be submitted for all western and Chinese medicines (including Chinese herbs and proprietary Chinese medicines).

If in doubt, please report. You do not need to be certain that the suspected drug is related to the ADR before making the report.

What happens to the report?

1. *All ADR reports are reviewed by professional staff;*
2. *Serious ADR reports may be reviewed by expert advisors if indicated;*
3. *Information of the report will be entered into the ADR databases system for analysis.*

The ADR reports may identify some unexpected ADR, or indicate that certain ADR occur more commonly than previously expected, or that some patients are more susceptible to certain problems than others. Such findings can lead to the following changes to the products, for example: restrictions in use, refinement of dose instructions or introduction of specific warnings in the product literature. Rarely when a hazard is considered as unacceptable, a medicine may have to be withdrawn from the market."

Regarding this new voluntary program on reporting of ADR, the HKPJ contacted Pharmaceutical Services, DH, and obtained the following clarification:

i. It is expected that other health professions, such as pharmacists, will be invited to participate in the reporting when the program has been run smoothly.
ii. Pharmaceutical industry is not involved at this stage of the program. Nevertheless, to better safeguard public health, mandatory reporting of post-marketing ADR from the pharmaceutical industry is being considered by the DH. Such a kind of reporting requirement is in line with international practices.

NEW PRODUCTS

POSTINOR-2
(Mekim)

Active ingredient:
Levonorgestrel

Presentation:
Each tablet contains 0.75mg levonorgestrel

Pharmacological Properties:
At the recommended regimen, levonorgestrel is thought to work mainly by preventing ovulation and fertilization if the intercourse has taken place in the preovulatory phase, when the likelihood of fertilization is the highest. It may also cause endometrial changes that discourage implantation. It is not effective once the process of implantation has begun.

Indications:
Emergency contraception within 72 hours of unprotected sexual intercourse or failure of a contraceptive method.

Dosages and Administration:
For oral administration, the treatment necessitates the intake of two tablets. The highest efficacy is achieved if the first tablet is taken as soon as possible (and no later than 72 hours) after unprotected intercourse. The second tablet should be taken 12 hours (and no later than 16 hours) after the first tablet. If the patient vomits within three hours of taking either tablet, another tablet should be taken immediately.

Contraindications:
Hypersenstivity to the active substance levonorgestrel or any of the excipients.

Precautions:
Emergency contraception is an occasional method. It should in no instance replace a regular contraceptive method. Emergency contraception does not prevent a pregnancy in every instance. If there is uncertainty about the timing of the unprotected intercourse or if the woman has had unprotected intercourse more than 72 hours earlier in the same menstrual cycle, conception may have occurred. Treatment with POSTINOR-2 following the second act of intercourse may therefore be ineffective in preventing pregnancy. If pregnancy occurs after treatment with POSTINOR-2, the possibility of an ectopic pregnancy should be considered. POSTINOR-2 is not recommended in patients with severe hepatic dysfunction.

Side effects:
The most frequent undesirable effects are nausea, low abdominal pain, fatigue, headache, dizziness, breast tenderness, vomiting.

Drug Interactions:
The metabolism of levonorgestrel is enhanced by concomitant use of liver enzyme inducers.

Medcinies containing levonorgestrel may increase the risk of cyclosporin toxicity due to possible inhibition of cyclosporin metabolism.

Forensic Classification:
P1S1S3

TARKA
(Abbott)

Active ingredient:
Verapamil hydrochloride and Trandolapril.

Presentation:
Available as 180 mg of verapamil hydrochloride in a sustained-release form and 2mg of trandolapril.

Pharmacological Properties:
TARKA is fixed combination of the heart-rate lowering calcium antagonist verapamil and the ACE inhibitor trandolapril.

Verapamil **-** The pharmacologic action of verapamil is due to inhibition of the influx of calcium ions through the slow channels of the cell membrane of vascular smooth muscle cells and of the conductile and contractile cells in the heart.

Trandolapril **-** It suppresses the plasma rennin-angiotensin-aldosterone system (RAS).

Indications:
Essential hypertension in patients whose blood pressure has been normalized with the individual components in the same proportion of doses.

Dosages and Administration:
The usual dosage is one TARKA capsule once daily, taken in the morning before, with or after breakfast. TARKA capsules should be swallowed whole.

Contraindications:
Known hypersensitivity to trandolapril or any other ACE inhibitor and/or verapamil, history of angioneurotic edema associated with previous ACE inhibitor therapy, hereditary / idiopathic angioneurotic edema, pregnancy and children.

Precautions:
Symptomatic hypotension - Under certain circumstances, TARKA may occasionally produce symptomatic hypotension. This risk is elevated in patients with a stimulated renin-angiotensin-aldosterone system (e.g. volume or salt depletion, due to the use of diuretics, a low-sodium diet, dialysis, diarrhea or vomiting; decreased left ventricular function, renovascular hypertension).

Proteinuria **-** Proteinuria may occur particularly in patients with existing renal function impairment or on relatively high doses of ACE inhibitors.

Side effects:
The adverse drug reactions for TARKA are consistent with those known for its components or the respective class of drugs. The most commonly reported adverse drug reactions are cough increased, headache, constipation, vertigo, dizziness and hot flushes.

Drug Interactions:
Potassium sparing diuretics **-** ACE inhibitors attenuate diuretic induced potassium loss.
Potassium supplements - May lead to significant increases in serum potassium.
Digoxin **-** Concurrent use of digoxin and verapamil has been reported to result in 50-75% higher digoxin plasma concentrations, requiring reduction of the digoxin dosage.
Cardiodepressive drugs **-** The concurrent use of verapamil and cardiodepressive drugs may produce undesirable additive effects.

Forensic Classification:
P1S1S3

Seeking The Best Chance for a Cure in Chronic Hepatitis C

PEGASYS®
peginterferon alfa-2a

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

Ease of Use
Simple fixed dose,
ready-to-use solution

Unsurpassed Efficacy
Particularly in patients with genotype 1 infection and high viral load

Sustained viral response rates for **PEGASYS®** plus ribavirin

- 63% in overall HCV patients[1], and
- 52% in HCV genotype 1 patients[1]

Full prescribing information is available upon request

Reference:

1. 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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