Malaysian Journal of Pharmacy

Volume 1 Number 3 April 2003

The Official Journal of the Malaysian Pharmaceutical Society

Publisher: Malaysian Pharmaceutical Society
5-B Lorong Rahim Kajai 13
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The Malaysian Journal of Pharmacy is a bi-annual publication of the Malaysian Pharmaceutical Society. Enquiries are to be directed to the Publisher at the above address or the Editor-in-Chief at the Pharmacy Department, Faculty of Allied Health Sciences, Universiti Kebangsaan Malaysia, Jalan Raja Muda Abdul Aziz, 53100 Kuala Lumpur.

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Editorial

Writing for Publication : Avoiding Bias or Perception of Bias

In its first three issues, the *Malaysian Journal of Pharmacy* has received and published different types of articles. Although different people read the *Journal* for different reasons, information published in it has the potential to influence the daily practice of many pharmacy practitioners. Readers expect to get up-to-date and unbiased information from it. Thus, the authors, reviewers and the editors have the responsibility of ensuring that articles published are free of bias.

The existence of bias may be related to personal, commercial, political, academic or financial interest of an individual or individuals involved in the publication of the paper. This issue has been addressed in the Guidelines on Good Publication Practice (1). Financial relationships are the most easily recognised, and they may exist with pharmaceutical companies, government or other agencies. As such, the Guidelines require authors and reviewers to disclose these interests to editors. Many journals have done so by revising their editorial policies, requiring authors to declare any financial relationships that might have biased their judgement in relation to the submitted paper (2 – 5).

Failure to disclose conflicts of interest may be due to the authors mistakenly overlooking the financial support, or believing that it had not influenced the paper, or deliberately concealing the information (2). Bias may be more difficult to detect in review articles compared to original research (4). Even without any financial support, the paper may still be perceived to be biased. To avoid ambiguity, some journals require authors to explicitly state whether potential conflicts do or do not exist (4, 6).

Publishing the authors' source of financial support will allow the reader to make an informed judgement regarding its significance. However, the decision to publish such disclosure lies with the editorial board. More importantly, the authors themselves must be aware about issues relating to conflicts of interest in order to avoid bias or perception of bias in the paper submitted for publication.

Ab Fatah Ab Rahman

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Malaysian Journal of Pharmacy 2003; 1(3):54-58 *Invited review*

The Full Extent of Alcoholism: A Worldwide Economic and Social Tragedy

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ABSTRACT

Alcohol abuse affects many people directly or indirectly all over the world. Alcoholism often causes major damage and can also lead to death. It seems as though people underestimate the prevalence of alcohol abuse and the damage done by alcohol abuse. Loss of labour, birth defects, liver cirrhosis, and damage from vehicle accidents, are a small portion of the damage caused by alcohol abuse. The damage caused by alcohol abuse affects people physically, emotionally, and economically. All this damage is preventable. Treatment for this problem is available, but the effects differ among patients. Pharmacotherapy and cognitive behavioural therapy are used separately or collectively. Results can vary depending upon the treatment and patient. The pharmacist plays an important role in the lives of alcoholic patients. Pharmacists can notice a patient's behaviour, notice their prescription patterns, and most importantly, the pharmacist is a knowledgeable mentor that many patients look up to. Feeling comfortable with and trusting the pharmacist is very important for the patient. Patients may come to the pharmacist with their problems, and the pharmacist should be able to offer sound medical advice.

Keywords: alcoholism, total cost of alcohol abuse, pharmacist intervention, pharmacotherapy for alcohol abuse, alcohol treatment

INTRODUCTION

When we think about the most prevalent life threatening, debilitating, and harmful diseases, we think of AIDS, diabetes, heart disease, depression, and others. Very few people acknowledge or are aware of the complete effect of alcoholism, and how it affects individuals, families, friends, strangers, co-workers and society in general. Alcoholism is a worldwide problem of chronic drinking that affects all aspects of one's life. We hear about drunk drivers, automobile accidents and domestic violence associated with alcoholism, but rarely do we look beyond the individual or family perspective, it is a preventable massive expense to individuals, governments and society. We probably don't take the consequences seriously enough because alcoholic beverages are sold openly everywhere and drinking is very much embedded in most cultures and societies. Let us look at the facts.

It has been found that alcohol dependence affects 7.5% of the US population. That represents approximately 14 million Americans. Alcoholism, untreated and treated, causes physical, emotional, and economic damage. The extent as to how many people are affected on a daily basis by this disease is innumerable. First, we will take a look at how individuals are affected. From the loss of earnings to the medical expenses, alcoholism can certainly cost an

alcoholic an immense amount of money. It has been found that almost two thirds of the costs of alcohol abuse are a result of loss of labour (1). Alcohol related problems cost the alcohol abusers about $66.8 billion, which is 45% of the annual total cost of alcohol abuse just in the USA. The actual cost that abusers pay may actually be less than this figure, this is due to the fact that their family members and others pick up some of the cost (2).

There are many health problems associated with alcohol abuse. The most prevalent health problems are gastrointestinal. Gastrointestinal pain, bloating, nausea, and vomiting are all associated with alcohol abuse. Alcohol decreases the rate of gastric emptying, increases gastric secretions, and also damages the gastric mucosa. Gastritis and ulcers are common, and with heavy drinkers, pancreatitis is prevalent. The liver is the organ most affected by alcohol. Liver problems are associated with upper-right quadrant pain. There are many liver disorders such as cirrhosis, hepatitis, cholestasis, and portal hypertension (3). Alcohol-related liver disease (ALD) is the most prevalent liver disease in the United States, and patients with this disease make up the largest portion of liver transplant recipients, almost 27% in 1995. Almost 20% of ALD patients require a liver transplant. The demand for human liver donations is much greater than the supply available in the United States. In 2000 only 4934 patients received liver transplants, by April of 2001, there were 17,520 Americans waiting for a liver transplant (4).

Alcohol abuse affects the entire body, it causes many cardiovascular, haematological, gynaecologic, metabolic, and central nervous system problems. Hypertension, stroke, sudden death and heart failure are common cardiovascular disorders associated with alcohol abuse. Long-term alcohol abuse can suppress the production of leukocytes, erythrocytes and platelets. Anaemia is very common, as are many vitamin deficiencies that are due to poor absorption and poor intake of vitamins. The fact that over half the alcoholic's caloric intake is alcohol further displays the problem, which causes electrolyte imbalances and also malnutrition. Alcoholism also affects neurological function, decreasing memory, motor skills, and affecting neuron transmittance. Alcoholism affects all aspects of the abuser, both physically and mentally. Not only can alcohol abuse result in physical problems, it can result in psychological disorders also. Depression affects approximately 33% of problem drinkers. Depression affects the response of patients to treatment and also their relapse rate. The high relapse rate results from negative emotional states and recurrent relapses may cause a feeling of helplessness, causing drinkers to feel that their drinking is out of control and that they will never be able to stop drinking (5).

Alcoholism and the side effects associated with it often lead to sudden and early death. Not only does alcoholism affect the abuser, non-abusers are also affected, it has been shown that alcohol abuse costs non-abusers $81.2 billion annually in the USA. Family members and household members are affected immensely. Non-abuser victims are directly responsible for 6% of the alcohol related costs, but indirectly much more, with taxpayers picking up the bill that the government has to pay.

In addition to adults and children being affected by alcohol abuse, foetuses are also affected by alcohol abuse. Almost 5,000 babies are born each year with Foetal Alcohol Syndrome (FAS). This is approximately one in every 750 births. The rate of FAS is much higher in Native Americans, than that of Caucasian or African-Americans. A child with FAS may have a variety of problems, such as pre-natal and post-natal developmental problems, various facial malformations, various organ malformations, and also central nervous system problems. Foetal Alcohol Effects (FAE) occurs in 3-5 out of 1,000 live births and it results in milder symptoms, such as low birth weight. Foetal Alcohol Effects results from pregnant mothers who drink less alcohol than those with FAS children. Treatment of infants, children and adults with FAS in 1992 cost over $1.9 billion. It costs about $1.4 million to treat a FAS affected child throughout his life. Additional healthcare, education, attention, etc. are factors affecting the cost of a FAS child to their family, private insurers, Health Maintanance Organisations, and the government (6). This disease is completely preventable, yet alcohol exposure is the most common cause for birth defects. Alcohol abuse during and prior to a pregnancy affects the development of the foetus during pregnancy and for the remainder of its life (7).

Employers are affected by this disease with lost productivity costing them about $66.7 billion per year (2). Lost earnings and decreased wages represent the lower productivity of an alcohol abuser. When workers perform below their

ability level it results in decreased profits.

The government is also affected by this major disorder, paying about $13.6 billion dollars in damage due to alcohol related accidents, incarcerating alcohol abusers, court costs, crime related costs, etc. They also accept 38.6% of the complete costs of alcohol abuse (2).

Health Maintenance Organisations and private insurers pay 10.2% of alcohol related abuse costs (2). Life insurance policies pay about $12,000 per death for the approximately 106,600 deaths per year where alcohol is responsible.

Various physical damages are caused and related to alcohol abuse. Alcohol related motor vehicle damage is approximated at $13.6 billion; this includes vehicle and road damage, court costs, and insurance administration.

Victims of violent and non-violent crimes are affected primarily in the form of lost earnings, the losses are estimated at $1 billion. Property crime related to alcohol abuse is estimated at $427 million, this represents lost cash and property. Together alcohol and drug abuse related property crimes, represent 30% of the value of total property crimes.

Approximately 140,000 alcohol related criminals are incarcerated annually, causing a major decrease in productivity. About $5.4 billion dollars are lost annually due to incarceration of alcohol related criminals; this loss of prospective productivity affects the economy greatly. Although this primarily is a loss to the inmate, it is also a loss to the government and to the society with the loss of potential tax revenue and the cost of keeping the inmate incarcerated, which is approximately $12,000 per year.

There are many additional disorders that result from alcoholism, which are additional factors in the cost of alcoholism. Depression, as described previously, is one of the major adverse concerns of problematic alcohol abuse.

Treatment

There are many different treatments for alcoholism, from detoxification to drug therapy and counselling. Treatment varies depending upon the length of illness, additional amount of alcohol-related problems, and whether or not the patient really wants to overcome his addiction. More than 700,000 people receive treatment everyday (8). Patients are either treated on an inpatient or outpatient setting. 13.5% of treated patients receive residential treatment, and 86.5% of patients receive outpatient treatment. The commonly used behavioural treatments are cognitive-behavioural therapy, motivational enhancement therapy, and Alcoholics Anonymous sessions. These treatments have an equal amount of effectiveness, as shown in the Project MATCH trial (9). Often, pharmacotherapy can supplement these treatments. These treatments can be very costly, but when factoring in the damage that a lifetime of problem drinking can cause, treatment appears to be quite a bargain.

Detoxification is the first step of treatment for many patients. It is a form of medically assisted withdrawal from alcohol. Medication is often required to prevent seizures and hypertension. After an extended period of heavy alcohol abuse people usually experience many alcohol withdrawal symptoms. Detoxification is intended to manage the medical and psychological symptoms of alcohol withdrawal. Patients can be treated by detoxification, in either an inpatient or outpatient setting (10). Price varies from centre to centre, but for example, at The Healing Centre in Raleigh, North Carolina, it costs $261 per day for a detoxification bed, $200-$500 per day for emergency services, and $58 per day for detention services. Treating alcohol-related problems costs society much less than if left untreated.

In the 1980s, alcoholism and other addiction problems were thought of as physical problems, with treatment mainly focused on detoxification. More recent research and a greater knowledge of brain biology have evolved addiction treatment to focus on lifetime abstinence. Long-term programs such as twelve-step and mutual help programs focus on lifetime abstinence and preventing relapse. Alcoholics Anonymous (AA) is one the oldest and most popular of the self-help groups for addicts. Established in 1935 and currently having over 2 million members, AA is clinically proven to reduce problem drinking and relapses and also results in a higher level of social functioning. AA is a very cost-effective treatment; the program is free to those who want to stop drinking. Donations are accepted and appreciated as they are used to off-set costs of meeting places and coffee. After the success of this twelve-step program, many private inpatient treatments have based their treatment on the

ideals of AA (11).

Naltrexone is an opioid antagonist approved by the Food and Drug Administration as an adjunct therapy to be used along with conventional psychosocial therapies for alcohol abuse. Although naltrexone is not a magic answer for alcoholics, as an additional therapy it greatly reduces relapses. The Brown University Center for Alcohol and Addictions Studies recently embarked upon a 5-year study of the effect of naltrexone on heavy social drinkers in their social environment (12). COMBINE is a recent study in progress that combines pharmacological and behavioural therapies for alcohol abuse. The completion of this study will provide researchers in this field with information to treat alcoholic patients more successfully (13).

Review:

Alcohol abuse has been recorded before agriculture was known. In the prehistoric period, people used whatever was available to create a fermented drink. Over the centuries alcohol has evolved from basic ethanol to wine and beer. The use and abuse of these alcoholic beverages began to increase in the 15th century. In London prices were raised on alcoholic beverages to discourage its use. It wasn't until the mid-nineteenth century that chronic alcohol abuse was studied. Some early treatments for alcohol abuse included apomorphine and emetine, which induced vomiting upon the consumption of alcohol. Physicians eventually focused on prophylaxis since positive cures seemed nearly impossible (14).

Current treatment of alcoholism involves private rehabilitation, drug therapy, counselling services, Alcoholics Anonymous, etc. Private rehabilitation has had a large increase since the 1970s, where the number of beds in private rehabilitation facilities quadrupled from 1978-1984. Many private insurance companies and the federal government bear the cost of this treatment, which is approximately $18,000 per hospital stay. This is a major burden on our healthcare system. It has been found that patients who undergo lengthy inpatient, residential treatments are no better off in overcoming their addiction than those left on their own for treatment. In a study done by George Vaillant, 95% of those treated as an inpatient at an urban hospital had a relapse. In another study done by Helzer *et al.*, findings showed that 93% of the patients at an inner-city hospital were either dead or still abusing alcohol five to seven years after treatment. Those treated at a private rehabilitation facility are more likely to show better results (15).

The best treatment for alcoholism is one that teaches life skills without alcohol. Programs need to incorporate training in stress management, life skills, social and negotiation skills, job skills, and work habits (15). In addition to these psychological and social treatments, recent drug therapy has produced some positive and productive results. Naltrexone, an opioid antagonist, decreases alcohol consumption by blocking the receptors in the brain that encourage drinking behaviour. Clinical trials done in the early 1990s have shown that naltrexone, in addition to psychosocial treatments, effectively reduces craving and relapse rates in alcoholic patients. It costs approximately $100/month for the average dosage of 50mg/day. Dosages may be adjusted on an individual basis (12).

What can the pharmacist do?

Depending on the circumstances of pharmacy practice in different countries, there are several avenues open to the pharmacist. The first step in any treatment is problem recognition and the pharmacist may be in a position to notice excessive sales and use of elixirs or other alcohol-containing medicines. The pharmacist may want to discuss this with the patient or a relative of the patient. The pharmacist can promise confidential treatment and service, and have information available for referrals to alcoholism treatment clinics.

Beyond such recognition of the problem, one can assume that an innocent patient question as to the existence of OTC products to help people with "a drinking problem" might be a lead to offer help.

The next task for the pharmacist is that of educator/counsellor and referral agent. The patient needs to know that competent help is available, and where, and what it might involve, and cost. It would be advisable if the pharmacist could ascertain if health insurance may pay for some or all of the fees. A wise pharmacist might attempt to seize the moment by making an appointment for the patient at such a clinic.

Thorough pharmaceutical service calls for the pharmacist to follow-up periodically with the patient, probably by telephone, or in-person, and

for encouragement to be offered while lauding the already completed steps for the patient.

The pharmacist can check that patient's profile in the future to see that medications containing alcohol are avoided. As newer therapies and techniques become known, the pharmacist should take it upon him or herself to stay up-to-date, in order to offer the best and latest information to their patients.

Perhaps even 80% to 90% of patients will ignore the pharmacist's advice, but the successfully treated 10 to 20% make that activity worthwhile and valuable to all concerned parties.

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Medication Safety Issues - 1

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ABSTRACT

Preventing medical or medication errors is pivotal in quality patient care and safety. Significantly, error prevention activities are multifactorial. These include, (i) enlisting staff creativity in improving safe practices, (ii) patient education, (iii) provision of information leaflet, (iv) clarity in instructions, (v) application of failure mode and effects analysis, and (vi) care in approving access to medications.

Keywords: medication safety, errors, patients care, prevention, safe practice

INTRODUCTION

Medication and medical errors are serious problems throughout the world. It has been estimated that between 44,000 and 98,000 Americans die each year as a consequence of medical errors, with the annual financial cost estimated at approximately US$40 billion (1-3). In Australia, the direct cost to the acute care system due to medication errors have been estimated to be between AUD$867 million to over AUD$1 billion annually (4,5). Importantly, a large proportion of medical errors or adverse drug events are preventable errors (1-3, 6-9).

Accordingly, the purpose of this series of articles is to increase the awareness of health professionals in Malaysia on preventable medication or medical errors. The issues highlighted in this article are drawn primarily from *ISMP Medication Safety Alert!*, and are used with permission from the Institute for Safe Medication Practices, Pennsylvania, USA (www.ismp.org). It is our hope that this contribution will result in safe medication or medical practices and improved patient care.

Systems thinking; Tap into staff creativity to unleash innovation (10).

A letter to the editor was published in the *New England Journal of Medicine* from a physician who suggested using metal detectors to prevent the risk of injuries from metal objects during magnetic resonance imaging (MRI) (11). Unfortunately, his suggestion was spurred by the recent tragic death of a six-year-old child in New York who suffered a skull fracture and intracranial haemorrhage after an oxygen tank was pulled by the magnet into the machine at high speed.

As noted by the author, injuries from undetected or misplaced metal objects (e.g. IV drug poles, sandbags containing metal filings, defibrillators, wheelchairs, etc.) brought into MRI exam rooms are not uncommon. Yet, staff training and patient questionnaires to detect metal implants remain the most common methods used to prevent such incidents.

In fact, education has been healthcare's bread and butter for preventing errors and injuries. And while education may prevent some errors, its success is limited because it relies heavily upon human memory and vigilance. More to the point, education alone fails to change the system in a way that would make it impossible for people to make mistakes.

More effective solutions require systems thinking. The suggestion to use highly sensitive

walkthrough metal detectors (which are available commercially for about US$2,000-$5,500 and require minimal maintenance) to prevent accidental introduction of a metal object into a MRI exam room is an excellent example of systems thinking. This coupled with staff education and patient screening has a high likelihood of *preventing* injuries. But how did the physician come up with such a powerful suggestion? In retrospect, it seems so obvious. Yet systems thinking is not as easy as it seems.

Our history of errors with potassium chloride concentrate for injection in patient care units demonstrates this very well. Until systems thinking prevailed, many organizations relied upon staff education and manufacturer label warnings to prevent administration of potassium chloride concentrate without proper dilution. Although lessened, errors persisted until the pharmaceutical industry manufactured premixed solutions, physicians standardized potassium replacement therapy to maximize use of commercially available solutions, and vials of potassium chloride were removed from patient care units. Unfortunately, it took years for the healthcare industry to come up with and implement such an effective system-based solution that now seems so simple and intuitive.

To become more proficient at systems thinking, multidisciplinary teams must openly discuss medication errors and refuse to settle for old familiar (and ineffective) ways of solving problems. If education is identified as an error reduction strategy, we can't stop there. Instead of just building inspections into processes to detect errors before they reach patients, we need to find ways to actually *prevent* them. We must always ask, "Are there ways to make it impossible, not just unlikely, for people to make such a mistake?" Systems thinking is the key needed to bridge the gap between understanding the causes of errors and selecting error reduction strategies that have the greatest likelihood of success. With practice and a little creativity, we can become more skilful and innovative in identifying system-wide strategies that work *continuously* and *automatically* to *prevent* errors and injuries.

Educating the patient – key to patient safety (12).

Education provided to patients while in the physician's office can arm them with the information needed to prevent errors. A patient was to receive methotrexate IV followed in an hour by fluorouracil IV as part of a treatment regimen for breast cancer. To reduce methotrexate toxicity, her oncologist prescribed oral leucovorin rescue to be started 24 hours after the methotrexate. He wrote the order as "leucovorin 25 mg, one every 6 hours x 6 *doses* starting 24 hours *after* chemotherapy." The pharmacy provided the correct medication, but the directions typed on the label were to "Take one tablet every 6 hours for 6 *days* starting 24 hours *before* chemotherapy." The patient remembered what she'd heard in the doctor's office and called her physician for clarification. Had she taken the drug as directed on the label, she would have negated the therapeutic effect of the chemotherapy.

Failure mode and effect analysis can help guide error prevention efforts (12).

Too often, marketing efforts, contractual agreements with purchasing groups or vendors, and cost serve as primary sources of information when making decisions about which medical products to purchase and use. Evaluation and input from those who would be using the products may not be sought and error potential may not be considered ahead of time. Later, this may lead to unforeseen problems in the hands of clinical users.

These pitfalls can be avoided by using a process known as Failure Mode and Effects Analysis (FMEA) to examine the use of new products and the design of new services and processes to determine points of potential failure and what their effect would be – *before any error actually happens*. In this regard, FMEA differs from Root Cause Analysis (RCA). RCA is a *reactive* process, employed *after* an error occurs, to identify its underlying causes. In contrast, FMEA is a *proactive* process used to look more carefully and systematically at vulnerable areas or processes. FMEA can be employed *before* purchase and implementation of new services, processes or products to identify potential failure modes so that steps can be taken to avoid errors *before* they occur.

How can FMEA be used to reduce the risk of medication errors? To cite just one example, an interdisciplinary committee could use FMEA to assess new drugs being considered for the formulary. Here's how the process would work.

- Step 1: The committee would explore how

the intended product would be procured and used, from acquisition through administration. Who would prescribe the drug and for what type of patient? Where would the drug be stored? Who would prepare and dispense it? How would it be administered?

- Step 2: Potential failure modes (how and where systems and processes may fail) would be identified while considering how the product would be used. Could the drug be mistaken for another similarly packaged product? Does the label clearly express the strength or concentration? Does the name sound or look like another drug on the formulary? Are dosing parameters complex? Is the administration process error prone?
- Step 3: Once failure modes have been identified, staff would determine the likelihood of making a mistake and the potential consequences of an error. What would happen to the patient if the drug were given in the wrong dose, at the wrong time, to the wrong patient, by the wrong route, at the wrong rate?
- Step 4: Staff would identify any preexisting processes in place that could help detect the error before it reaches the patient, and evaluate their effectiveness based upon knowledge of human factors.
- Step 5: If failure modes could cause errors with significant consequences, actions would be taken to prevent the error, detect it before it reaches the patient, or minimize its consequences. A few examples include using an alternative product; preparing the drug in the pharmacy; standardizing drug concentrations, order communication and dosing methods; using auxiliary warning labels or computer alerts; and requiring entry of specific data into computer systems before processing orders.

Care with what you write! (13).

A hospital reported mix-ups between two different "rubicin" products (anthracyclines). A nurse called the pharmacy to report that the colour of the idarubicin dispensed from the pharmacy was different than the colour of the dose she had given the day before. Further investigation revealed that the patient had received daunorubicin instead of idarubicin on the previous day because staff thought they were both the same drug. With five different "rubicin" products on the market, each with similar names, and two with liposomal forms, mix-ups are not surprising. To avoid confusion, prepare a chart for the pharmacy and the oncology unit that displays all the anthracycline products by generic name, brand name(s), investigational drug name/identifier, and liposomal forms if available. Include dosing information if desired. By the way, we heard that the "Rubicin" family does not like to be identified by first name only. So don't use Val, Ida, Donna or Epi. Doc's full name should also be used.

Care with what you use and who has access to medications (14).

TIMENTIN® (ticarcillin and clavulanate potassium) 3.1 grams IV was ordered for a patient after the pharmacy had closed. A nursing supervisor went into pharmacy, but could only find the pharmacy bulk package which contains 31 grams. She selected two vials and brought them to the patient care unit. A staff nurse assumed that each vial contained one dose. She gave the patient one vial at 1 am and another at 5 am. The patient developed seizures, acute renal failure, congestive heart failure, and eventually died. When questioned, both the supervisor and nurse said that they had misread the 31 grams as 3.1 grams. For a time, a shortage of 3.1 gram Timentin vials resulted in availability of only the 31 gram bulk containers in the pharmacy. Lesson to be learned: Patients are at risk when non-pharmacists have complete access to a pharmacy after hours. With current technology, planning, and cooperation from medical and nursing staff, night access to the pharmacy can be eliminated, even in rural hospitals. If there's any chance that medications packaged in pharmacy bulk packages might somehow reach patient care areas, make sure that extra warnings are affixed to the containers.

Drug information leaflets in error prevention (15).

Drug information leaflets handed to patients can help prevent errors. A verbal order was given to a pharmacist for **NOROXIN** (norfloxacin) 400 mg bid x 5 days. However, the pharmacist heard, transcribed, and dispensed **NEURONTIN** 400 mg instead. When the patient got home, he read the leaflet and called the pharmacy to ask why he'd been given medicine for seizures instead of the anticipated antibiotic for a urinary tract infection. The prescription was clarified with the patient's physician and the error was corrected. While there are many ways that errors like this

can be prevented, it's important to point out the value of patient information leaflets as a backup when other systems fail. Instruct patients about the importance of seeking counselling from pharmacists when obtaining prescriptions and reading leaflets when they are provided. Armed with proper information, patients can be a strong defence against errors.

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Continuing Pharmacy Education

Managing Cytotoxic Drugs

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ABSTRACT

Cytotoxic drugs are used in the management of malignant diseases. They have been found to be carcinogenic, teratogenic and mutagenic. There is growing concern that the handling, preparation, administration and disposal of these substances may constitute an occupational hazard. These guidelines aim to identify, and help avoid or minimize occupational exposure to cytotoxic drugs and related wastes within health care establishments. It is necessary that individuals involved in the use or handling of cytotoxic drugs are made aware of associated matters relating to the safe handling of such drugs.

Keywords: cytotoxic drugs, occupational exposure, mutagenic, teratogenic, carcinogenic

INTRODUCTION

Cytotoxic drugs are therapeutic agents which are known to be toxic to cells principally through their action on cell reproduction and are primarily intended for the treatment of cancer. Currently there is no established data for safe level of exposure to these drugs. While health care establishment workers involved in the handling of these group of drugs do not receive therapeutic doses, there is concern that unless suitable protective measures are in place, these personnel may be subjected to low level doses in the long term.

Occupational exposure may occur through the inhalation of aerosols and drug particles, skin absorption, ingestion and needle stick injuries resulting from:

- transport of cytotoxic drugs
- cytotoxic drug preparation and administration
- contamination of surfaces with cytotoxic drugs
- handling, transportation and disposal of cytotoxic waste (1-3).

Personnel likely to be involved in these processes are nurses, medical officers and pharmacy staff. The greatest risk of occupational exposure to cytotoxic drugs is during their preparation and administration. The need for safe handling of cytotoxic drugs is not confined to injectable dosage forms only. For example, oral dosage forms may shed respirable dust, and when used to prepare oral suspensions, may distribute dust and fragments. Other aspects of patient care such as spill and waste management may also pose a risk of occupational exposure.

Potential effects of exposure

Many published studies are inconclusive and little is known of long term effects of exposure to cytotoxic drugs in health care workers. However, there is sufficient evidence to indicate potential adverse effects as a result of occupational exposure (4-7). Studies have reported the following effects amongst personnel preparing and administering cytotoxic drugs:

- contact dermatitis, local toxic or allergic

reaction, which may result from direct contact with skin or mucous membranes
- cytogenetic abnormalities and mutagenic activity related to biological uptake by exposed personnel
- alteration to normal blood cell counts
- excretion of the drugs or metabolites in the urine in exposed personnel
- symptoms including abdominal pain, hair loss, nasal sores and vomiting
- liver damage
- foetal loss in exposed pregnant women and malformation of the offspring of pregnant women

Although the long term effects of occupational exposure to cytotoxic drugs are inconclusive, it is not appropriate to wait for indisputable evidence of harm.

Drug preparation

In general, the principle focus of safety during cytotoxic drug preparation should be on:
- education and training of personnel
- control of the working environment
- adoption of safe working procedure

Education and training of health professionals in cytotoxic drug preparation and handling is recommended to ensure that safe work practices are understood, developed, implemented and maintained. Use of cytotoxic drug safety cabinet, pharmaceutical isolators and other appropriate equipment is recommended to facilitate safe preparation of cytotoxic drugs and to ensure that products, operator and working environment are protected. In order to provide drug containment and aseptic manipulation, all preparation of cytotoxic drugs should take place in a separate, dedicated cytotoxic safety cabinet or in pharmaceutical isolators.

The health care establishment management is responsible for ensuring that personnel who are designated to perform cytotoxic drug preparation procedures are provided with an accredited level of training, and that they have attained proficiency prior to undertaking preparation procedures (8). Accredited training in drug preparation procedures should be undertaken prior to commencement of duties and when new equipment is introduced or procedures changed. Procedures should be in place to ensure that accredited staff are kept informed of new developments, such as changes in technology and preparation procedures. Validation of accreditation criteria should occur at intervals no greater than two years.

Personal Protective Equipment should be worn by personnel using an approved cytotoxic drug safety cabinet to prepare cytotoxic drugs:
- long sleeved coverall of impermeable material, e.g. made from bonded polyethylene fibre with a closed front and elasticized cuff, with suitable head protection
- overshoes of a similar impermeable material
- suitable respiratory protection
- long PVC, surgical latex, or purpose manufactured gloves

Special precautions are required for the laundering of used Personal Protective Equipment (garments) which may be contaminated with cytotoxic drugs. The conditions required for the laundering of potentially contaminated items should be established to:
- protect laundry personnel who are involved in this process from cytotoxic drug residue
- prevent contamination of other materials being laundered
- ensure the garments are decontaminated prior to sterilization or reuse

Attention to occupationally related work practice will maximize efficiency and productivity and minimize operator errors. Cytotoxic clean room equipment layout should be designed properly. To determine appropriate work periods the entire task should be assessed taking into consideration the:
- level of concentration and visual control required
- precision of movements
- design of equipment and availability of adjustable furniture, e.g. chairs, stools and foot rests
- aesthetic effects of the working environment

Drugs and its storage area and equipment need to be identified. Intravenous equipment and devices containing cytotoxic drugs should be clearly labelled with a permanent, adhesive and recognizable cytotoxic drug label.

For drug storage, the quantities of cytotoxic drugs stored in pharmacy departments, wards,

clinics and satellite pharmacies should generally be restricted to the quantities for short term use. A dedicated area for the storage of cytotoxic drugs should be provided in pharmacy departments and storage areas. Use of a dedicated area facilitates quick and efficient containment and management of a spill.

Oral solid cytotoxic doses should be individually packaged. Automatic tablet counters, or other equipment which may generate particulate matter, should not be used in the packaging of cytotoxic drugs. If a prepared therapy has to be transported on-site, it should be in a transport container which is of sufficient strength to prevent leakage of its contents and should be securely closed and labelled with cytotoxic warnings. Cytotoxic drugs should not be transported in pneumatic automated tube systems.

Standard operating procedures for the preparation of cytotoxic drugs should be documented and should include:

- using specially dedicated equipment in a pharmacy to provide containment of powder where there is a requirement for compounding cytotoxic preparations
- operational specifications for the use of cytotoxic drug preparation facilities including cytotoxic drug safety cabinet
- initial and ongoing validation of operator competence
- reconstitution procedures
- routine and emergency cleaning and decontamination protocol
- spill management
- maintenance and certification of equipment and facilities
- availability of drug safety information
- documentation and records
- maintenance of daily records
- labelling and packaging for transport internally or externally

Health care establishments which are unable to provide facilities, equipment and training to employees, should not undertake to provide a cytotoxic drug service. Alternative arrangements could include:

- purchase and supply of the prepared cytotoxic drug in a single dose delivery unit.
- establishment of supply arrangements with a health care institution which has the required facilities, equipment and trained personnel to provide prepared cytotoxic drug doses.

Drug administration

Nursing, medical and other personnel may be involved in administering oral, parenteral and topical cytotoxic drugs. A number of factors influence their level of risk of exposure to cytotoxic drugs during administration. Exposure may occur due to contamination from solid or liquid spills or splashes and needle stick injuries.

Many factors contribute to the risk of exposure, including:

- poor technique, improperly used or inappropriate equipment
- patient behaviour, when it increases the difficulty of administration, for example, if the patient is uncooperative
- the route of administration, for example, the risk of splashes in the eyes of the operator or assistant during an intrathecal injection is increased owing to the proximity of the face to the injection site
- an inappropriate working environment

It is important that practitioners identify the level risk, then use appropriate work practices and Personal Protective Equipment to minimize the risks.

All staff administering cytotoxic drugs should be appropriately trained (9) in the following aspects of cytotoxic drug handling and demonstrate proficiency prior to commencing duties:

- potential occupational hazards
- approved work practice
- specialized operator techniques
- waste containment and handling
- spill management techniques
- proper use of Personal Protective Equipment

The following Personal Protective Equipment should be considered for use during administration of cytotoxic drugs:

- a particulate respirator type mask
- a long sleeved gown of impermeable material
- safety spectacles or goggles
- long PVC, surgical latex, or purpose manufactured gloves

Personal Protective Equipment should be removed following completion of procedures and appropriately cleaned or disposed of.

Spill management

Strategically, small spills that occur on-site and during transportation should be managed by the health care establishment. Procedures must specify under what conditions emergency services should become involved. Spill containment should be the principle role of health personnel in gross spill management, pending the attendance of the emergency spill management team.

Procedures should be established for small spills. The management should ensure that safe work practices are developed, understood, implemented and maintained by all personnel who handle cytotoxic drugs and who may be involved in spill management. Training in spill containment and decontamination procedures should be provided to personnel likely to be involved in spill management including:

- pharmacy personnel
- store personnel
- nursing and medical personnel
- cleaners
- waste collectors

Spill kits should be located so that they are readily available for immediate use at all sites where cytotoxic drugs and waste are handled, stored and transported.

Standard operating procedures for spill management should specify:

- the trained personnel approved for spill management
- spill strategies for specific location, e.g. wards, or in transit
- procedures for using decontamination solutions
- where and how to obtain decontamination solutions
- who is responsible for providing and maintaining spill management supplies
- the personnel protective equipment to be used

Waste management

Cytotoxic waste includes any residual drug following patient treatment and the material associated with the preparation or administration of cytotoxic drugs such as sharps, syringes, IV infusion sets and containers, ampoules, vials and disposable gowns, caps and gloves and swabs and materials used to clean and contain spills. All cytotoxic waste need proper identification, segregation and containment. An easily identifiable symbol that denotes cytotoxic materials can be used. Containers and plastic bags to contain cytotoxic waste should be:

- of any selected colour, e.g. purple
- marked "CYTOTOXIC WASTE"
- placed in a rigid-walled container for transport to a designated storage area

All sharps should be:

- placed in a rigid-walled containers
- labelled "CYTOTOXIC SHARPS"
- disposed of according to recommended procedures

Personnel management

Little is known about the long term effects of occupational exposure to low level doses of cytotoxic drugs. Therefore the primary focus of safety during use of cytotoxic drugs must be on the control of the working environment and safe work practices.

However, there are variables that need to be considered in determining occupational hazards of cytotoxic drugs to an individual:

- chemical properties of the drugs
- the susceptibility of the individuals to the drug's toxic effects
- cofactors such as dietary habits, smoking and natural or manmade environment contamination
- type of exposure, e.g. skin contact, inhalation, ingestion

It is important that the health status of employees is monitored. There is currently no biological health assessment technique that is sufficiently specific to adequately predict the effects of exposure to cytotoxic drugs. Employers should investigate and use the most appropriate and recent method of health surveillance available and ensure that baseline data are collected. Records should be maintained of all health assessment and biological monitoring results related to occupational cytotoxic drug exposure. One purpose of these records is to facilitate retrospective studies to assess risk of exposure to employees.

Where any form of health surveillance is undertaken, confidentiality should be ensured. Requirements such as employee consent, record

retention and security should be achieved and maintained. Employees should receive duplicates of health surveillance test as soon as available. Employees who are pregnant, breast-feeding or planning parenthood and involved in the preparation or administration of cytotoxic drugs should be informed of the risks of reproductive effects and possible effects on foetal development. Personnel required to perform these may elect to not to do so. In such cases appropriate and suitable alternative duties must be provided.

Employees should report any effects of, or exposure to cytotoxic drugs related to handling of the drugs or contaminated waste. The report should be made to the supervisor through the normal workplace incident reporting procedures. Any near miss incident or accident involving the handling of either cytotoxic drugs or waste, should be investigated to determine the cause. Appropriate action to prevent a recurrence should be determined and taken. A listing of personnel approved to undertake cytotoxic drug preparation and administration should be maintained.

The management is responsible for maintaining, in perpetuity (e.g. 25 years minimum), the following records for employees handling cytotoxic drugs:

- accreditation or training status and type and extent of training period
- record of time spent in the preparation and administration of cytotoxic drugs
- activity logs including name of the drug and activity undertaken)
- protective equipment used (e.g. cytotoxic drug safety cabinet, Personal Protective Equipment)
- unusual equipment (e.g. for managing spills).

In view of the long latency for some toxic effects, each employee should receive, on termination of employment, a statement indicating the cytotoxic drugs used and results of any biological monitoring carried out.

CONCLUSION

Although there are many reports and studies that have been carried out to show the relationship between cytotoxic exposure and risk to health, it is still difficult to confirm it. This is perhaps due to the small sample size, difficulty in quantifying exposure or protection used and latency period between exposure and health effects. Despite these limitations, there is enough information to warrant prudent action when handling cytotoxic drugs. Therefore, the safe handling of cytotoxic drugs is an issue that must be addressed in health care settings.

See next page for the CPE questions

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Continuing Pharmacy Education questions:

Study the questions below and send your answers (only one of A, B, C and D is correct) to the MPS-CPE Secretariat at the Malaysian Pharmaceutical Society, P.O. Box 158, Jalan Sultan, 46710 Petaling Jaya, Selangor. You may earn up to 2 CPE points.

1. **The most common routes of occupational hazard from handling cytotoxic drugs are**
   - A. accidental injection, gastric absorption
   - B. direct contact, gastric absorption
   - C. inhalation, direct contact
   - D. mucosal absorption, inhalation

2. **Potential effects of exposure to cytotoxic drugs in health care personnel are**
   - A. contact dermatitis and cardiotoxicity
   - B. foetal loss or malformation in pregnant women
   - C. liver damage and phlebitis
   - D. extravasation at the injection site

3. **The greatest risk of occupational exposure of cytotoxic drugs is during**
   - A. preparation and transportation
   - B. administration and disposal
   - C. preparation and administration
   - D. transportation and disposal

4. **The advantage of having a dedicated area for storage of cytotoxic drugs in pharmacy departments is to**
   - A. facilitate searching of stock
   - B. facilitate quick and efficient containment and management of spill
   - C. provide proper stock management
   - D. provide better control and monitoring of cytotoxic drugs usage

5. **Standard operating procedures for preparation of cytotoxic drugs should include those below, EXCEPT**
   - A. documentation and record
   - B. reconstitution procedures
   - C. maintenance and certification of equipment
   - D. potential hazard of cytotoxic drugs

6. **The following are the variables that can be considered in determining occupational hazards of cytotoxic drugs to health personnel, EXCEPT**
   - A. chemical properties of the drugs
   - B. toxic effects of the cytotoxic drugs
   - C. type of exposure
   - D. cofactors such as dietary habit

Brief History And Development Of Parenteral Nutrition Support

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ABSTRACT

Patients who are unable to use their gastrointestinal system for feeding purposes are now usually started on parenteral nutrition. It is a therapeutic tool used in the clinical management of patients requiring special nutritional care both in the hospital, and at home (home parenteral nutrition). The idea of providing nutrients intravenously in humans was first realised when Sir Christopher Wren injected wine and ale in dogs way back in the middle of the 17th century. The historic experiment initiated further investigation and studies on this novel approach to nutrition. Better understanding of the metabolic and pharmacological properties of the macronutrients (protein, carbohydrates, and lipid), the micronutrients (trace elements, and vitamins), and the electrolytes have made it possible to administer parenteral nutrition safely to all types of patients where it is indicated. Continuous development and improvement in the pharmaceutical presentations of these nutrients have helped to minimise the metabolic problems seen in the early days of parenteral nutrition administration. Production of the single- or multilayered parenteral nutrition bags using materials which are inert and capable of reducing oxygen permeability such as the combination of ethylenevinylacetate-polyvinylidine chloride has ensured better stability of the parenteral nutrition admixture. The multicompartmental bag has provided a much more simpler and convenient way of initiating parenteral nutrition. The increase in knowledge, development and improvement in parenteral nutrition support has made it possible to provide parenteral nutrition support at home.

Keywords: parenteral nutrition, enteral nutrition, macronutrients, micronutrients, convenience bags

INTRODUCTION

Parenteral nutrition (PN) is a relatively new therapeutic tool used in the clinical management of patients. Arguably, the era of modern clinical nutrition can be said to have dawned around 35 years ago when Dudrick and colleagues reported their work on the successful administration of long-term PN in an infant (1). In Malaysia, PN service was established in late 1986 at the Kuantan General Hospital (Hospital Tengku Ampuan Afzan, Kuantan, Pahang) (2), while Bahari reported that formal parenteral nutrition rounds led by pharmacists were initiated at the university hospital of Universiti Sains Malaysia (HUSM) a year later (3).

PN is a mode of providing nutritional supplement that involves the administration of nutrients through the intravenous route (viz *par*

enteral). It is also widely and affectionally known as total parenteral nutrition or TPN, although intravenous nutrition, and artificial nutrition are accepted terms to convey the same meaning. Hyperalimentation, that is the provision of nutrients at high concentration intravenously, was the term used during the early days of this novel nutritional approach (which, literally, was the reason for most of the adverse effects of PN therapy back then!). Nowadays, the term PN is widely used in the literature to denote the administration of nutrients intravenously.

Basically, PN is only indicated when the oral, or enteral route (i.e. the use of the gastrointestinal system) of nutrition cannot be established, or is insufficient for the maintenance of the patient's nutritional requirements in relation to his/her clinical status. Partial parenteral nutrition (PPN) is the concurrent intravenous administration of nutrients together with oral or enteral nutrition for the same therapeutic objective.

The dietary components of a standard PN regimen are the macronutrients (protein or amino acids, carbohydrate, and lipids or fats), the electrolytes, the micronutrients (trace elements, and vitamins) and water. Carbohydrate, in the form of glucose or dextrose, and lipids are the major energy providers.

Early work on intravenous nutrition

The main role and function of the major components of the diet in human growth and development were recognised only around a century ago (4). Nevertheless, the history of intravenous infusion of nutrients began in 1665, when Sir Christopher Wren injected wine and ale to dogs, and noted that intravenously administered alcohol had the same effect as alcohol taken orally (5).

Indeed, investigators and clinicians have long realised the importance of providing adequate nutrition to patients, more so to those with gastrointestinal problems. The intravenous route of nutrient administration was seen to be one possible avenue to venture into in the nutritional management of patients who cannot consume food orally. Ever since the historic experiment by Wren, various workers had experimented providing nutrients such as carbohydrates and lipids in animals, and also humans in their effort to understand and develop this novel approach to nutrition.

Stirius, in 1668, published a review on this subject of intravenous experiments in which he deduced that intravenous infusions were, or could be applicable to nearly all disease states, except where pregnant women and newborn children were involved. These patients were considered by Stirius as difficult and bad subjects to treat (6).

Although the deduction of Stirius still holds some relevance today, advances in the knowledge and technical capabilities in the administration of PN over the last two decades have made it possible to administer intravenous nutrition even to pregnant mothers (7) and low birth-weight neonates (8,9), the so called difficult and bad subjects!

Early results of intravenously administered nutrients were not promising because of the adverse effects associated, although the desired outcomes were also observed. These unwanted effects, caused by poor administration techniques, and the use of crude compounds led to some of the work in this field of intravenous nutrition research being prematurely abandoned (10). One such incident is the work of Friedrich in 1904, in which he administered what can be considered the first total PN in man, subcutaneously. These infusions of peptone, fat, glucose and electrolytes were so painful that not even Dr. Friedrich wanted to pursue development in this area of research (10). Also, it can be safely deduced that the lack of pharmaceutical and microbiological knowledge meant that problems of stability (incompatability and interactions included), and sterility were not recognised and duly addressed during those early years.

Intravenous administration of proteins

Ever since the 19th century, protein has been seen to have an important role in the growth and development of humans (11). The special nature of protein and its metabolism made it a challenge to find suitable ways of administering it intravenously. The first study in the intravenous administration of proteins was made in goats in the form of protein hydrolysates by Herriques and Andersen in 1913 (10). These hydrolysates were products of the naturally occurring proteins such as fibrin and casein. Positive nitrogen balanced was achieved, thus demonstrating the role of intravenous protein hydrolysates as possible alternative to dietary protein in animals.

It was only after 1937, when Elman published his pioneering studies on the intravenous infusion of protein hydrolysates in man (12), that investigations of complete intravenous nutrition (i.e. the intravenous administration carbohydrate, protein, and lipids concurrently) were initiated worldwide. Due to serious complications such as high concentration of di- and tripeptides resulting from incomplete hydrolysis, poor utilisation of nitrogen, and hyperammonaemia (13), the use of protein hydrolysates in PN has now been superseded by the more flexible crystalline amino acids.

Today, various parenteral amino acid preparations for specific clinical states have been developed and marketed such as Aminoplasmal Hepa® (B.Braun Germany) for PN patients with liver dysfunction; Vaminolact® (Fresenius Kabi, Sweden) and Promene® 10% (Baxter, UK) for neonates and infants, and Glamin® (Fresenius Kabi, Sweden), which is an amino acid formula with a higher concentration of glutamine. For patients with renal impairment, amino acid solutions without electrolytes such as Vamin® 14 EF (Fresenius Kabi, Sweden) are recommended.

Intravenous glucose infusion

At the turn of the century, in 1896, Beidl and Kraus administered the first intravenous infusion of glucose solution in man, around 40 years after the importance of glucose for metabolism was first demonstrated. 200-300 ml of a 10% glucose solution was administered with no glucosuria observed although severe fever resulted (10). Glucose infusion was recognised as the only source of energy before the advent of a suitable lipid emulsion that could be safely administered intravenously in humans. In the desire to obtain higher calorie supplement, higher concentrations of glucose solution were infused. Inevitably, vein irritation and thrombophlebitis ensued when high concentrations of glucose solution were infused peripherally. These problems were overcome when Dudrick and co-workers showed that higher concentrations of glucose could be administered safely through the central veins in dogs (1). Ever since then, PN admixtures with high concentrations of glucose have been safely administered in humans through the subclavian vein or the central intravenous route.

Early intravenous administration of lipids

The earliest published record of intravenous lipid administration was made by Courten in 1712, when he infused 1 g per kg body weight of olive oil in a dog. However, severe respiratory distress symptoms were observed, and the dog eventually died (10). It was then assumed that all oils or fats, for that matter, should only be infused in a specialised and suitable form. Further investigations by Menzel and Perco more than 150 years later, also in dogs, showed that large amounts of lipids could be administered intravenously without adverse effects (10).

The interest in using lipids in PN led various investigators to work on lipid emulsions of various composition such as castor oil (14), olive oil (15) and cottonseed oil (16). All these lipid emulsions caused side effects in humans such as nausea, vomiting and fever. Other serious adverse reactions notably liver damage, jaundice and bleeding tendency were also observed leading the United States of America to ban the usage of lipid emulsions for PN in 1964. During this time in Europe, Schuberth and Wretlind developed a safe and efficacious form of lipid emulsion from soybean oil using egg yolk phospholipids as the emulsifying agent (17). This lipid emulsion (consisting of long chain triglycerides, LCT) marketed as Intralipid® (Fresenius Kabi, Sweden) became one of the most widely used lipid emulsions in PN administration until today. [N.B. intravenous lipid emulsions were subsequently reintroduced in the U.S. market in 1975 (18)].

Today, various concentrations (10, 20 and even 30%), and composition of lipid emulsion (LCT, and combination of LCT and medium chain triglycerides, MCT [Lipofundin® MCT/LCT, B. Braun Germany]) are used in PN therapy. Investigations into the use of parenteral fish oil emulsion (n-3 fatty acids) (e.g. 10% Omegaven® [Fresenius, Germany]), and the re-emergence in the use of olive oil in combination with soya bean (ClinOleic® 20% [Baxter, UK]) in the last 10 years suggest new alternatives in the use of lipid emulsion in PN (19).

Electrolytes and the micronutrients in parenteral nutrition

The importance of salts in humans was realised when the blood chemistries of cholera patients were investigated by O'Shaughnessy in 1839, and Latta followed up these findings in the same year by infusing, intravenously, solutions of the salts that were found low in the blood of dying

cholera patients. Majority of these patients remarkably recovered (20). Various concentrations of sodium chloride infusions (e.g. 0.9% sodium chloride, and 0.45% sodium chloride) are now used for parenteral fluid and electrolyte therapy. These findings coupled with the work of Beidl and Kraus in 1896 on the infusions of glucose in humans led to the salt-glucose solutions which became the so-called standard parenteral solution of the early part of the 20th century (20). These solutions are now still used as dextrose-saline combinations in intravenous fluid therapy in the various clinical settings.

The need to provide trace elements or the micronutrients in PN came to light only around 25 years ago when it was shown by Jeejeebhoy and co-workers that long-term PN caused chromium deficiency (21). Work by Buzzeti and colleagues a few years later confirmed the existence of hypocupraemia in a patient attributed to PN administration (22). Trace elements are now normally added in the PN admixture in the form of standard trace element preparations such as Additrace® (Fresenius Kabi, Sweden), Peditrace® (Fresenius Kabi, Sweden) and individual injections (e.g. zinc sulphate, and magnesium sulphate injections) to supplement the daily needs for these micronutrients.

The importance of vitamins, another group of micronutrients, in nutrition was first appreciated in the early part of the twentieth century when researchers found that animals required more than carbohydrate, protein, fat, minerals and water to support life and growth (23). In the parenterally-fed malnourished patients, signs of vitamin deficiencies were observed in the blood levels after a few days on vitamin-free PN (24). Vitamins are now routinely added in the PN admixture using various products such as multiple vitamins preparations (Soluvit®, Vitalipid® [Fresenius Kabi, Sweden]) which have been developed based on the American Medical Association guidelines for vitamins for parenteral use (25). These vitamins can also be added as individualised vitamin preparations (e.g.Vit K).

Complete intravenous provision of nutrients from a single bag

Originally, PN administration constituted the use of separate glass bottles. A 2-in-1 method was adopted where the amino acids solution and glucose were admixed together with the other components of the PN regimen. Lipid emulsion was administered from a separate bottle. This system, which is still being adopted in some hospitals, requires two sets of intravenous tubings and infusion pumps leading to high cost and problems of sepsis, vein patency and lines management (26).

In the seventies, the All-in-One (AIO) system was introduced by Solassol and colleagues to allow for the direct administration of PN in the ambulatory patient (27). This system involved the mixing of the main components of a PN regimen (the amino acids, glucose and lipid emulsion and other nutrient components – the AIO admixture) in a single silicone rubber bag. They showed that this admixture was stable and safe to be administered to patients leading to a more cost-effective and simple approach to PN administration. This method has now been widely accepted and is used worldwide although the type of bags used has changed considerably.

Development of the PN bag

When it was shown that mixing of the major nutrients was possible, the components of the PN admixture (except lipids) were first mixed in bottles (26). The use of these bottles slowly lost favour because of their bulkiness, and losses of costly materials if they were inadvertently dropped and broken.

In light of this, a more flexible container was needed leading to the use of polyvinyl chloride (PVC) bags. However, it was later shown that the use of PVC bags were not suitable due to adsorption of the components such as vitamin A to the bags (28, 29) and also the risk of plasticisers from the PVC matrix leaching out or being extracted by the contents of the admixture (30). Plasticisers can be extracted by the organic contents of the admixtures such as the lipids and vitamins.

The practice of adding all the components (including lipid) of the PN regimen together (the AIO admixture) posed the inherent risk of physicochemical stability problems. As the use of materials such as PVC will only compound this problem, the ethylene-vinylacetate (EVA) bag which is more inert was introduced. The EVA bags possess advantageous thermoplastic properties and favourable toxicological and biocompatibility aspects (31). These bags are

now commonly used for the AIO admixtures.

Nowadays, multilayered bags have been introduced to ensure a greater stability profile of the PN admixture against oxidation. These bags consist of multiple-layered plastic produced from the combination of EVA-polyvinylidine chloride (PVDC) (32) or EVA-modified EVA ethylvinyl alcohol (EVOH) for example, which reduces the permeability of oxygen by 100 times compared to conventional EVA bags thus ensuring better stability of the admixture (33).

Further understanding of the physico-chemical aspects of the PN regimens, and recent technological advances have led to the development of the prefilled multi-compartmental bags for PN administration. The introduction of these bags has provided easy mixing of the PN regimens and also provided a close system which guarantees sterility of the admixture.

The Easy-to-Mix System

During the late eighties, an easy-to-mix (ETM) system was introduced to facilitate quick and easy mixing of PN regimens by pharmacy and nursing staff. This system comprises of a two-bottle system (Vitrimix^{R} [Fresenius Kabi, Sweden]). One bottle contains a glucose-amino acid solution, whereas the lipid component is contained in the other bottle. Compounding of a PN regimen (minus the micronutrients) involves the simple transfer of the lipid emulsion into the glucose-amino acid solution via a tranfer pin. This system has now been superseded by another ETM system which was developed in the early nineties.

The new ETM system uses multi-compartmental EVA bags or the convenience bags (please refer preceding section) prefilled with the nutrients and electrolytes required for PN therapy. These bags are presented as the double chamber (Nutriflex^{R} [B Braun, Germany]), and triple chamber bags (Kabiven^{R} [Fresenius Kabi, Sweden], Clinomel™ [Baxter, UK]). The chambers are separated by various mechanisms such as a breakable port, peel-seal system, or a pull-away flexible rod clamp. In the double chamber bag, one compartment is filled with the amino acids solution, while the other compartment is filled with glucose based on a standard nutritional regimen (the lipid component is kept in a separated bottle, which is then added to the system). In the triple-chamber bags, the third compartment is filled with the lipid emulsion. To use these bags, firm and gentle squeezing of the bag will break the intercompartmental seals; or the separating rod removed, thus mixing the nutrients. Other nutrients such as the electrolytes, trace elements and vitamins can then be added based on the daily allowances, and the bags are ready for administration. The use of these bags, or the ETM system ensure better stability of the AIO admixtures and minimise the risk of contamination during compounding.

Home Parenteral Nutrition

Home parenteral nutrition (HPN) is the provision of parenteral nutrition at home. The need to provide HPN was realised in the effort of reducing treatment cost due to long hospital stay, and to avoid hospital-acquired complications (e.g. infection) in the stabilised patients whose main reason for continued hospitalisation is for PN therapy. With the increase in knowledge, development, and improvement in PN support, the provision of HPN provides a comforting environment, and gives patients the freedom to return to normal activities such as work, and even travelling (34). HPN is indicated in patients who have to rely on long-term PN such as those with Crohn's disease and short bowel syndrome. HPN is also administered to patients suffering from acquired immunodeficiency syndrome (AIDS), chronic pancreatitis, hyperemesis gravidarum, and neoplasm (35).

HPN should be administered exclusively from an AIO admixture in a single bag. As such the compounding of a stable admixture is usually carried out by experienced pharmacy personnel in established centres. A patient needs only to attach the outlet port of the compounded bag, aseptically, to the inserted catheter of the central route (established by the surgeon in the hospital). It is common for the pharmacy department in the hospital where the patient has been treated to supply compounded bags ready for use at home. Storage advice and correct use of the compounded bags for HPN are usually provided by the pharmacist to these patients to avoid physicochemical stability problems, and also clinical complications such as infection, and other metabolic derangements. Monitorings during HPN administration by the nutritional support team help to provide safe and cost-effective nutritional therapy to these patients.

CONCLUSION

In perspective, PN has now been accepted as part of the overall therapeutic management of the hospitalised patients when indicated. It is not only limited to preventing starvation or correcting deficiencies (36). In more advanced countries, the instigation or cessation of PN therapy is subject to the same legal and moral constraints as apply to other recognised therapies 37). Refinement and sophistication of techniques have made optimal nutrition possible in virtually all patients regardless of the status of their gastrointestinal tract, or the presence of complicating metabolic disorders. Today, these advances have also made home parenteral nutrition possible in stabilised patients who require this mode of nutritional support for a longer period of time.

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Malaysian Journal of Pharmacy 2003;1(3) 76-85 *Research article*

Awareness of Hepatitis A and Hepatitis B among Residents in Kuala Lumpur and Selangor

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ABSTRACT

A survey was carried out to assess the level of knowledge and vaccination coverage of hepatitis A and B among 753 subjects (>12 years of age) from rural areas, town areas, undergraduates and healthcare workers. The main objective of the study was to assess the relationship between the extent of hepatitis A and B knowledge and vaccination status of the participants. A questionnaire was distributed and completed by the subjects. The results showed that the overall level of knowledge among the public was low compared to healthcare workers and undergraduates. The hepatitis A vaccination coverage was very low among all the groups (<8%). The hepatitis B vaccination coverage was generally low among the groups of non-healthcare workers (<35%) and higher among healthcare workers (65.6%). There was a strong correlation between the extent of knowledge of hepatitis A and B and the status of vaccination among the participants ($p<0.01$). The study concluded that health education on hepatitis A and B should be provided and vaccination programmes should be held more frequently among the public, especially in rural areas.

Keywords: hepatitis, healthcare workers, knowledge, survey, vaccination

INTRODUCTION

Hepatitis A and B continue to be a major health problem in Malaysia and also worldwide. Although hepatitis B and A vaccines were approved in late 1981 (1) and in 1992 (2), respectively, hepatitis A and B continue to be the most frequently reported vaccine-preventable diseases. Data from Ministry of Health Malaysia (2000) (3) indicated that the incidence of viral hepatitis was 1 326 cases with 13 fatalities in 1991 and this was reduced to 686 cases with 7 fatalities in 1995. The average incidence rate from 1991 to 1995 was about 4.2 per 100,000 population. As most of the infections are asymptomatic and subclinical, it is almost certain that cases of hepatitis are under-reported. According to the Malaysian Liver Foundation (1999) (4), there are 2.4 million hepatitis B virus (HBV) carriers in Malaysia, and they will continue to be the source of HBV infection to the others.

Both hepatitis A virus (HAV) and hepatitis B virus (HBV) infections may result in a wide spectrum of clinical outcomes, ranging from silent anicteric infection to subclinical disease and classical icteric hepatitis to fulminant hepatic

failure with coma and occasionally death (5). Hepatitis A will not lead to long term complications, and most of the patients recover within two months from the onset of illness (6), however, acute liver failure due to severe hepatitis A is well documented and no specific drug treatment is available (7). Exposure to HBV, particularly in early in life, may also result in an asymptomatic carrier state that can progress to chronic active hepatitis, cirrhosis of the liver and eventually hepatocellular carcinoma (8). As both infections can spread from person to person, the key control of HAV and HBV infections is immunoprophylaxis.

This study was carried out to determine the level of knowledge and the vaccination coverage of both hepatitis A and B in different groups of population, including the general public, healthcare workers and undergraduates. The relationship between the extent of hepatitis A and B knowledge and vaccination status of the participants was assessed. Hopefully this study can provide the information relevant to the development of the vaccination strategies for both hepatitis A and B and contribute to the elimination of hepatitis A and B in Malaysia.

METHOD

Study design

The study was conducted from January to July 2000 in Kuala Lumpur and Selangor. A cross-sectional survey was carried out to identify the level of knowledge of hepatitis A and B and the vaccination coverage among the population through questionnaires.

Study population

The study population consisted of subjects above 12 years of age. The study population was made up from four groups: (I) residents from rural areas i.e. Kampung Nakhoda and Sungai Tua Bahru, Selayang, Selangor Darul Ehsan; (II) residents from town areas who were mainly from Serdang, Sri Kembangan, Balakong, Cheras, Kajang and Bangi; (III) healthcare workers from the nephrology unit and blood bank, Hospital Kuala Lumpur; and (IV) undergraduates from Faculty of Dentistry and Faculty of Allied Health Sciences, Universiti Kebangsaan Malaysia (UKM). Sampling was on voluntary basis.

Questionnaires

Questionnaires were presented in English and Malay. The survey was carried out in divided sessions. Participants were given a questionnaire and explanation was provided to assist them in completing the questionnaire. Participants who were illiterate were interviewed with understandable language. The information obtained through the questionnaires included age, gender, race, occupation, education level, household income, knowledge about hepatitis A and B, awareness of vaccination for hepatitis A and B, awareness of blood testing for hepatitis A and B virus, and family members' or subject's previous diagnosis of hepatitis.

After completing the questionnaires, participants were given brochures about hepatitis A and B. Brochures in different languages, including Malay, English, and Chinese were available. Posters about prevention of hepatitis A and B were also exhibited. Participants were encouraged to seek vaccination for both hepatitis A and B. All the brochures and posters were provided by SmithKline Beecham Sdn. Bhd (now known as GlaxoSmithKline Sdn. Bhd.).

Statistical analysis

Data were analysed using *Statistical Package for Social Sciences* (SPSS) version 9.05. Descriptive statistics, including frequencies and percentages, were calculated for each item on the questionnaires; cases with missing data were excluded. In addition, comparisons of the level of knowledge on the diseases and vaccination rate among four groups of subjects were made by descriptive analysis.

In order to enable further assessment on the relationship between the extent of knowledge and the vaccination status of hepatitis A and/or B among the participants, answers to questionnaires were marked. One mark was given to each correct answer and the total mark was 15. The subjects were classified into three groups based on their overall knowledge about hepatitis A and B. The classification is as following:

Degree of knowledge	Score of correct answers
Low	≤ 5
Intermediate	6-10
High	≥ 11

Chi-squared test (testing of independence) was performed to evaluate the correlation of the extent of knowledge and receiving hepatitis A and/or B vaccine(s) among the participants. The two parameters were considered not independent if the p value was less than 0.01.

RESULTS

A total of 753 subjects were enrolled in the survey from 4 study groups: (I) residents from rural areas i.e. Kampung Nakhoda and Sungai Tua Bahru, Selayang, Selangor Darul Ehsan (n=165) with a mean age of 37.7±12.1; (II) residents from town areas (n=206), mainly from Serdang, Sri Kembangan, Balakong, Cheras, Kajang and Bangi with a mean age of 24.8±8.2; (III) healthcare workers (HCWs) (n=194) from the nephrology unit (64.0%) and blood bank (36.0%) from Hospital Kuala Lumpur with a mean age of 32.3±93.2 and mean working period of 98 months; and (IV) undergraduates (n=188) from the Faculty of Dentistry (24.5%) and Faculty of Allied Health Sciences (75.5%), Universiti Kebangsaan Malaysia (UKM) with a mean age of 22.1±1.9.

Generally, the mean age of the participants from rural areas and HCWs were higher than the participants from town areas and undergraduates. Female participants outnumbered males. Most of the residents from the rural areas, HCWs and undergraduates were Malays (97.6%, 84.3% and 73.5%, respectively). However, the percentage of Malay and Chinese participants from town areas were almost equal, with 49.5% and 47.5%, respectively.

Most of the participants from rural areas (59.4%) had secondary education, however, most of the participants from town areas (67.8%) had tertiary education. There was an almost equal percentage of HCWs with secondary education and tertiary education. 41.5% and 40.4% of the participants from rural areas were from low and middle income groups, respectively. For those from town areas, 29.3%, 42.5%, and 28.2% were from low, middle and high income groups, respectively. Most of the HCWs were in the middle income group (69.1%), while most of the undergraduates were from the low (36.5%) and middle (37.7%) income groups. Demographic details of the subjects are shown in Table 1.

Knowledge of hepatitis A and B

A high proportion of undergraduates (85.0%) had knowledge on hepatitis compared to the public from town areas (63.6%) and rural areas (52.7%). Most of the public knew about the diseases through the mass media; undergraduates, however, acquired knowledge of the diseases through formal education. All

Table 1: Demographic data of patients.

Groups	Public from rural areas (%)	Public from town areas (%)	Health care workers (%)	Undergraduates (%)	Total subjects (%)
No. of subjects (n)	165	206	194	188	753
Mean age (years)	37.67	24.75	32.29	22.06	28.87
Gender					
Male	63 (38.2)	84 (40.8)	33 (17.3)	45 (24.3)	225 (30.1)
Female	102 (61.8)	122 (59.2)	158 (82.7)	140 (75.7)	522 (69.9)
Race					
Malay	161 (97.6)	102 (49.5)	161 (84.3)	136 (73.5)	560 (75.0)
Chinese	2 (1.2)	98 (47.5)	10 (5.2)	30 (16.2)	140 (18.7)
Indian	1 (0.6)	3 (1.5)	18 (9.4)	12 (6.5)	34 (4.6)
Others	1 (0.6)	3 (1.5)	2 (1.1)	7 (3.8)	13 (1.7)
Education level					
Primary school	25 (15.6)	8 (3.9)	11 (6.1)		44 (6.0)
Secondary school	95 (59.4)	58 (28.3)	81 (45.3)		235 (32.1)
College/University	40 (25.0)	139 (67.8)	87 (48.6)	188 (100)	453 (61.9)
Family monthly income					
<RM 1000	39 (41.5)	53 (29.3)	48 (27.0)	55 (36.5)	195 (32.3)
RM 1000-2500	38 (40.4)	77 (42.5)	123 (69.1)	57 (37.7)	295 (48.8)
RM 2500-4000	9 (9.6)	28 (15.5)	5 (2.8)	27 (17.9)	69 (11.4)
>RM 4000	8 (8.5)	23 (12.7)	2 (1.1)	12 (7.9)	45 (7.5)

Note: The total number of respondents does not equal 753 due to missing values.
The percentages are based on the number of subjects who responded to the items.

Table 2: Knowledge about hepatitis (hep.) A and B among respondents.

Knowledge about hep. A or B	Public		Healthcare workers (%)	Undergraduates (%)	Total (%)
	Rural areas (%)	Town areas (%)			
Know about hepatitis.					
Yes	87 (52.7)	131 (63.6)	-	159 (85.0)	377 (63.4)
Through media	*66 (76.7)*	*78 (59.5)*		*54 (34.0)*	
Education	*17 (20.0)*	*45 (34.4)*		*140 (88.1)*	
Family	*10 (11.6)*	*18 (13.7)*		*10 (6.3)*	
Friends	*13 (15.1)*	*17 (13.0)*		*21 (13.2)*	
Healthcare workers	*10 (11.6)*	*9 (6.9)*	-	*5 (3.1)*	
No	51 (30.9)	20 (9.7)	-	2 (1.1)	55 (9.2)
Not sure	27 (16.4)	55 (26.7)		26 (13.9)	163 (27.4)
Knowledge of organ affected					
Liver	78 (50.3)	143 (69.4)	190 (99.0)	186 (100.0)	579 (78.3)
Heart	27 (17.4)	31 (15.0)	1 (0.5)	0 (0.0)	59 (8.0)
Kidneys	10 (6.5)	23 (11.2)	22 (11.5)	0 (0.0)	55 (7.4)
Brain	3 (1.9)	6 (2.9)	2 (1.0)	0 (0.0)	11 (1.5)
Not sure	43 (27.7)	20 (9.7)	1 (0.5)	0 (0.0)	64 (8.7)
Knowledge of spreading by virus					
Yes	81 (50.3)	120 (58.5)	176 (95.1)	182 (96.8)	559 (75.6)
No	15 (9.3)	19 (9.3)	5 (2.7)	0 (0.0)	39 (5.3)
No sure	65 (40.4)	66 (32.2)	4 (2.2)	6 (3.2)	141 (19.1)
Knowledge of causing jaundice					
Yes	84 (52.2)	107 (52.7)	190 (99.0)	164 (87.7)	545 (73.4)
No	14 (8.7)	10 (4.9)	2 (1.0)	3 (1.6)	29 (3.9)
Not sure	63 (39.1)	86 (42.4)	0 (0.0)	20 (10.7)	169 (22.7)
Knowledge of transmission of hep. A through food & water					
Yes	68 (42.5)	100 (48.6)	177 (91.8)	147 (79.0)	492 (60.2)
No	22 (13.8)	26 (12.6)	8 (4.1)	4 (2.2)	60 (7.4)
Not sure	70 (43.7)	80 (38.8)	8 (4.1)	35 (18.8)	265 (32.4)
Knowledge of mode of hep. B transmission					
Blood	94 (60.6)	106 (51.7)	180 (93.8)	168 (89.8)	548 (74.2)
Saliva	34 (21.9)	60 (29.3)	80 (41.7)	87 (46.5)	261 (35.3)
Sexual	26 (16.8)	35 (17.1)	99 (51.6)	140 (72.9)	300 (40.6)
Mother to child	42 (27.1)	63 (30.7)	106 (55.2)	112 (58.3)	323 (43.7)
Casual contact	8 (5.2)	13 (6.3)	2 (1.0)	14 (7.3)	37 (5.0)
Not sure	38 (24.5)	20 (9.8)	1 (0.5)	0 (0.0)	59 (8.0)
Knowledge of complications of hep. B					
Liver damage	86 (55.1)	114 (55.9)	158 (82.7)	172 (93.5)	530 (72.1)
Liver cancer	44 (28.2)	57 (28.9)	112 (58.6)	113 (61.4)	326 (44.3)
Death	33 (21.2)	62 (30.4)	49 (25.7)	96 (52.2)	240 (32.7)
Heart disease	22 (14.1)	20 (9.8)	4 (2.1)	4 (2.2)	50 (6.8)
Kidney failure	27 (17.3)	23 (11.3)	6 (3.1)	8 (4.3)	64 (8.7)
Knowledge of treatment availability for hep. B					
Yes	82 (50.9)	94 (46.1)	105 (56.4)	86 (51.5)	367 (51.1)
No	32 (19.9)	51 (25.0)	63 (33.9)	63 (37.7)	209 (29.1)
Not sure	47 (29.2)	59 (28.9)	18 (9.7)	18 (10.8)	142 (19.8)
Knowledge of availability of hep. A vaccine					
Yes	91 (56.5)	137 (66.5)	107 (57.5)	153 (81.8)	488 (65.9)
No	24 (14.9)	14 (6.8)	63 (33.9)	4 (2.1)	105 (14.2)
Not sure	46 (28.6)	55 (26.7)	16 (8.6)	30 (16.1)	147 (19.9)
Knowledge of availability of hep. B vaccine					
Yes	91 (56.5)	133 (64.6)	183 (94.3)	175 (93.1)	582 (77.7)
No	24 (14.9)	17 (8.2)	5 (2.6)	1 (0.5)	47 (6.3)
Not sure	46 (28.6)	56 (27.2)	6 (3.1)	12 (6.4)	120 (16.0)
Knowledge of number of shots in a full course of hep. B vaccination					
1X	19 (13.4)	19 (9.5)	4 (2.2)	9 (5.0)	51 (7.2)
2X	27 (19.0)	46 (22.9)	8 (4.4)	8 (4.4)	89 (12.6)
3X	34 (23.9)	111 (55.1)	167 (91.3)	155 (86.1)	467 (66.2)
4X	3 (2.1)	7 (3.5)	3 (1.6)	1 (0.6)	14 (2.0)
Not sure	59 (41.6)	18 (9.0)	1 (0.5)	7 (3.9)	85 (12.0)

Note: The total number of respondents does not equal 753 due to missing values.
The percentages are based on the number of subjects responded to the items.

the undergraduates and almost all the HCWs knew that hepatitis would affect the liver compared to only 69.4% and 50.3% of the public from town areas and from rural areas, respectively. A relatively high percentage of the undergraduates and HCWs knew that some types of hepatitis are caused by viruses and can cause jaundice compared to only about 50% of the public with that knowledge.

HCWs (91.8%) were superior in knowing that food and water are the sources of transmission of hepatitis A, followed by undergraduates (79.0%), participants from town areas (48.6%), and those from rural areas (42.5%). Blood is generally more acknowledged as a transmission mode of hepatitis B among the participants with 93.8% for HCWs, 89.8% for undergraduates, 60.6% for those from rural areas, and 51.7% for those from town areas. Generally, half of the HCWs and undergraduates recognised that sexual, mother to child and saliva as transmission modes of hepatitis B, compared to a relatively low percentage (<30%) of the public.

Undergraduates were superior to the other groups in knowing liver damage (93.5%), liver cancer (61.4%) and death (52.2%) as the complications of hepatitis B, followed by HCWs with 82.7%, 58.6% and 25.7, respectively; participants from town areas with 55.9%, 28.9% and 30.4%, respectively; and those from rural areas with 55.1%, 28.2% and 21.2%, respectively. 31.4% and 21.1% of the public from rural areas and town areas, respectively, said that hepatitis B can cause complications of heart disease and renal failure, which is not correct.

The availability of hepatitis A and B vaccines was generally well known among HCWs and undergraduates (81.7%), with the exception that only 57.5% of HCWs knew about the availability of hepatitis A vaccine. About half of the participants from town and rural areas knew about the availability of hepatitis A and B vaccines. Details of the knowledge about hepatitis A and B among the four different groups are shown in Table 2.

Vaccination coverage of hepatitis A and B

Majority of the participants were not vaccinated for hepatitis A with only 7.8% of the participants from town areas, 3.6% of the participants from rural areas, 3.2% of the HCWs and none of the undergraduates was vaccinated for hepatitis A. From the total of those who received the vaccination, 100% of the HCWs had received the full course of the vaccination. However, all the participants from rural areas and 31.2% of those from town areas, who had received the hepatitis A vaccination could not remember the number of doses taken.

65.6% of the HCWs were vaccinated against hepatitis B compared to a relatively low percentage of participants from town areas (31.6%), undergraduates (21.9%), and those from rural areas (13.9%). From those who had received the vaccination, 73.0% of HCWs, 56.9% of those from town areas and 39.0% of undergraduates had fulfilled the 3- dose vaccination course. However, a relatively low percentage of them, ranging from 5% to 19.5%, had received the vaccine in the last five years. Most of the HCWs were exposed to blood or body fluids of patients everyday (>90%) and only 6% of them were not exposed to blood or body fluids of patients.

Investigation on the previous diagnosis of hepatitis of the subjects or their household members showed that the average prevalence of hepatitis infection for subjects or their household members was 6.6% with the highest prevalence among participants from rural areas (9.3%), followed by participants from town areas (8.3%), undergraduates (8.0%), and HCWs (1.0%). Hepatitis B was the major type of infection.

A relatively small proportion of participants from rural areas (17.2%), participants from town areas (25.7%), and undergraduates (19.8%) have had a blood test conducted before, compared to HCWs (67.7%). Again, hepatitis B was the more common disease tested for. Details of the results are shown in Table 3.

Association between the extent of knowledge and the vaccination status among the study population

Figures 1 and 2 depict the level of knowledge and vaccination status for hepatitis A and/or B among the subjects of different groups, respectively. Figure 3 shows the association between the level of knowledge and vaccination status. There was a strong association between the level of knowledge and vaccination status among the study population. For those with a low level of knowledge, only a small proportion

Table 3: Vaccination of hepatitis A & B coverage among respondents.

	Public		Healthcare workers (%)	Undergraduates (%)	Total (%)
	Rural areas (%)	Town areas (%)			
Ever received hepatitis A vaccine					
Yes	6 (3.6)	16 (7.8)	6 (3.2)	0 (0.0)	28 (3.7)
Dose: 1X	*0 (0.0)*	*4 (25.0)*	*0 (0.0)*		*4 (14.3)*
2X	*0 (0.0)*	*7 (43.8)*	*6 (100.0)*		*13 (46.4)*
cannot remember	*6 (100.0)*	*5 (31.2)*	*0 (0.0)*		*11 (39.3)*
No	139 (84.3)	134 (65.0)	157 (83.5)	148 (79.1)	578 (77.5)
Not sure	20 (12.1)	56 (27.2)	25 (13.3)	39 (20.9)	140 (18.8)
Ever received hepatitis B vaccine					
Yes	23 (13.9)	65 (31.6)	126 (65.6)	41 (21.9)	255 (34.0)
Dose: 1X	*2 (10.0)*	*9 (13.9)*	*11 (8.7)*	*3 (7.3)*	*25 (9.9)*
2X	*0 (0.0)*	*10 (15.4)*	*18 (14.3)*	*1 (2.5)*	*29 (11.5)*
3X	*0 (0.0)*	*37 (56.9)*	*92 (73.0)*	*16 (39.0)*	*145 (57.5)*
cannot remember	*18 (90.0)*	*9 (13.8)*	*5 (4.0)*	*21 (51.2)*	*53 (21.1)*
Time: <5 years ago	*1 (5.0)*	*8 (12.3)*	*24 (19.0)*	*8 (19.5)*	*41 (16.3)*
5-10 years ago	*0 (0.0)*	*12 (18.5)*	*21 (16.7)*	*12 (29.3)*	*45 (17.9)*
>10 years ago	*1 (5.0)*	*3 (4.6)*	*8 (6.3)*	*8 (19.5)*	*20 (7.9)*
cannot remember	*18 (90.0)*	*42 (64.6)*	*73 (57.9)*	*13 (31.7)*	*146 (57.9)*
No	124 (75.2)	87 (42.2)	55 (28.7)	117 (62.6)	383 (51.1)
Not sure	18 (10.9)	54 (26.2)	11 (5.7)	29 (15.5)	112 (14.9)
Household member or subject ever had hepatitis					
Yes	15 (9.3)	17 (8.3)	2 (1.0)	15 (8.0)	49 (6.6)
hepatitis A	*0 (0.0)*	*3 (17.6)*	*0 (0.0)*	*2 (13.3)*	
hepatitis B	*15 (100.0)*	*13 (76.5)*	*2 (100.0)*	*13 (86.7)*	
hepatitis C	*0 (0.0)*	*1 (5.9)*	*0 (0.0)*	*0 (0.0)*	
No	146 (90.1)	184 (89.3)	188 (98.0)	162 (86.6)	680 (91.0)
Not sure	1 (0.6)	5 (2.4)	2 (1.0)	10 (5.4)	18 (2.4)
Ever had blood test for hepatitis					
Yes	28 (17.2)	49 (25.7)	86 (67.7)	35 (19.8)	198 (30.1)
hepatitis A	*0 (0.0)*	*9 (18.4)*	*23 (26.7)*	*2 (5.7)*	
hepatitis B	*27 (96.4)*	*45 (91.8)*	*77 (89.5)*	*34 (97.1)*	
cannot remember	*1 (3.6)*	*0 (0.0)*	*0 (0.0)*	*1(2.9)*	
No	135 (82.8)	137 (71.7)	37 (29.1)	136 (76.8)	445 (67.6)
Not sure	0 (0.0)	5 (2.6)	4 (3.2)	6 (3.4)	15 (2.3)

Note: The total number of respondents does not equal 753 due to missing values.
The percentages are based on the number of subjects who responded to the items.

of them (17.0%) had been vaccinated against hepatitis A and/or B. In contrast, a higher proportion of those with intermediate or high level of knowledge had been vaccinated, i.e. 41.8% and 42.5%, respectively. In conclusion, the level of knowledge and vaccination status were significantly dependent in this study ($p<0.01$).

DISCUSSION

The overall level of knowledge about hepatitis A and B was generally poor among the general public. In comparison, HCWs and undergraduates had far better knowledge about hepatitis A and B (Table 2) as they had a higher level of education and were more exposed to health information. Participants from town areas had slightly better level of knowledge about hepatitis A and B than those from rural areas which could be attributed to the fact that a higher number of them had tertiary education compared to participants from rural areas (Table 1). This agreed with the findings of the study of Wiecha (9) and Taylor et al. (10) that there is a significant association between the level of knowledge about hepatitis B and the education level.

Both of the groups from rural and town areas were poor in recognising the modes of transmission of both hepatitis A and B. Awareness of the transmission modes is important, so that effective preventive measures could be taken such as modification of lifestyles and vaccination against hepatitis A and B.

In East and Southeast Asian countries, 30 to 50% of all chronic infections among children result from perinatal transmission and 9 500 infants

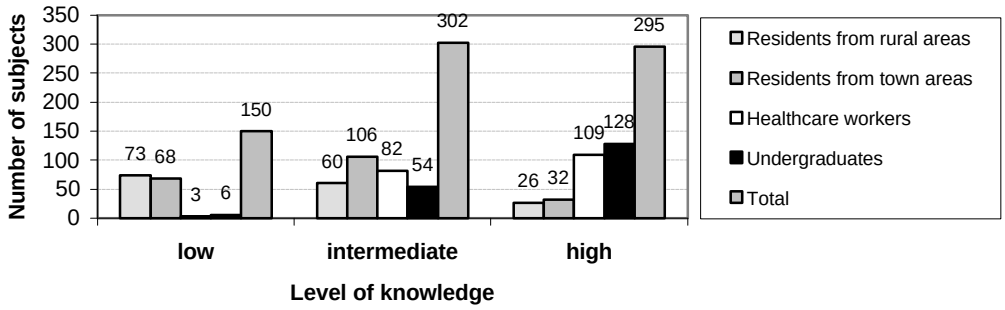

Figure 1. Level of knowledge among the different subject groups.

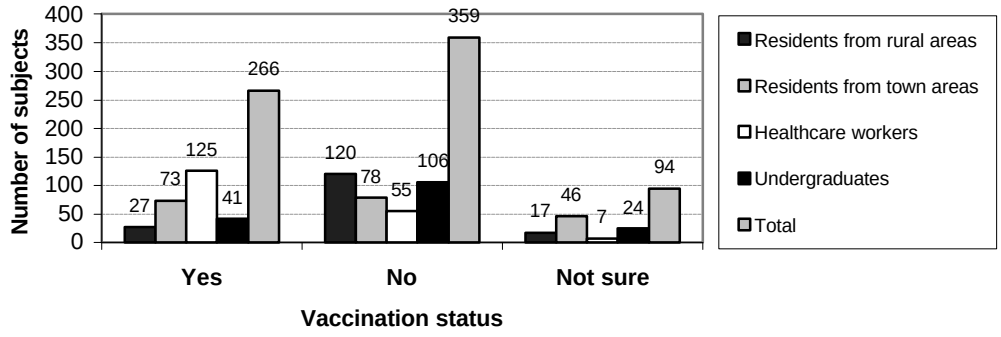

Figure 2. Hepatitis A and/or B vaccination coverage among subjects in different groups.

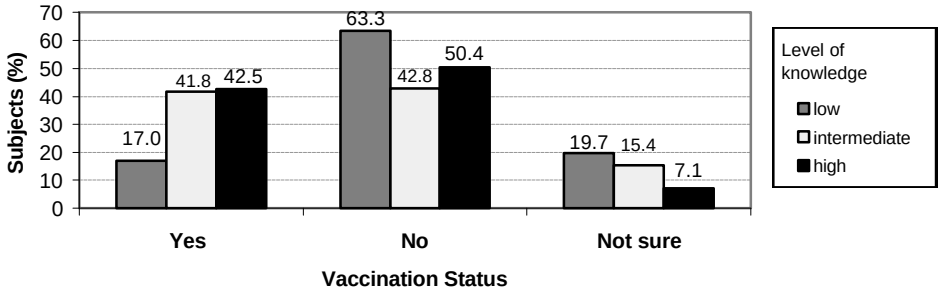

Figure 3: Association of the extent of knowledge with hepatitis A and/or B vaccination status (n=719, p< 0.01)

would become infected if prophylaxis is not provided (11). Understanding the possibility of HBV transmission from mothers to babies would enable women to be more aware about the importance of hepatitis B surface antigen (HBsAg) screening, so that prophylactic measures could be taken to protect the babies from HBV infection.

With the successful implementation of the national childhood immunisation programme against hepatitis B in Malaysia, sexual transmission would inevitably emerge as the leading cause of HBV infection among healthy susceptible adolescents and adults as in the West. So, the public should be aware that their sexual behaviour could lead to HBV infection.

Awareness of the complications of hepatitis B is also important, so that people would realise about the importance of taking preventive measures, especially vaccination against the disease. Unfortunately, most of the public did not know that hepatitis B can lead to severe complications of liver cancer and death (Table 2).

Malaysia had incorporated hepatitis B vaccination into the national immunisation programme since 1989. According to Ministry of Health Malaysia (12), the vaccination coverage among babies is 98.3% for first dose, 91.6% for second dose and 89.6% for third dose. However, there is no data available about the rate of hepatitis A or B vaccination among adults in Malaysia. According to the results in this study, the overall vaccination coverage was very low for hepatitis A (3.7%) and low for hepatitis B (34.0%). Only about 2% of the total study population received both hepatitis A and B vaccines (not shown in results). The results also implicated that most of the subjects who had been vaccinated, did not complete the course of vaccination and also did not follow-up on their immunisation status. Preventive strategies against the diseases, especially vaccination programmes, should be developed and taken aggressively to improve the vaccination coverage among the adults.

A study by Chen et al. (13) and Hsu et al. (14) showed that after a nationwide mass vaccination programme was launched in Taiwan in July 1984, the HBsAg prevalence decreased markedly from the year 1984 to 1994. Chang et al. (15) reported that after the implementation of nationwide hepatitis B immunisation programmes, the annual incidence of hepatocellular carcinoma in children had declined. So, immunisation programmes have proven effective not only in controlling hepatitis B infection, but also in controlling hepatocellular carcinoma in Taiwan.

A low vaccination rate among participants from rural areas was probably due to the low level of knowledge about the diseases and the availability of the vaccines. Compared to those from rural areas, vaccination coverage of participants from town areas was slightly better probably as they had a higher level of knowledge about hepatitis A and B. However, undergraduates, who had a high level of knowledge, had a very low vaccination coverage for both hepatitis A (none) and hepatitis B (21.9%) (Table 3). This might be due to their dependence on parents or study loans for financial assistance.

HCWs are always at the risk of HBV infection because of the occupational exposure to blood borne pathogens (16). Risk increases with percutaneous exposures involving deeper penetration, larger volume of blood, high viral titres and repeated or prolonged exposures (16-18). It is noteworthy to mention that in this study most of the HCWs (over 90%) were exposed to blood and other body fluids of patients everyday, however, only about two thirds of them received the hepatitis B vaccine and only 73% of them completed the 3-dose course.

Only six of the total number of HCWs in this study received the hepatitis A vaccine (Table 3). This might be due to the fact that HAV is not a blood-borne pathogen and that the disease is usually self-limiting and non-fatal. So, there is less emphasis on the risk of hepatitis A among the HCWs and this was proven by a lower percentage of HCWs (57.5%) knowing about the availability of the hepatitis A vaccine compared to the hepatitis B vaccine (94.3%) (Table 2). Although HAV generally will not be transmitted through blood or blood products, however, prevention of hepatitis A is potentially important among HCWs and particular care should be required when nursing patients with diarrhoea (19).

Considering the long-term consequences of HBV infection, the health of the HCWs is at risk. The health of the general population is also at risk considering the transmission risk of the virus to the patients treated by the infected HCWs. In 1991, the Centers For Disease Control And Prevention (CDC) estimated that during the past 20 years more than 300 patients in the USA had

been infected with HBV 'in association with treatment' by infected HCWs (20).

Over 80% of 84 nurses and 26 physicians from five St. Louis-area hospitals agreed that every hospital employee should get the hepatitis B vaccine (17). Mahoney et al. (21) showed that the number of infections among HCWs declined from 17 000 in 1983 to 400 in 1995 after the implementation of hepatitis B vaccination and barrier precautions for blood exposure. So, all HCWs should be vaccinated against hepatitis B.

This study revealed a strong correlation between the extent of knowledge and vaccination status of hepatitis A and/or B among the participants ($p<0.01$) (Figure 3). Similar studies by Adebamowo & Ajuwan (22) and Kamolraranakul et al. (23) showed that the overall level of knowledge about HBV infection was deemed poor and lack of knowledge on HBV infection was one of the reasons that leads to non-immunisation.

Limitations

There are some limitations to the findings in this study. Firstly, the study only involved certain groups of the population from particular residential areas or working places, so the results may not represent the general population in Malaysia. Secondly, by using the convenience sampling based on voluntary basis, the proportion of races, gender, age, numbers of subjects were not the same in each group, thus potentially introducing bias into the analysis. Thirdly, all data were self-reported and the validity of the responses were not evaluated. Fourthly, the history of vaccination and blood tests was based on the ability to recall and this might introduce inaccuracy in recording of the data. Fifth, the inclusion of 13-16 year old subjects could have caused a problem of irreliability of information. Lastly, people with a low literacy level may have had difficulty with comprehension and tended not to answer the questions, especially those regarding knowledge of the disease.

CONCLUSION

Generally the degree of knowledge about hepatitis A and B among the public was low. Undergraduates and HCWs had a high degree of knowledge about hepatitis A and B. The overall vaccination coverage for hepatitis A and B was poor and the vaccination rate for hepatitis B was higher than hepatitis A. Not all the HCWs were vaccinated against hepatitis B as they were supposed to be. Most of them who received the hepatitis B vaccine did not follow up on their immunisation status. Quite a number of the public did not know their immunisation status. The extent of knowledge is a crucial factor in determining the vaccination status of the participants ($p<0.01$).

The results of this study showed that more attention should be addressed at providing health education on hepatitis A and B to the public, particularly those in the rural areas. Large scale nationwide awareness programmes, campaigns, and vaccination programmes should be carried out frequently in various states, especially in rural areas. More specific educational efforts should start before launching vaccination programmes in order to increase acceptance. As most of the public got to know about hepatitis through the mass media, information about the disease and its preventive measures can be broadcasted to the public through television, radio, newspapers and magazines. HCWs and undergraduates should be routinely immunised before starting work in health institutes, especially in hospitals.

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Outpatient Prescription Intervention Activities by Pharmacists in a Teaching Hospital

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ABSTRACT

Prescriptions with prescribing errors received by an outpatient pharmacy of a teaching hospital were sampled. The types of pharmacist interventions on problematic prescriptions and its outcome were identified and documented. From a total of 6340 prescriptions processed by the outpatient pharmacy in a one-week period, 43 prescriptions (0.68%) required interventions by the pharmacy staff. These included 54% of the prescriptions that were incomplete or inadequately written (errors of omission) and 46% that contained the wrong drug, dose regimen, strength and dosage form (errors of commission). A total of 62 types of action were taken by the pharmacy staff to resolve the 43 problematic prescriptions. These include contacting the prescribers concerned (24.2%), clarifying with the patient or his/her representative (19.4%), contacting the prescriber's nurse (17.7%) and checking the patient's appointment or identity card (4.8%). Of the 43 problematic prescriptions, 48.8% were clarified without any change and dispensed while 32.6% were changed and dispensed. The study reinforces the importance of prescription screening and interventions by pharmacists in minimising preventable adverse events attributed to medication errors. It also emphasizes the necessity of interdisciplinary communication and cooperation in identifying and resolving prescribing errors and irregularities in order to achieve optimal therapeutic outcomes for the patient.

Keywords: prescription, pharmacist, intervention, errors of omission, errors of commission

INTRODUCTION

The dispensing "chain" may be conceptualised as a sequence of interrelated, interdependent, and at least historically, interdisciplinary activities that result in the delivery of the prescription drug and appropriate drug-use information to the patient (1).

A study showed that 99% of the 137 general practitioners surveyed agreed that pharmacists have a role to play in the screening of prescriptions for possible problems (2). Most pharmacists would probably agree that the screening of prescriptions is one of the

professional responsibilities assumed by every pharmacist but the degree to which prescription screening is performed varies greatly among different drug-delivery systems and even among different pharmacists' practices. Thus, prescription screening represents a legitimate value-added pharmaceutical service in practice, if not in principle (3).

Many studies had identified and documented problems associated with prescribing errors. The extent of such errors varied from 2.6% to 15.4% or estimated as 2.87 to 4.9 per 1000 medication orders (1, 4-11). An audit on community pharmacies found that 2.6% of the prescriptions required active pharmacist intervention to resolve a prescribing error (1). Another study conducted in outpatient pharmacies found that approximately 4 per 100 dispensed prescriptions had problems and required pharmacists intervention (5). In 44% of the intervention, the outcome was a change in drug, strength or directions of drug use (5).

Most prescription interventions by pharmacists have a limited potential for medical harm although it may be inappropriate in some instances as mentioned by Hawkey and colleagues (7). However, it should be noted that a small number of detected prescribing errors have a major potential for medical harm if not corrected and hence, the importance of pharmacist interventions is not overemphasized. The ultimate goal for combining the unique knowledge and competencies of both medical and pharmaceutical professionals is to achieve optimal therapeutic outcomes and quality of life for the patient. Therefore, both professions have a definite role to play and should work hand-in-hand towards achieving this common goal.

Although most pharmacists in Malaysia are involved in prescription screening and interventions to varying degree, documentation of such activities appeared scarce in the literature. Therefore, the present study was conducted to identify and document the types of pharmacist intervention and its outcome on problematic prescriptions.

METHOD

This study was conducted over a one-week period in May 1998 in the Outpatient Pharmacy Department (OPPD) of a large teaching hospital in Malaysia. This OPPD received an average of 1057 prescriptions per day during the study period and was run by one registered pharmacist, 3 trainee pharmacists and 8 pharmacy assistants.

The study sampled problematic prescriptions received by the OPPD within the one-week period (excluding the Sunday). Senior pharmacy assistants act as the front line for the screening of prescriptions received by this OPPD. Any problematic prescriptions would be referred to the trainee pharmacist or the pharmacist. The researcher would then record the type of intervention made by the pharmacy staff and its outcome prospectively. A standard format recommended by Rupp (3) was used to record all the data. Reasons for pharmacist intervention were classified according to the types of prescribing errors used by Rupp (3), that is errors of omission and errors of commission.

RESULTS

Of the 6340 prescriptions received by the OPPD during the one-week sampling period (excluding the Sunday), 43 required intervention by the pharmacy staff. This gives an overall intervention rate of 0.68% and an average of 7.2 prescriptions intervened per day.

A total of 50 different errors were identified in the 43 prescriptions with an average of 1.2 errors per prescription. Most of the prescriptions had one error (37 prescriptions) while another 5 had 2 errors and 1 prescription had 3 errors. These errors are classified as in Table 1 with examples for each type of errors. Violation of legal or procedural requirements such as absence of the prescriber's name or signature, registration number for psychotropic agents and patient particulars are also included. The prescription intervened in the category of drug therapy monitoring was due to a possibility of hypokalaemia from the use of Lasix^{R} without the concurrent use of Slow K^{R}.

A total of 62 types of action were taken by the pharmacy staff to resolve the 43 problematic prescriptions, giving an average of 1.4 actions per problematic prescription. These include contacting the prescribers concerned (24.2%), clarifying with the patient or his/her representative (19.4%), contacting the prescriber's nurse (17.7%) and checking the patient's appointment or identity card (4.8%).

Of the 43 problematic prescriptions, 48.8% were

Table 1: Classification of reasons for pharmacist intervention.

Reasons for pharmacist intervention	**Frequency (%, n=50)**	**Examples**
Errors of omission		
Quantity to supply not specified	9 (18)	T. Pantoprazole 40mg bd T. Daonil 5mg bd T. Imipramine 25mg on Morphine Mixture 10mg tds
Dose / regimen not specified	5 (10)	Glibenclamide od x 12/52 'O' Cephalexin 250mg x 1/12
Form / strength not specified	4 (8)	Dipyridamole 1 tab od x 16/52 Humulin 10 IU tds x 1/52 Zocor 1 daily x 3 mths
No signature or name of prescriber	2 (4)	
No registration number	1 (2)	
No patient's name	1 (2)	
Illegible	5 (10)	Patient's name Captopril 0.25 daily x 2/52 Sy. Prednisolone 25mg tds HCT (hydrocortisone or hydrochlorothiazide)
Subtotal	***27 (54)***	
Errors of commission		
Wrong dose / regimen	12 (24)	Famotidine 200mg Diamicron 1 gm tds Metformin 80mg bd Thyroxine 200mcg bd Lisinopril 10mg tds Nuelin 5mg on Bactrim 250mg bd x 1/52. Prednisolone 60mg/m^2 130mg x 28 days
Required strength not available	5 (10)	Prothiaden 100mg nocte x 16/52 (only 75mg available)
Wrong drug / indication	1 (2)	Magnesium sulphate (should be magnesium trisilicate)
Wrong dosage form	2 (4)	Humulin R 8IU tds x 8/52 (should be penfill)
Dose did not correlate with quantity	1 (2)	Methotrexate 25mg (1 tab) should be 10 tablets
Required brand not available	1 (2)	Sy. Vermox 5ml stat
Possible side effects / toxicity	1 (2)	Lasix given without Slow K^R
Subtotal	***23 (46)***	
Total	**50 (100)**	

clarified without any change and dispensed while 32.6% were changed and dispensed. Three prescriptions were dispensed as written and this included the prescription where addition of Slow K^{R} was suggested for the patient on Lasix^{R}. The other two prescriptions involved methotrexate 5 mg daily and a prescription with three different types of syrups for a baby. Two patients were sent back to the clinics concerned with their problematic prescriptions but did not return while the prescribers for another two prescriptions could not be contacted. One prescription was not dispensed as the strength requested by the prescriber was not available in the hospital and the patient was asked to buy it from another pharmacy.

DISCUSSION

The rate of omission errors (54%) and commission errors (46%) obtained in this study are comparable to that reported by Rupp and colleagues (1), with 51% and 29%, respectively. It should be emphasized that one of the main errors in the present study involved wrong dose or regimen prescribed (24%). The study by Rupp and colleagues (1) showed similar results. This error of commission could lead to fatal consequences if left unidentified and uncorrected. For example, famotidine was prescribed as 200 mg instead of 20 mg. This represents a 10 times overdose if the error has not been detected. Decimal points in drug dosage should also be clearly written especially for drug with a wide dose range such as prednisolone that may be prescribed as 2.5mg or 25mg, depending on the condition of the patient. Additionally, drugs with similar names often cause confusion as in the case of magnesium sulphate being prescribed instead of magnesium trisilicate. Aronson (12) had suggested some measures to minimize such confusion.

From the results of the study, the proportion of prescription interventions appeared small (0.68%) compared to other studies where intervention rate of 2.6 and 2.9% had been recorded (1, 7). Some problematic prescriptions especially those with errors of omission may have been dispensed with some assumptions and hence no pharmacist intervention was documented. The possibility of some prescriptions with errors being dispensed to the patients without being detected could not be ruled out. The utilisation of information technology via computerization of prescription screening and electronic prescribing may minimise such occurrence. However, the standardization of processes and the expanded use of the expertise of pharmacists through better integration of the health care team are just as important.

The pharmacist or trainee pharmacist had to contact the prescriber or the prescriber's nurse 26 times to resolve 23 problematic prescriptions (53% of the 43 problematic prescriptions). This emphasizes the importance of interdisciplinary communication and cooperation in identifying and resolving prescribing errors and irregularities. The community pharmacists in the study by Rupp and colleagues (1) had to contact the prescriber or prescriber's assistants to resolve 80% of the problematic prescriptions. This higher rate could be explained by the difference in the sampling frame between the two studies. The present study involved prescription screening by the pharmacy staff who were more familiar with the prescribing habits of the prescribers in the same hospital. Therefore, the pharmacy staff could resolve a higher proportion of the problems encountered without contacting the prescribers than the community pharmacists in the study by Rupp and colleagues (1) who received prescriptions from many different clinics and hospitals.

The results also showed that the prescribers subsequently changed 32.6% of the problematic prescriptions identified by the pharmacy staff. Another 48.8% of the prescriptions were clarified without any change and dispensed. This is comparable to the study by Rupp and colleagues (1) that showed similar outcome description of 32% and 53.8%, respectively. These results further support the importance of pharmacist intervention in minimising preventable adverse events attributed to medication errors.

Although the present study was conducted in only one hospital, research of such nature could provide an invaluable database for future reference and for identifying specific individual and institutional deficiencies in prescribing. Consequently, appropriate design and implementation of strategic educational programmes or institutional procedures could be developed to eliminate the occurrence of such preventable medication errors and to limit the risk to patients.

CONCLUSION

The study reinforces the importance of prescription screening and interventions by pharmacists in minimising preventable adverse events attributed to medication errors. It also emphasizes the necessity of interdisciplinary communication and cooperation in identifying and resolving prescribing errors and irregularities in order to achieve optimal therapeutic outcomes for the patient.

ACKNOWLEDGEMENT

The authors wish to thank the staff of the Outpatient Polyclinic Pharmacy Unit, Universiti Malaya Medical Centre for their assistance and cooperation.

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