PHARMACOVIGILANCE STUDIES INVOLVING HEALTHCARE PROFESSIONALS AND STUDENTS IN NEPAL: IMPACT ASSESSMENT ON KNOWLEDGE, AWARENESS, ADVERSE DRUG REACTIONS REPORTING AND DRUG SAFETY COMMUNICATIONS

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BY

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DEDICATION

I dedicate this piece of work to my friend Mr. Harish Kamalapuram who passed away during his Final year M.Pharm study in 2004. Mr. Harish was my friend during my B. Pharm and M.Pharm programs. May his soul rest in eternal peace.

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ABBREVIATIONS

ADR	Adverse Drug Reaction
ADE	Adverse Drug Event
ADRAC	Adverse Drug Reactions Advisory Committee of Australia
BNF	British National Formulary
CDC	Centers of Disease Control
CPE	Continuing Pharmacy Education
CSM	Committee on Safety of Medicine
COX-2	Cyclooxygenase-2
CTVET	Council of Technical Education and Vocational Training
DBN	Drug Bulletin of Nepal
DDA	Department of Drug Administration
DHHS	Department of Health and Human Services
DIC	Drug Information Center
DOTS	Directly Observed Therapy, Short course
DRCs	Drug Related Complications
DTC	Drug and Therapeutics Committee
ED	Emergency Department
EMEA	European Agency for the Evaluation of Medicinal Products
eTG	Electronic Therapeutic Guidelines
EU	European Union
FDE	Fixed Drug Eruption
ICH	International Conference on Harmonization
GI	Gastrointestinal
ISDB	International Society of Drug Bulletins
ISoP	International Society of Pharmacovigilance
ISPE	International Society of Pharmacoepidemiology
KAP	Knowledge, Attitude and Practice
MCA	Medicine Control Agency
MCOMS	Manipal College of Medical Sciences

MER	Medication Error Reporting
MICU	Medical Intensive Care Unit
MSON	Manipal School of Nursing
MTH	Manipal Teaching Hospital
NCDA	Nepal Chemists and Druggists Association
NHS	National Health Service
NMCH	Nepal Medical College Hospital
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OPD	Out Patient Department
ORS	Oral Rehydration Salt
OTC	Over The Counter
SMON	Subacute Myelo-optic Neuropathy
TEN	Toxic Epidermal Necrolysis
TUTH	Tribhuvan University Teaching Hospital
UK	United Kingdom
UMC	Uppsala Monitoring Center
US	United States
US FDA	United States Food and Drug Administration
VAERS	Vaccines Adverse Event Reporting System
WHO	World Health Organization

KAJIAN FARMAKOVIGILANS MELIBATKAN PROFESIONAL DAN PELAJAR PENJAGAAN KESIHATAN DI NEPAL: PENILAIAN KESAN KE ATAS PENGETAHUAN, KESEDARAN, PELAPORAN KESAN MUDARAT UBAT DAN KOMUNIKASI KESELAMATAN UBAT

ABSTRAK

Konsep farmakovigilans di Nepal adalah baru. Kajian ini menilai corak kesan mudarat ubat yang dilaporkan ke pusat farmakovigilans di kawasan barat Nepal, dan menilai pengetahuan, tingkah laku dan praktis profesional penjagaan kesihatan di *Manipal Teaching Hospital* (MTH) terhadap keselamatan ubat. Kajian ini juga fokus kepada menilai modul pendidikan farmakovigilans untuk ahli farmasi komuniti, dan pelajar perubatan, farmasi dan kejururawatan dan menilai komunikasi keselamatan ubat yang dihasilkan oleh pusat farmakovigilans. Laporan kesan mudarat ubat yang diterima oleh pusat tersebut dalam tempoh 14 September, 2004 sehingga 13 September, 2008 telah dinilai. Pengetahuan, tingkah laku dan praktis profesional kesihatan dari MTH dan ahli farmasi komuniti dari kawasan Nepal barat telah dinilai menggunakan dua soal selidik yang telah diuji serta berbeza dengan nilai *Cronbach alpha* 0.72 dan 0.61, setiap satu. Tiga puluh ahli farmasi komuniti dengan skor pengetahuan, tingkah laku dan praktis yang tinggi telah dilatih dalam aspek farmakovigilans dan telah mencatatkan penambahbaikan skor. Maklum balas mereka berkaitan dengan latihan telah diperolehi menggunakan soal selidik dengan skala jenis Likert. Modul-modul pendidikan telah dibangunkan untuk pelajar farmasi, perubatan dan kejururawatan dan dinilai dengan membandingkan skor pengetahuan, tingkah laku dan praktis pelajar sebelum dan selepas intervensi dan maklum balas terhadap sesi tersebut. Komunikasi keselamatan ubat yang dihasilkan dalam tempoh

14 September, 2004 sehingga 13 September, 2008 telah dinilai. Daripada sejumlah 266 kesan mudarat ubat yang telah diterima, 153 (57.7%) adalah daripada individu perempuan. Peratusan kesan mudarat ubat yang tinggi (22.2%) adalah disebabkan oleh antibiotik. Nilai awal skor pengetahuan, tingkah laku dan praktis adalah 38.82 $\pm$ 3.75 untuk jururawat (n=46), 40.06 ± 3.51 untuk doktor (n=29) dan 38.92 ± 4.83 untuk ahli farmasi (n=14); skor maksimum adalah 50. Di antara 108 ahli farmasi komuniti yang terlibat, 78.7% (n=85) adalah lelaki. Nilai min $\pm$ sd skor keseluruhan bagi pengetahuan, tingkah laku dan praktis adalah 31.48 ± 2.25 (skor maksimum adalah 40). Daripada 71 kesan mudarat ubat yang dilaporkan oleh mereka, 42.0% (n=37) adalah berkaitan antibiotik/antibakterial. Nilai median (julat interkuartail) bagi skor maklum balas adalah 79.0 (73.5–81.0); skor maksimum adalah 100. Kesemua 124 pelajar farmasi, 116 pelajar jururawat dan 229 pelajar perubatan telah terlibat dalam kajian ini. Nilai median awal (julat interkuartail) skor total adalah 39.0 (37.0-41.0) untuk farmasi (skor maksimum adalah 50); 32.5 (31.0-34.0) untuk jururawat (skor maksimum adalah 40) dan 31.0 (29.0-33.0) untuk pelajar perubatan (skor maksimum adalah 38). Selepas intervensi, skor mereka menjadi lebih baik. Nilai median (julat interkuartail) skor maklum balas adalah 86.0 (81.5-90.0), 85.0 (80.8-88.3) dan 83.0 (78.0- 87.0) untuk pelajar farmasi, jururawat dan perubatan, setiap satu; skor maksimum adalah 100. Di antara 18 laporan kes yang telah diterbitkan, oleh pusat farmakovigilans kawasan Nepal barat kebanyakannya mengikuti garis panduan *International Society of Pharmacovigilance/International Society of Pharmaepidemiology*. Kesimpulannya, aktiviti farmakovigilans di kawasan Nepal barat adalah berjaya dan keperluan aktiviti perlu diperteguhkan dan kesinambungan terjamin.

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ABSTRACT

The concept of pharmacovigilance is new in Nepal. The present study analyzed the pattern and cost of pharmacotherapy of Adverse Drug Reactions (ADRs) reported to the western regional pharmacovigilance center at Nepal, and evaluated the Knowledge, Attitude and Practices (KAPs) of healthcare professionals in *Manipal Teaching Hospital* (MTH) towards drug safety. It also aimed at evaluating pharmacovigilance education modules for community pharmacy practitioners, medical, pharmacy and nursing students and analyzed the drug safety communications produced by the western regional pharmacovigilance center. ADR reports received and the drug safety communications produced by the center from 14th September 2004 till 13th September 2008 were analyzed. KAP of the healthcare professionals from MTH and community pharmacy practitioners from Pokhara valley, western Nepal were evaluated using two different pretested questionnaires with *Cronbach alpha* of 0.72 and 0.61, respectively. Thirty community pharmacy practitioners with high KAP scores were trained in pharmacovigilance and the KAP improvements were noted. Their feedback on the training was obtained using a Likert-type scale questionnaire. Educational modules were developed for pharmacy, medical and nursing students and evaluated by comparing the students' knowledge and perception scores prior and following interventions and their feedback on the sessions. Of the total 266 ADRs received, 153 (57.7%) were reported from females. Antibiotics caused the highest percentage (22.2%) of ADRs. The baseline

KAP scores were 35.8±3.7 for nurses (n=46), 40.0±3.5 for doctors (n=29) and 38.9±4.8 for pharmacists (n=14); the maximum possible score was 50. Among the 108 community pharmacy practitioners enrolled, 78.7% (n=85) were males. The mean±sd baseline KAP scores was 31.4±2.2 (maximum possible score was 40). Of the 71 ADRs reported by them, antibiotics/antibacterials accounted for 42.0% (n=37) of the ADRs. The median (interquartile range) feedback score was 79.0 (73.5-81.0); maximum possible score was 100. Altogether, 124 pharmacy, 116 nursing and 229 medical students were enrolled. The baseline median (interquartile range) of the total score was 39.0 (37.0-41.0) for pharmacy (maximum possible score was 50); 32.5 (31.0-34.0) for nursing (maximum possible score was 40) and 31.0 (29.0-33.0) for medical students (maximum possible score was 38). Upon educational intervention, their scores improved. The median (interquartile range) feedback scores were 86 (81.5-90.0), 85.0 (80.7-88.2) and 83 (78.0-87.0) for pharmacy, nursing and medical students, respectively; the minimum possible score was 50 and the maximum possible score was 100. Among the 18 case reports published by the pharmacovigilance center, a majority followed the *International Society of Pharmacovigilance/International Society of Pharmaepidemiology* guidelines. In conclusion, the pharmacovigilance activity in western Nepal is successful and needs to be strengthened and sustained.

CHAPTER ONE

GENERAL INTRODUCTION

1.1 Background

Although medicines are very vital in ameliorating disease conditions, often they are associated with certain risks. Adverse Drug Reactions (ADRs) are one of the major risk factors associated with the use of medicines, ranging from a mild skin rash to death. The World Health Organization (WHO) defines an ADR as 'a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease or for the modification of physiological function' (Lee and Thomas, 2003). One of the simplest means of classifying ADRs is proposed by Rawlins and Thompson (Rawlins and Thompson, 1977). According to this classification, ADRs are classified into 'type-A' and 'type-B' reactions. Type-A reactions include normal and augmented response to drugs and are dose dependent. These reactions are usually predictable and are due to the known pharmacology of drug and thus considered to be preventable. The incidence of type-A reactions is high and they are responsible for considerable morbidity. Reducing the dosage or changing the therapy can overcome this type of reactions. Simple examples for type-A reactions are bradycardia with beta adrenoreceptor blockers and bleeding with anticoagulants. Type-B reactions are unrelated to the known pharmacological action of the drug and are often caused by immunological and pharmacogenetic mechanisms. These reactions are generally unrelated to dosage and, although comparatively rare, they often cause serious illness and death. They are often not predictable and un-preventable. Examples include

malignant hyperthermia caused by anesthetics, acute porphyria and many immunological reactions (Rawlins and Thompson, 1977). Certain ADRs do not fit into either category and hence it is difficult to decide whether certain reactions are type-A or type-B. According to this classification, everything that is not a type-A reaction got classified as type-B, rendering the latter a highly heterogeneous group.

An Adverse Drug Event (ADE) is 'any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment' (Anon, 2008). An ADE, is characterized by the suspicion of a causal relationship between the drug and the occurrence, i.e. judged as being at least possibly related to treatment by the reporting or a reviewing healthcare professional (Anon, 2008). ADRs are a cause of significant morbidity and mortality, affecting a huge population worldwide. ADRs are responsible for hospital admissions, with reported rates ranging from 0.3% to as high as 11%. Overall**,** the incidence of ADR induced hospital admissions accounts for 3% of all medical admissions (Lee and Thomas, 2003). In the United States (US) alone, over 77 000 people are injured or killed each year from ADEs (Classen *et al*., 1997).

In addition to their health hazards, ADRs also increase the hospital stay and cause huge economic loss. A study from the US demonstrated that an ADE extended the hospital stay by nearly two days and increased the cost of hospitalization by about US$ 2 000 (Classen *et al*., 1997). Another study from Colombia reported the costs resulting from medical care of ADRs to be US$ 35 014.92 to US$ 45 680.94 (Tribiño *et al*., 2006). It has been found that the total cost of medicine related morbidity and mortality exceeds the cost of medications themselves (Smith, 1993). The cost associated

with medicine related morbidity and mortality is exceedingly high in the US, and is estimated to range between US$ 30.1 billion and US$ 136.8 billion annually if direct and indirect costs are included (Johnson and Bootman, 1996). The limited resources of healthcare delivery systems in developing countries are stretched even further by ADR-related admissions. The economic impact of ADRs is less documented from developing countries. However, a recent study from South India identified the total cost incurred in managing ADRs to be Indian rupees 76 564 (US$ 1 595) with an average cost of Indian Rupees 690 (US$ 15) per ADR (Ramesh *et al*., 2003). Although ADRs presents as a major problem in the healthcare system, a high percentage of them are preventable if adequate measures are taken (Kanjanarat *et al*., 2003). One of the strategies to minimize the occurrence and severity of ADRs is through effective monitoring of ADRs in a systematic manner, involving all the key players in medicine use.

During the 1960s, in the aftermath of the thalidomide disaster, national pharmacovigilance centers were established in several countries around the world (Meyboom *et al*., 1999). This was later strengthened worldwide by the events of Subacute Myelo-Optic Neuropathy (SMON) syndrome due to clioquinol (1969), venous thromboembolism due to oral contraceptives, oculo-muco-cutaneous syndrome due to practolol (1975), blood dyscrasias and Gastrointestinal (GI) bleeding due to Non-Steroidal Anti- Inflammatory Drugs (NSAIDs) (Edwards and Olsson, 2002).

In recent days, the importance of medicine safety monitoring has been felt in many countries worldwide. The drug regulatory authorities have taken the initiatives and are involved in safety monitoring of medicines. The WHO program was established in 1968 as a pilot project with the participation of ten countries initially and later

strengthened by many. In the United Kingdom (UK), the United Kingdom's Medicine Control Agency (MCA) and the Committee on Safety of Medicine (CSM) were set up in 1964. Similarly, in the US, the Vaccines Adverse Event Reporting System (VAERS) was set up in 1990 and co-administered by the Department of Health and Human Services (DHHS). Countries like Australia and Canada also established Adverse Drug Reactions Advisory Committees (ADRAC) and Canadian Adverse Drug Reaction Monitoring programs, respectively (Anon, 2002). The list of member countries increased steadily and as of March 2009, there were 94 member countries in the WHO international drug monitoring program (The Global Network for Benefits and Risks in Medicinal Products, 2009).

Nepal is a landlocked country situated between India and China. It encompasses a total area of 147 181 square kilometers and an estimated population of 21.1 million. Geographically, Nepal is divided into five regions- eastern, central, western, mid-western and far-western regions. The capital city, Kathmandu is located in Central Nepal. The geography of Nepal varies from the alpine grass lands to mountains. The health status of Nepalese people is generally poor. This is reflected in low life expectancy at birth of 61 years (2004), high maternal mortality of 281 per 100 000 live births (2006), and high infant mortality of 48 per 1000 live births (2005) (Nepal Health System Profile, 2007). The government run hospitals usually lack sophisticated equipment, qualified manpower and medicines due to which private hospitals are preferred. The annual medicine consumption in Nepal is estimated to be over 3 719.3 million Nepalese rupees (approximately US$ 46 million), with an estimated 28.5% rate of increase in consumption every year (Anon, 2006a). Domestic pharmaceutical

companies produce only 35.4% of all medicines consumed in the country, the rest, 64.6% being imported mainly from India (Anon, 2006a). However, in the recent past, the situation is changing. Local pharmaceutical companies are attracting a huge amount of prescribers in the country and their manufacturing capacity is increasing steadily.

The use of allopathic and ayurvedic medicines in Nepal, their manufacturing, importing, exporting, procurement, and sales are regulated at the Nepal Department of Drug Administration (DDA) which is the national drug controlling authority. The manufacturing companies require permission from the DDA in order to manufacture medicines in Nepal. For marketing medicinal products in Nepal by foreign companies, all the products should be registered with the DDA. The DDA registers medicinal products based on their safety, efficacy, quality and affordability.

1.2 Problem statement

Safety and efficacy studies conducted prior to the introduction of a new medicine (clinical trials) into the market are designed to identify any ADRs that may occur with the medicines. However, only a relatively limited number of patients are evaluated in these studies. Moreover, the exclusion criteria of many of these studies eliminated patients with multiple disease states and other contributing factors to ADRs. In addition, special patient populations such as pediatric, geriatric and pregnant ladies are not studied well in the clinical trials. Besides, most of these studies are of short term and are thus, unable to recognize any ADR associated with long term use (Alastair, 2001). Therefore, it is essential to monitor the ADRs of medicines even after once they are launched in the market.

In the past, pharmacovigilance was considered as a mere adverse drug monitoring or drug surveillance activity. But, nowadays it is considered as the quality control system of the society (Olsson, 2001). Its broader aim is to check if medicines fulfill their intended role in alleviating human suffering, and reducing disease related economic loss, with the best acceptable patient safety. The ultimate aim of pharmacovigilance is to attain safe and rational use of medicines once they are released for general use in the society. The most important outcome of pharmacovigilance is the prevention of negative consequences of pharmacotherapy (Olsson, 2001). Pharmacovigilance is defined as the 'science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine related problems' (Olsson, 2001). Even though pharmacovigilance is considered useful, many developing countries have not been successful in establishing a stringent pharmacovigilance system in their countries (Couper, 2006).

Several guidelines have been developed regarding the use of medicines in the past, by the medicine regulatory authorities, professional bodies and voluntary organizations including the Joint Commission on the Accreditation of the Healthcare Organization (JCAHO), American Society of Health System Pharmacists (Rollins, 2000), ERICE declaration (Edwards, 2000), and Berlin declaration by International Society of Drug Bulletins (ISDB) (ISDB EU, 2005). In spite of several strategies being implemented worldwide, the under-reporting of ADRs is a major problem (Alvarez-Requejo *et al*., 1998). According to Rogers *et al*, many times healthcare workers either do not understand the importance of ADR reporting or do not find the current system convenient to report ADRs (Rogers *et al*., 1988).

Spontaneous reporting schemes for suspected ADRs have been a major source of information in pharmacovigilance (Meyboom *et al*., 2002). Spontaneous reporting can prevent the development of new medicine tragedies and can improve the safety labeling of many effective pharmaceutical products (Anon, 2002; Hartigan-Go, 2001). Hence, healthcare professionals should report ADRs as a part of their professional responsibility. They should be knowledgeable about the ADR reporting systems in their region and country and should be aware of the importance of reporting ADRs. Developed countries have incorporated pharmacovigilance teaching into medical and pharmacy curricula (Zenut *et al*., 1998; Cox *et al*., 2004). However, in developing countries pharmacovigilance has not found a place in most medical, nursing and pharmacy schools. ADRs are only included as a topic in didactic lectures and the practical aspects is lacking (Shankar *et al*, 2006a).

At present, there are four regional pharmacovigilance centers in Nepal. These centers are located at Manipal Teaching Hospital (MTH) in Pokhara, Tribhuvan University Teaching Hospital (TUTH) in Kathmandu, Nepal Medical College Hospital (NMCH) in Kathmandu and KIST Medical College in Lalitpur. These regional centers report ADRs to the national centre through a web based system for ADR management called 'VigiFlow'. The initial two centers were started in 2004 and 2006, respectively and the third and the fourth ones were established in 2008. These centers are all hospital based and are involved in collecting the ADRs occurring in the hospitals in which they are affiliated. Thus, there was no established system to collect the ADRs occurring in the community settings.

The success of a pharmacovigilance program depends largely upon the communication of the medicine safety related information generated through the program. But, in developing countries, there are only limited pharmacovigilance programs in place and often the little information available on medicine safety issues is not communicated adequately. Specifically, in Nepal, there is very little information available on medicine safety. The DDA publishes a quarterly bulletin, the Drug Bulletin of Nepal (DBN) that focuses on medicine safety issues. But, the information presented are from developed countries and hence, difficult to generalize for the local population.

1.3 Rationale of the study

In Nepal, nearly 65% of the medicines are imported from foreign countries and only 35% are manufactured in Nepal (Anon, 2006a). Prior to marketing a medicine in Nepal, the DDA evaluates it thoroughly based on the available literatures and then approves it. The DDA was established in 1979 after promulgation of the 'Drug Act 1978'. The main objective of the act is to assure safety, efficacy and quality of medicines available in the Nepalese market. As per the Drug Act 1978, 'every drug shall have to be safe for the use of the people, efficacious and of standard quality' (Anon, 1978). In the above view, the DDA in the past has banned several medicines to ensure medicine safety in Nepal. Some of the examples include amidopyrin, phenacetin, clioquinol, analgin (metamizole) along with several other harmful irrational combinations. Also, registration of products like gatifloxacin and Cyclooxygenase-2 (COX-2) inhibitors were denied due to safety concerns (Thapa, 2006). These decisions were taken by the DDA based on the information available in the literature since no

system existed to monitor ADRs within the country. Although, these regulatory mechanisms were in place, they were restricted only to limited medicines and the decision on ban/denial of registration of these medicines were made based on the existing literature available from developed countries.

Out of 75 districts in Nepal, about two-thirds are located in hilly regions and mountains and the remaining in plains (called as 'terai'). The climatic conditions in the country vary from season to season and from place to place. This variation in climate is known to be a predisposing factor for the occurrence of ADRs (Subish *et al*., 2005). Moreover, there are several races of people having different cultural and social beliefs. The use of alternative medicines (for example ayurveda and siddha) is common in Nepal, which may interact with allopathic medicines and predispose to ADRs. The manufacturing facilities in Nepal are limited and thus, majority of the medicines used in Nepal are manufactured in foreign countries (especially India). The nature and safety of the excipients used in these formulations are unknown. Moreover, the number of medicinal preparations available in the Nepalese market is high (7299 in the year 2004/05 and 7237 in 2005/06) and thus, people are exposed to more items and varieties of medicines (Subish *et al*., 2007). The genetic makeup of the Nepalese population may vary and hence predispose to ADRs. There are no mandatory requirements for clinical trials on the Nepalese population prior to approval of a medicine in Nepal. Hence, the risk of occurrence of ADRs can be very high and is infact unknown.

The infrastructure in Nepal is limited and the country has a poor development. The doctor to population ratio is very poor (1:23 000) and the utilization of government health services averages only 0.2 visits per person per year. Retail pharmacies are more

in number than the health posts/ health centers in the country by a ratio of 4:1 and drug retailers are often the only sources to modern medicines for the rural population. In some cases, they are the only source of healthcare outside the home thus making a lot of people to rely upon them for the healthcare needs (Kafle *et al*., 1992). This makes the people dependent on self-medication (Kafle *et al*., 1996) with the medicines obtained from drug retailers. Self-medication may contribute to ADRs either by the medicine itself or by causing an interaction with a prescription medicine. Moreover, the literacy ratio in Nepal is also poor (total adult literacy rate, 2000-2005 is only 49 %) (Anon, 2006b). All these problems collectively increase the risk for ADRs in the community settings of Nepal.

In developing countries, quality of medicines is a major concern (Jayasuriya, 1991). By encouraging ADR reporting, the quality of medicines can be predicted. For example, substandard or counterfeit medicines may cause ADRs suggesting their poor quality. A pharmacovigilance program can also identify the safety of medicines used in public health programs such as the vaccines, antitubercular drugs and antiretroviral drugs. Moreover, if an indigenous pharmacovigilance program is developed in Nepal, it will be helpful in developing the ADR profile of medicines (ADR database) in the local population.

Though, the role of healthcare professionals is important, there is only a limited focus on teaching pharmacovigilance to the healthcare students in Nepal. Many of the institutions in Nepal also lack competency in terms of staffing, infrastructure, and facilities to teach modern pharmacotherapy. In contrast to the existing education system in Nepal, the Manipal College of Medical Sciences (MCOMS) has taken several

initiatives to teach rational pharmacotherapy to their medical students. Pharmacology is taught using a combination of didactic lectures and problem-stimulated learning sessions. This department also runs a Drug Information Center (DIC) and a pharmacovigilance center in the Manipal Teaching Hospital (MTH), the teaching hospital attached to the college (Shankar, 2006c).

Since, there is no mandatory clinical trial that needs to be done in the local population prior to approval of a new medicine in the country, institutional based pharmacovigilance programs are the key for ensuring medicine safety. One of the objectives of the regional pharmacovigilance center at the western Nepal is to communicate medicine safety issues. The regional pharmacovigilance center has taken several initiatives to communicate the medicine safety related issues with the objective of ensuring medicine safety in the country. All the ADR reports from the center are reported to the WHO global ADR database through the 'VigiFlow' online program. Periodic evaluation of the communication produced on medicine safety can be beneficial in better dissemination of the existing medicine safety information.

1.4 Research questions

The overall study had the following research questions:

1. Are the adverse drug reaction patterns in western Nepal similar to the patterns documented in the literature?

2. What is the knowledge, attitude and practice level of the healthcare professionals in western Nepal towards adverse drug reactions and pharmacovigilance?

3. Can educational intervention improve adverse drug reaction reporting by the community pharmacy practititoners in western Nepal?

4. Can educational intervention improve the knowledge, attitude and practice of the medical, nursing and pharmacy students in western Nepal?

5. Do the scientific communications on medicine safety produced by the regional pharmacovigilance center in western Nepal comply with international standards?

1.5 Study objectives

The whole study was conducted based on the following objectives:

1. To analyze the pattern and cost of pharmacotherapy of the adverse drug reactions reported to the regional pharmacovigilance center in western Nepal,

2. To study the knowledge, attitude and practices of the healthcare professionals in Western Nepal towards adverse drug reactions and pharmacovigilance,

3. To develop and evaluate a community based pharmacovigilance educational program in western Nepal,

4. To develop and evaluate the impact of education modules on knowledge and perception among the medical, pharmacy and nursing students in western Nepal, and

5. To evaluate the pattern of scientific communications on medicine safety produced by the regional pharmacovigilance center in western Nepal.

1. 6 Significance of the study

In Nepal, as such there was no standard system which existed to ensure medicine safety until 2004. Considering its importance, the DIC at MTH, a tertiary care teaching hospital in Western region of Nepal has decided to start a spontaneous ADR reporting program. The program has been established in September 2004 with a pharmacovigilance center, as a unit of the DIC of the hospital that has been functioning since November 2003. The Uppsala Monitoring Center (UMC), the WHO collaborating center for international drug monitoring provided the technical support by providing literature and booklets necessary to begin the program. The DDA has established regional centers which report the ADRs to the national center through the 'VigiFlow' online program which are then submitted to the WHO global ADR database. The DDA acts as the national center for pharmacovigilance activities. As of March 2009, more than 300 ADR reports were sent to the national pharmacovigilance center from the various pharmacovigilance centers. In collaboration with UMC, Nepal has also been able to contribute to the global database by sharing information with UMC. This program though in its initial phase, has given a good platform to promote the culture of ADR reporting among the healthcare professionals and to be vigilant. DDA has been working towards addition of more teaching hospitals for ADR reporting so as to strengthen the pharmacovigilance program. The revised National Medicine Policy 2009 (Anon, 2009) of Nepal has also recognized the need for a pharmacovigilance program in Nepal and has aimed for implementation of the programme for effective post-marketing surveillance and ADR reporting to ensure safe use of medicines in the country.

Ensuring safe use of medicines is a collective responsibility of the healthcare team, including the doctors, nurses, pharmacists and other supporting staffs. One of the important means of ensuring medicine safety is reporting of ADRs by the healthcare professionals. Pharmacists being knowledgeable in medicine related aspects have got an important role in ensuring medicine safety. The involvement of pharmacists in pharmacovigilance programs is considered vital (van Grootheest *et al*., 2002; van Grootheest *et al*., 2004; van Grootheest *et al*., 2005). However, contrary to their vital role, studies from the developed countries have acknowledged either a poor knowledge (Toklu *et al*., 2008) or less experience among the pharmacists regarding ADR reporting (Granas *et al*., 2007). Researchers suggest the need for education of pharmacists on pharmacovigilance (Green *et al*., 2001). One of the better ways to do this is by educating when they are students. The education provided for the medical and pharmacy students even in developed countries like the United Kingdom (UK) was found to be inadequate. A study found that both medicine and pharmacy courses differed substantially in teaching about the Yellow Card Scheme and ADRs (Cox *et al*., 2004). Authors found a huge scope for increased involvement of the medicines and healthcare products regulatory agency in undergraduate education (Cox *et al*., 2004). The present study also noted a similar observation, suggesting huge scope for improvements. Nurses, who record signs and symptoms of the patients, play an increasingly important role for detection of suspected ADRs (Ulfvarson *et al*., 2007). A recent study from Sweden reported that ADR reporting by nurses could improve the overall safety of medicines (Bäckström *et al*., 2007). The pharmacovigilance center at western Nepal was successful in teaching pharmacovigilance to the medical, nursing

and pharmacy students in the region. The findings of the present study can be useful for researchers in different parts of Nepal and other developing countries in educating their students in the area of pharmacovigilance.

Qualified doctors in Nepal are less willing to set up practice in the villages and as a result, rural patients often rely upon traditional healthcare practitioners for their healthcare needs (Sharma *et al*., 2001). In addition, due to remoteness, poor socioeconomic status, high cost of modern medicines and non-availability of doctors in rural areas, it has been difficult to access modern healthcare in Nepal. This leaves people dependent on self-medication which is known to cause ADRs. Retail pharmacies are the primary point of contact with the healthcare system for the rural and remote population. Although, there are four regional pharmacovigilance centers in operation, the activities are much focused on the hospital settings. ADRs following self-medication and ADRs occurring outside the hospital remain unreported. Hence, the regional pharmacovigilance center of western Nepal has started a community-based pharmacovigilance program in the year 2008 in which the community pharmacy practitioners report the ADRs. During the initial six months of establishment of the program, the center received more than 70 ADR reports from the community pharmacy practitioners of western Nepal.

CHAPTER TWO

EVALUATION OF THE PATTERN AND COST OF PHARMACOTHERAPY OF ADVERSE DRUG REACTIONS

2.1 Introduction

This part of the chapter provides an overview on the background, problem statement, literature review, rationale and objectives of the study.

2.1.1 Background

With the increase in use of medicines, the incidence of Adverse Drug Reactions (ADRs) is increasing rapidly. ADRs are considered to be associated with significant morbidity, mortality and huge economic impact (Johnson and Bootman, 1996). Safety and efficacy studies conducted prior to the introduction of a new medicine into the market try to identify any ADRs that may occur with the medicines. However, only a relatively limited number of patients are evaluated in these studies (Striker and Psaty, 2004). Exclusion criteria of many of these studies eliminate patients with multiple disease states or other contributing factors to ADRs. Moreover, special patient population such as pediatrics and geriatrics are not studied well in the clinical trials. Also, most of the studies are of short term medicine use and thus eliminate the ability to recognize the ADRs associated with long term use (Alastair, 2001). Thus, many ADRs escapes from the early safety studies done by the manufacturer (phase I through III) and thus making it necessary to monitor the ADRs even after the medicines are being launched in the market (Stricker and Psaty, 2004).

2.1.2 Problem statement

In developed countries, the concept of ADR monitoring is well developed and plays an active role in ensuring safe use of medicines including withdrawal of potentially harmful medicines from the market. On the other hand, in developing countries like Nepal, the regulatory mechanisms monitoring medicine safety is very weak. In Nepal, irrational use of medicines is very much in evidence, some examples are polypharmacy, use of expired medicines, irrational combination drugs, overuse of antibiotics, vitamins and herbal remedies, brand prescribing, retail pharmacists prescribing and unethical medicine dispensing (Blum, 2002). Such irrational practices, combined with lack of patient information on proper handling and uses of medicines can lead to pharmaceutical wastage as well as other serious consequences like ADRs and drug interactions (Blum, 2002). Moreover, there is no mandatory rule for the pharmaceutical companies to produce medicine safety data prior to marketing medicines. Medicine safety is one of the most neglected areas in Nepal, although there are few reports available in the literature (Shakya *et al*., 2004; Shrestha *et al*., 2006).

2.1.3 Literature review

ADRs are unwanted or unintended effects of medicines which occur during their normal therapeutic use. Safe use of medicines is an important issue for prescribers, pharmacists, nurses, regulatory authorities, the pharmaceutical industry, patients and the public. Although, prescribers aim to use medicines that help patients and do no harm, no medicine is administered without risks. Minimizing the occurrence of ADRs is an important challenge in medicine use, and helps to improve patient care.

2.1.3.1 Literature from developed countries

A study from Italy analyzed the data from the national spontaneous reporting system and described the types and patterns of fatal ADRs reported to the national ADR monitoring system (Leone et al., 2008). The pharmacovigilance database maintained by the Italian Medicines Agency was reviewed for all the case reports from 1st January 2001 till 31st December 2006. Among the reports, the ones with a fatal outcome were analyzed. Authors found 1.66% of the total ADRs to have a fatal outcome. A highest percentage of the fatal ADRs were related to 'systemic anti-infective' drug class accounting for 21.9% of the total fatal ADRs. Ceftriaxone, ticlopidine and nimesulide were the individual drugs responsible for a highest incidence of fatal ADRs. The study also notified certain lacunae in the medicine prescribing by the physicians and recommended the need for continuing clinical pharmacology training.

Wester *et al*., (2007) described the pattern of spontaneously reported fatal ADRs documented at the national spontaneous reporting system in Sweden. All the suspected fatal ADRs reported to the Swedish Medicine Agency during the study period (1st January 1995 to 31st December 2004) were evaluated for the types of drugs administered, the types of ADRs, causality assessment, and the patient demographic parameters, sex and age. A total of 3.1% of the ADRs were found to be fatal. The most common fatal ADRs were caused by hemorrhage (60.9%) and warfarin was responsible for maximum number of hemorrhages. Sudden death was seen in 3.8% of the total cases and the drugs responsible for sudden death were clozapine, citalopram and propoxyphene. In this study, considering the amount of anticipated under-reporting, authors claimed ADRs to be one among the top 12 causes of death in Sweden.

Pirmohamed *et al*., (2004) evaluated the burden of ADRs in England through a 6-month prospective analysis of hospital admissions in United Kingdom (UK). The study was conducted in two hospitals in United Kingdom (UK), both together serving for a total population of 630 000. The patients aged less than 16 years and women with gynecological problems were excluded from the study in order to maintain uniformity between the study populations. Altogether, 18 820 hospitalized patients were assessed for the cause of hospitalization. Among these patients, 1225 (6.5%) were admitted due to ADRs. ADRs were more commonly seen in patients belonging to a higher age group. Authors found, 72% of the ADRs were 'avoidable' if proper precautions were taken. In this study, 16.6% of the ADRs were caused due to drug-drug interactions. The cost of ADRs in this study accounted for 466 million Euros (Approximately US$ 659.3 million) to the National Health Service (NHS) of the UK. The major strength of this study is that it is a prospective study thus allowing a detail workout of the cases implied with ADRs.

van der Hooft *et al*., (2006) conducted a nationwide survey on drug-related hospitalizations in Netherlands. Authors retrieved the hospital discharge records through a nationwide computer database. A total of 668 714 patients admitted in the hospitals throughout country in the year 2001 with an acute, non-planned hospital admissions were included. Of these total hospitalizations, 12 249 were related to ADRs accounting for an incidence of 1.83% of all acute, non-planned hospitalizations in the country. Moreover, 6 % (n=734) of the patients admitted with ADRs died during the hospitalization. The mean duration of stay in the hospital was 12.5 days for patients with an ADR in comparison with 10 days in other cases of acute hospitalizations. This

study also identified a significant level of under-reporting in Netherlands. As per the study findings, only 59 (approximately 1%) of the total 6 209 hospital admissions were actually reported to the national pharmacovigilance program spontaneously.

Alexopoulou *et al*., (2008) prospectively evaluated the pattern of ADR related hospital admissions in an internal medicine department in Greece. Authors evaluated all hospital admissions occurring at the internal medicine department for a 6-months period. During the study period, there were 548 admissions, among which 70 were related to ADRs (12.8%). These 70 patients experienced 74 ADRs. The most commonly seen ADR was hemorrhage (37.3%) followed by metabolic complications caused by oral hypoglycemic agents (10.8%). Of the total ADRs, 89.2% were of 'type-A reactions' and the remaining were 'type-B reactions' suggesting a high percentage to be pharmacologically related and hence avoidable. A high percentage (81.4%) of the ADRs evaluated in this study was of 'moderate' severity. In this study, authors noted polypharmacy to be a predisposing factor for ADRs.

Moore *et al*., (1998) prospectively assessed the pattern of ADRs leading to hospitalization or prolonging hospitalization in France. All the patients getting admitted to a 29-bedded internal medicine ward of a general hospital were prospectively followed for 6 months by a physician. The physician everyday followed the patients for the presence of serious ADRs. All the cases known to have a serious ADR were further reviewed by a specialist in drug induced illness. Over the period of 6 months, 31 patients, among 329 had ADRs. Among these 31 patients, ADRs were responsible for hospitalization in 10 patients and in the remaining 21 patients, the ADRs occurred during their hospital stay. Among the 31 patients, four of them died due to the ADRs.

All the 10 patients presenting with ADRs (100%) and 14 of 21 patients (66.0%) who developed ADRs in the hospital had 'type-A' ADRs suggesting them to be pharmacologically related to the suspected drug (s).

Another study from France evaluated the prevalence, incidence and preventability of ADRs occurring in hospital and ADRs that lead to hospitalization. Authors also evaluated the direct costs of these ADRs (Lagnaoui *et al*., 2000). Authors prospectively followed all the patients getting admitted to the internal medicine ward of a hospital for four months. A total of 444 patients were admitted during the study period. Among these patients, 116 (26.1%) experienced an ADR. In 32 patients (7%), ADR was the reason for hospitalization. It was seen that 64.7% (n=101; total 156 ADRs) of the ADRs were related to the pharmacological properties of the drugs (type-A reactions). Among the 32 ADRs that caused hospitalization, the most common ones were neurological disorders, hypoglycemia, autoimmune diseases and hematological disorders. In this study, the mean cost an ADR related to hospitalization was Euro 2721 (approximately US$ 3850). Authors found 80% of the ADRs occurred to be 'preventable'.

A study from Belgium by Somers *et al*., (2003) evaluated the ADRs occurring in a geriatric ward of a university hospital and compared the ADRs reported spontaneously by the physicians and nurses with the ADRs identified by the pharmacists through direct patient interview. During the study period (8 months), 168 patients were admitted to this 27 bedded geriatric ward. In this period, 12 ADR reports were received through the spontaneous reporting (physicians and nurses). Of these ADRs, four were related to cardiovascular drugs followed by centrally acting drugs in another four cases. Among

these ADRs, six were classified as ‘serious’. But, during the direct patient interview of 56 patients, by pharmacists, there were 32 ADRs from 23 patients. Of these 32 ADRs, 10 were caused by cardiovascular drugs, followed by drugs acting on respiratory system (n=7) and centrally acting drugs (n=5). Authors suggested a combination of both spontaneous reporting by physicians and nurses, and patient interview by pharmacists to be a useful method for successful ADR monitoring program.

The above literature revealed ADRs to be a common cause of hospitalization and death in the developed world. In these studies, the incidence of hospitalization due to ADRs varied from 6.5% in UK (Pirmohamed *et al*., 2004) and 7% in France (Lagnaoui *et al*., 2000). The drug class responsible for ADR also varied from antibacterials to cardiovascular drugs depending upon the study setting and the drug utilization pattern. The mortality rates due to ADRs ranged from 1.66% in Italy (Leone, 2008), to 3.8% in Sweden (Wester *et a*l., 2007), and 6% in Netherlands (Van der hooft *et al*., 2006), suggesting ADRs to be a major cause for mortality in these countries. The ADRs responsible for mortality also varied among studies and in one study, hemorrhage being responsible for 60.9% of the fatal ADRs (Wester *et al*., 2007).

In most of these studies, majority of the ADRs were related to the pharmacological properties of the suspected drug (type-A) and a high percentage of them were considered ‘preventable’, suggesting preventable ADRs to be common even in developed countries. In one of the studies, authors noted polypharmacy to be a predisposing factor for the occurrence of ADRs (Alexopoulou *et al.,* 2008). Among these studies, two of them reported the economic impact of the ADRs. One study reported, the total cost of the ADRs to be approximately US$ 659.3 million for the

national health service of the UK (Pirmohamed *et al*., 2004) and another calculated the mean cost an ADR related to hospitalization as approximately US$ 3850. These findings suggest a huge economic loss due to ADRs in developed world. It is evident that proper monitoring of ADRs targeted at early detection and prevention can help in minimizing significant morbidity, mortality and economic losses.

2.1.3.2 Literature from developing countries

Pourseyed *et al*., (2009) from Iran evaluated the nature and pattern of ADRs in an internal medicine department. Authors prospectively studied all the patients getting admitted to the 35-bedded internal medicine ward of a general hospital in the capital city, Tehran, for four and half months. Among the 400 admissions that occurred during the study period, 47 (11.75%) cases experienced at least one ADR. In seven (1.75%) of the cases, ADR were responsible for hospitalization and in the remaining 40 (10%) cases, ADRs occurred during the hospital stay. The mean ± sd age of the patients experiencing ADRs was 54.29± 2.08 years. The Gastrointestinal (GI) (44.3%) related ADRs were seen in higher number of cases followed by psychiatric disorders (11.4%) and skin disorders (11.4%). Nausea and vomiting were the most common manifestations of the ADRs accounting for 32.2% of the total manifestations. Half (50%) of the ADRs were categorized as 'preventable' type of reactions. The individual drug responsible for more number of ADRs was fluorouracil causing 15 ADRs, followed by cisplatin causing 14 ADRs. This study was conducted in internal medicine ward that also treated cancer patients and thus, the findings cannot be generalized to a mere internal medicine ward.

Another prospective, observational study from South Africa (Mehta et al., 2008) compared the pattern of ADRs, both occurring in and reported to two medical wards of a hospital. This hospital is a 300-bedded secondary care hospital that serves for a community with a higher incidence of Human Immunodeficiency Virus (HIV) infected patients. The clinical pharmacologists evaluated the patients for presence of ADRs. Totally, 665 patients were studied, among which 93 (14%) had an ADR. Of these 93 patients, 52 were admitted due to an ADR, 38 developed an ADR during the hospital stay and three patients had both ADR in the hospital plus had an ADR prior to hospital admission. In general, the patients who got admitted due to an ADR had a higher age pattern. Of the ADRs occurring prior to hospitalization, 84% were of type-A reactions. The drug category responsible for ADRs in these patients was cardiovascular drugs, followed by antiretroviral and oral hypoglycemic agents. Among the ADRs that occurred in the hospital, 74.5% were of 'type-A', and one third (33.3%) were considered 'preventable'. This study recommended for better drug selection procedures and patient monitoring in order to minimize the burden of preventable ADRs.

Jose and Rao, (2006) analyzed the pattern of ADRs reported to a pharmacovigilance center located in a tertiary care teaching hospital in South India. Authors also analyzed the outcomes of the ADRs, causality, severity, preventability assessments along with the predisposing factors for ADRs. During the one year study period (March 2004-February 2005), 408 ADRs were reported from 382 patients. The overall incidence of the ADRs was 0.15%. Authors noted at least one ADR per 1.14% of hospitalized patients and 0.012% of the outpatients. A high percentage of the reported ADRs were of type-A reactions (72.5%). Skin was the most commonly