REPORT

SYSTEMIC ADVERSE DRUG REACTIONS: A PRELIMINARY REPORT FROM THE REGIONAL PHARMACOVIGILANCE CENTER, WESTERN NEPAL

SUBISH P*[+#], MISHRA P*[+] AND SHANKAR PR[#]

**Department of Pharmacology, [+]Department of Hospital and Clinical Pharmacy*
Manipal College of Medical Sciences/ Manipal Teaching Hospital, Phulbari-11, Pokhara, Nepal
#Discipline of Social and Administrative Pharmacy, School of Pharmaceutical Sciences
Universiti Sains Malaysia, 11800 Penang, Malaysia

ABSTRACT

Present study analyzed the pattern, causality, severity and preventability of the systemic adverse drug reactions reported to the regional pharmacovigilance center during the period 14th September 2004 till 13th September 2005. Altogether the centre received 22 systemic adverse drug reactions [males 12 (54.55%), females 10 (45.45%)]. Among the total adverse drug reaction 5 (22.73%) were reported by the Department of Orthopedics. Of the 22 drugs responsible for the suspected adverse drug reaction, majority belongs to the class of Opoid analgesics [n=7, (31.82%)], followed by non steroidal anti-inflammatory drugs [n=5, (22.73%)]. Tramadol was the individual drug responsible for 6 (27.27%) adverse drug reactions and vomiting was the most common adverse drug reactions [n=6, (27.27%)]. The causality assessment revealed 7 (31.82%) of the adverse drug reaction to have a probable relationship with the suspected drugs.

Keywords: Adverse drug reactions, Nepal, pharmacovigilance, systemic toxicity.

INTRODUCTION

Adverse Drug Reactions (ADRs) are one of the major causes of morbidity and mortality. The data from the United States (US) suggest ADRs to be one of the top ten causes of death in US accounting for nearly hundred thousand deaths annually (Lazarou *et al*., 1998). With the increasing awareness regarding the harmful effects of drugs, several countries have started their own Pharmacovigilance programs. Pharmacovigilance is a science relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems (Lee and Thomas, 2003). Nepal is a developing country with a population of nearly 25 million people. Irrational use of drugs is well documented in Nepal (Blum NL, 2000). Drug safety was one of the most neglected areas in Nepal though there was one multicentric study from Nepal that identified the pattern of ADRs in Nepalese population (Shrestha *et al*., 2006). Recently, in the year 2004, a structured Pharmacovigilance program was started in Nepal and Nepal was added to WHO list of member countries for the global ADR monitoring program. Manipal Teaching Hospital, a tertiary care teaching hospital in western Nepal was the pioneer in starting Pharmacovigilance program in Nepal and is the regional PV centre for western Nepal. A preliminary study evaluated the pattern and economic impact of cutaneous ADRs received by the centre during its initial one year of functioning (Mishra *et al*., 2006). However, the data regarding the systemic ADRs is not yet studied. Hence the present study was carried out with the following objectives.

1. To study the pattern of the systemic adverse drug reactions reported to the centre.
2. To carry out the casualty, severity, and preventability of the reported adverse drug reactions.

Methodology

All the ADRs reported to the regional PV centre during the period of 14th September 2004 (time of initiation) to 13th September 2005 were separated. Necessary patient's details were collected from the patient's confidential case records. The casualty, severity and preventability assessments were carried at as per the Naranjo (Naranjo *et al*., 1981) Hartwig (Hartwig *et al*., 1992) and Modified Schumock and Thronton (Lau *et al*., 2003) scales respectively.

Results

Altogether the centre received 22 systemic ADRs during the study period [males 12 (54.55%), females 10 (45.45%)]. Among the total 22 ADRs 3 (13.64 %) occurred in the age group between 0-20 years followed by 11 (50.00%) in 21-40 years, 5 (22.73%) in 41-60 years and 3 (13.64%) in patients belonging to more than 60 years of age.

Among the total ADRs 5 (22.73%) were reported by the department of Orthopedics followed by Pharmacy [n=4,

**Corresponding author:* e-mail: subishpalaian@yahoo.co.in, subishpalaian@gmail.com

(18.18%)], Nursing and Psychiatry [3, (13.64%) each], Dermatology [n=2, (9.09%)] and Medicine, Pediatrics and Surgery 1 (4.55%) each. One (4.55%) ADR was also reported by a patient and the other one (4.55%) by a student. Of the 22 suspected drugs responsible for the ADRs, majority belongs to the class of Opoid analgesic [n=7, (31.82%)], followed by Non Steroidal Anti-Inflammatory Drugs (NSAIDs) [n=5, (22.73%)]. The remaining drugs belong to the drug group antibiotics, antidepressants, antiepelipitics, antigout, antileprotic, bisphosphates, hypnotics, intravenous fluids and proton pump inhibitors each. There was one ADR that belongs to a combination of NSAIDs + muscle relaxant category. The individual drugs responsible for the ADRs were also studied and the details are listed in table 1 and the various types of ADRs reported are listed in table 2.

Among the various system affected by the ADRs, the most common was Gastrointestinal [n=6, (27.27%) followed by Cardiovascular system [n=5, (22.73%), Immune system [n=3, (13.64%)], Central nervous system [n=2, (9.09%)]. There was also one ADR each affecting the Renal, Hepatobiliary and Hematological systems.

The causality assessment revealed 7 (31.82%) to be 'probable', 6 (27.27 %) to be 'possible' and 1 (4.55%) to be 'definitely' related to the suspected drugs. We could not carry out the causality assessment of 8 ADRs due to the unavailability of the patients' details. The severity assessment revealed 10 (45.45%) ADRs to be of 'mild (level 2)', 4 (18.18%) to be of moderate (level 3)' and 1 (4.55%) of 'mild (level 1)'. We could not carry out the severity assessment of 7 ADRs due to lack of sufficient information.

The preventability assessment revealed 13 (59.09%) ADRs to be 'Non Preventable' and 2 (9.09%) were 'Definitely Preventable' type. The preventability assessment was not carried out in 7 patients due to the unavailability of sufficient information.

DISCUSSION

Present study identified the pattern, casualty, severity and preventability of the systemic ADRs reported to the regional pharmacovigilance centre during its initial one year of functioning. Men were at a higher risk of ADRs in our study. However, in general women are more prone to ADRs (Bates and Leape, 2000; Puavilai and Timpatanapong, 1989). Since the number of patients were very low in our study, it is very difficult to generalize our findings.

In our study more number of patients was in the age group 21-40 years. In a study from a South Indian hospital, the majority of patients experiencing ADRs were in the age group 21- 40 years. (Sushma *et al*., 2005) Another study in a tertiary care center in South India identified the age group 20-39 years as being more predisposed to ADRs (Pudukadan and Thappa, 2004). The results of these studies are more or less in agreement with our study.

Tramadol was the drug responsible for more number of ADRs. Tramadol is a synthetic opioid analgesic used in pain management. The safety of tramadol is already questioned by researchers (Kaye, 2004). We also observed a higher incidence of ADRs with this drug. This observation suggests that the decision on the use of tramadol should be evaluated thoroughly before prescribing. In the literature reports, nausea occurred in 24, 34 and 40% of patients, and vomiting occurred in 9, 13 and 17% of patients receiving the drug for up to 7, 30, and 90 days, respectively. Nausea and vomiting may occur more frequently with higher doses and following rapid intravenous injection (McEvoy *et al*., 2003).

Establishing the causality helps the clinician to conclude that a particular drug has caused an ADR. Based on this the treating clinician can stop, withhold, reduce the dose or change the suspected drug causing the ADR. In our study we found more number of the ADRs to have a 'probable' association with the suspected drugs.

Establishing the severity is very much essential in pharmacovigilance studies as the management pattern of the ADRs including the hospitalization is mainly based on the severity of an ADR. Moreover, severe ADRs require special attention by the clinician and may require an emergency intervention including the stoppage of the suspected drug (s). In our study nearly half of the total number of ADRs was of 'mild (level 2)' type of ADRs suggesting The ADR requires that the suspected drug be withheld, discontinued, or otherwise changed. No antidote or other treatment is required, and there is no increase in length of stay.

Establishing the preventability status of the ADRs is essential to adopt appropriate strategies to prevent the occurrence of similar ADRs in the future. Several strategies may be adopted to prevent the occurrence of ADRs especially the type-A ADRs. Since, the most common type of drug-induced disorder is dose-dependent and predictable and occurs as a result of drug-drug, drug-disease or drug-food interactions, it is preventable (Holland and Degruy, 1997).

Limitations

The numbers of ADR reports received were low and hence may not be possible to extrapolate our findings. This also limited us in applying statistics to the data. Since we did not have adequate information regarding some of the patients and hence we could not carry the casualty, severity and preventability of few ADRs.

Table 1: Individual drugs responsible for the ADRs

Drugs	No. of reports
Tramadol	6
Diclofenac	2
Naproxen	2
Caramazepine	1
Chloroxazone+Paracetamol	1
Dapsone	1
Dothiepin	1
Gentamicin	1
Indomethacin (Sustained release)	1
Intravenous fluid	1
Omeprazole	1
Pamidronate	1
Pethidine	1
Zolpidem	1
Allopurinol	1

Table 2: Types of adverse drug reactions

Reaction type	No. of reports	Percentage
Vomiting	6	27.27
Generalized Edema	2	9.09
Brown colored urine	1	4.55
Ejaculatory failure	1	4.55
Facial puffiness and pitting edema on lower limbs	1	4.55
Fever, rigor and chills	1	4.55
Hypereactivity	1	4.55
Itching	1	4.55
Jaundice	1	4.55
Nephrotoxicity	1	4.55
Oral ulcer	1	4.55
Papular rash, fever, chills	1	4.55
Sinus tachycardia	1	4.55
Swelling in upper and lower limbs	1	4.55
Tingling in body, giddiness	1	4.55
Vasculitis	1	4.55

CONCLUSION

The study was the first study from Nepal that studied the systemic manifestations of ADRs. Tramadol was the drug responsible for more number of ADRs and the system most commonly affected was gastrointestinal. More number of ADRs had a 'probable' relationship with the suspected drug. Similar studies conduced over longer period are necessary to validate our findings.

REFERENCES

Bates DW and Leape L (2000). Adverse drug reaction. *In*: *Morreli's Clinical Pharmacology*, Carvuthers SG, Hoffman BB, Melmon KL and Nierenberg DW (editors), McGraw-Hill, Boston, pp.1223-1257.

Blum NL. Rational pharmaceutical management project United States Pharmacopoeia: Drug information Development. A case study, Nepal

Hartwig SC, Siegel J and Schneider PJ (1992). Preventability and severity assessment in reporting adverse drug reactions. *Am. J. Hosp. Pharm*., **49**: 2229-2232.

Holland EG and Degruy FV (1997). Drug-Induced Disorders. *Am. Fam. Physician*. **56**: 7.

Kaye K (2004). Trouble with tramadol. *Aust. Prescr*., **27**: 26-27.

Lau PM, Stewart K and Dooley MJ (2003). Comment: hospital admissions resulting from preventable adverse drug reactions. *Ann. Pharmacother.,* **37**(2): 303-304.

Lazarou J, Pomeranz BH and Corey PN (1998). Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *J. Am. Med. Assoc.*, **279**(15): 1200-1205.

Lee A and Thomas SHL (2003). Adverse drug reactions In: Walker R and Edward C. Clinical pharmacy and Therapeutics. 3rd edition, Churchill Livingstone, pp.33-46.

McEvoy GK, Miller J, Litvak K, Dewey DR, Bollinger LA, Shick J, Millikan EDDouglas PM (editors) (2003). AHFS Drug Information United States of America: American Society of Health-System Pharmacists, pp. (1-3732).

Mishra P, Subish P, Gupta S, Shankar PR, Bista D, Chhetri AK and Bhandari RB (2006). Pattern and economic impact of cutaneous adverse drug reactions; initial experiences from the regional pharma-covigilance center, Western Nepal. *International Journal of Risk and Safety in Medicine*, **8**(3): 163-171.

Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ. (1981). A method for estimating the probability of adverse drug reactions. *Clin. Pharmacol .Ther.,* 30: 239-245.

Puavilai S and Timpatanapong P (1989). Prospective study of cutaneous drug reactions, *J. Med. Assoc. Thai.,* **72**: 167-71.

Pudukadan D and Thappa DM (2004). Adverse cutaneous drug reactions: clinical pattern and causative agents in a tertiary care center in South India, *Indian. J. Dermatol. Venereol. Leprol.,* **70**: 20-24.

Shrestha R, Shakya S, Bista D, Shrestha RK, Khan GM, Joshi S, Rao BS. (2006). Case studies of hospitalized patients due to drug related complications. Kathmandu university journal of science, engineering and technology, Vol.II, No.1, February (available on: http://www. ku.edu.np/kuset/second_issue/o2/Rajeev.pdf).

Sushma M, Noel MV, Ritika MC, James J and Guido S (2005). Cutaneous adverse drug reactions: a 9-year study from a South Indian hospital. *Pharma-coepidemiol. Drug Saf.,* **14**: 567-570.