CASE STUDIES OF HOSPITALIZED PATIENTS DUE TO DRUG RELATED COMPLICATIONS

Rajeev Shrestha, Sony Shakya, Durga Bista, Rojeena Koju Shrestha,
Gulam Muhammad Khan, Shreena Joshi, B.S.Rao

Department of Pharmacy, Kathmandu University, Dhulikhel, Kavre,
P.O. Box: 6250, Kathmandu, Nepal

Corresponding author: pharmacy@ku.edu.np, gmkhan@ku.edu.np

ABSTRACT
A cross sectional survey, involving five major hospitals in Nepal covering Kathmandu, Bharatpur and Palpa was conducted during 22nd February to 30th May 2003. Pharmacists and doctors collected the data from the in-patient file those who were admitted due to drug related complications (DRC) and entered the details in the study-encounter form. The study excluded outpatients and patients experiencing DRCs in the hospital. Among 15,624 hospital admissions, 63 (0.4%) were attributed to DRCs. Analgesics were responsible for 1/4th of the complications. Hypersensitivity and gastrointestinal (GI) bleeding separately accounted for nearly 1/5th of the complications. Adverse Drug Reactions (ADRs) caused 51 (80.96%) of the complications followed by overdose (17.46%) and wrong dose (1.58%). Higher incidence of ADRs was due to analgesics (23.82%) followed by antibacterial (17.46%), antitubercular agents (15.87%), central nervous system drugs (11.12%), steroids (4.76%) and miscellaneous (7.93%). Analgesics were the main therapeutic category causing DRCs. Hypersensitivity and GI bleeding were the major complications and ADRs to be the major cause with higher incidence attributable to analgesics and antibacterial. The study was evident in finding the incidence of DRCs.

Key words: Adverse Drug Reactions, Drug Related Complications

INTRODUCTION
More than 1 million hospitalized patients are injured and approximately 1, 80,000 die due to DRCs annually with an estimated cost more than $136 billion Holland, 1997). ADRs are responsible for a significant number of hospital admissions with reports ranging from 0.3 to as high as 11%.The total number of deaths occurring as a result of ADRs are estimated to be 1,06,000, making ADRs the fourth to sixth major causes of death in the US (Beard, 1992, Lozarou, 1998). Furthermore, an evaluation of a large sample of 30,195 randomly selected hospital records revealed that 1,133 patients (3.7%) experienced a disabling injury caused by medical treatment while hospitalized (Bernnan, 1991). In the ambulatory care environment, the incidence of drug-induced disorders not causing hospitalization or death is less well known because different, less effective methods are used to collect data. Reported rates have ranged from 2.6 to 50.6%, depending on the source of the data. The lower rates generally reflect data collected from physicians, and the higher rates come from patient surveys (Holland, 1997). There are several predisposing factors for ADRs. These include multiple drug therapy, age sex, and polypharmacy; inter current diseases, race and genetic polymorphism (Lee, 2003).

New Chemical entities (NCE), as well as new formulations of existing medications, are increasing at rapid rate. NCEs are released to the market after phase III trials. In phase-I trials the drug is tested on normal volunteers to determine their pharmacodynamic effects and possible toxic effects. In phase -II the new compound is compared either with a placebo or with an existing compound with similar pharmacological effects with the limited number of subjects. Phase-III trials involve a much lager number of patients, are carried out in several centers often situated in several countries. Even after phase-III there is only limited experience with the use of the drug. Trials up to this point may be sufficient to detect ADRs that may occur with a relatively high frequency, but rare events may go undetected. Some of these will manifest as ADRs during phase IV or post-marketing surveillance (Noan, 2000). Even after phase IV studies many ADRs remains undetected and gets noticed only when used in larger patient population. This necessitates an ongoing ADR monitoring program.

Nepal is a developing country having a multidimensional variation in several aspects. Among the total of 75 districts about two third are located in hilly regions and the remaining in plains. The effect of drugs may vary from place to place. The climatic condition also varies from season to season and from place to place. This may predispose the occurrence of ADRs (Leppik, 1985). Moreover; there are several races of people having different cultural and social beliefs. Alcohol consumption is very common and may predispose to the occurrence of ADRs (Anon, 1998). The use of complementary medicine is another aspect to be kept in mind. These medicines may interact with allopathic drugs and predispose the occurrence of ADRs (Abebe, 2002). Majority of drugs used in Nepal are manufactured in foreign countries and the excipients used may vary. The pharmaceutical excipients are known to one a potential cause several ADRs, (Wong, 1993). The Nepalese population mainly has their main meal of twice daily but in case of few drugs the dosage regimen is three times daily. Here the occurrence of Gastric related ADR may vary. The genetic make up of Nepalese population may vary and hence predispose ADRs. There are no clinical trials done on the Nepalese population prior to approval in Nepal. Hence the risk of occurrence of ADRs is very high and is in fact unknown.

There are several ways to monitor ADRs. These methods include case reports, anecdotal reporting, Spontaneous reporting system, intensive event recording, cohort studies (prospective studies, Case-control studies (retrospective studies, case-cohort studies, meta analysis and record linkage) (Lee, 2003). 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 and, therefore, are preventable by exercising a high degree of suspicion and close attention (Holland, 1997).

We could not locate any data related drug related complications in Nepal. Hence the present study was conducted with the following objectives.

Objectives

The study had objectives of identifying the prevalence of drug related complications leading to hospitalizations; identifying the various causes for drug related complications; categorizing the drug related complications based on the age groups of patients, complications and drug classes and studying in detail the commonly observed drug related complications

MATERIALS AND METHODS

Study type: Cross sectional

Study duration: The cases collected from 22nd February 2003 to 30th May 2003 were considered as valid data for this research. All the cases were collected within the above specified time duration

Study site: The study sites were selected considering the patient inflow probability and rural and urban areas. For this purpose following five hospitals were chosen. Bir Hospital Kathmandu, Tribhuvan University Teaching Hospital (TUTH), Kathmandu, Kanti Children Hospital (KCH), Kathmandu, College of Medical Sciences Teaching Hospital, Bharatpur, United Mission Hospital, Tansen, Palpa.

Inclusion and exclusion criteria: All those cases requiring hospital admission due to health problem primarily due to drug used for therapeutic purpose were included for the study. Cases which were treated from the Out Patient Departments (OPDs), and which do not require hospital stay, were excluded from the study.

Data collection and analysis: Information related to the patients was collected from the patient files by using a structured questionnaire designed in English language. While collecting data, face-to-face enquiries were done with patients along with their attendants and also attendant doctors, if required. Where the regular visits were found difficult, the concerned doctors with their consent were requested to note the details. Proper details and information regarding the matter was discussed with the concerned doctors before entrusting the responsibility. All the available medical records of the patient were studied from the patient's history. The data were analyzed by using SPSS (version 11) program and Microsoft Excel in a computer. Data analysis has been presented in tabulated as well as graphical form. Some of the data were analyzed using Chi-square test.

RESULTS AND DISCUSSION

Among the total 15,624 patients admitted, 63 cases were found to be due to DRCs. The incidence was found to be 0.403%.

Age distribution: The study found that 64% of the patients experiencing DRCs belonged to the age group of 14-45, 11% belonged to 0-14 yrs, and 25% belonged to more than 45 yrs.

Causes of DRC due to various drugs: Table-1 lists the name of culprit drugs for the genesis of drug related complications.

Table1: Drugs responsible for the complications

DRUG	ADR (%)	Overdose (%)	Wrong dose (%)	Total (%)
Analgesics	15 (23.82)	2 (3.17)	-	17 (26.99)
ATT	10 (15.87)	-	-	10 (15.87)
DANS	7 (11.12)	7 (11.12)	1 (1.58)	15 (23.82)
Antibacterial	11 (17.46)	-	-	11 (17.46)
Steroids	3 (4.76)	-	-	3 (4.76)
Miscellaneous*	5 (7.93)	2 (3.17)	-	7 (11.1)
Total (%)	**51 (80.96)**	**11 (17.46)**	**1 (1.58)**	**63 (100)**

*Miscellaneous: Iron, Digitalis, Glibenclamide, and Clopidogrel.

Prevalence of various complications due to DRC: Table 2 lists the nature of complications induced by DRCs.

Table2: Complications due to ADRs

Complications	Frequency	Percent (%)
Hypersensitivity	13	20.6
GI bleeding	13	20.6
Steven Johnson Syndrome	7	11.1
Liver Disorder	10	15.9
Neurological Disorder	11	17.7
Miscellaneous*	9	14.3
Total	**63**	**100**

*Miscellaneous: Hypotension, Tachycardia, Cardiac arrhythmia, Decold overdose, Toxic Epidermal necrolysis

Complications in various age groups: Table 3 shows complications due to DRC in corresponding age groups.

Table3: Complication observed in different age groups

Age Gr.	Hypersensitivity (%)	GI bleeding (%)	SJS (%)	Liver Disorder (%)	Neurological Disorder (%)	Misc. (%)	Total (%)
< 14	2 (3.17)	1 (1.58)	1 (1.58)	1 (1.58)	2 (3.17)	-	7 (11.12)
14-45	10 (15.87)	6 (9.52)	5 (7.96)	7 (11.12)	6 (9.52)	6 (9.52)	40 (63.49)
> 45	1 (1.58)	6 (9.52)	1 (1.58)	2 (3.17)	3 (4.76)	3 (4.76)	16 (25.39)
Total (%)	13 (20.63)	13 (20.63)	7 (11.12)	10 (15.87)	11 (17.46)	9 (14.28)	63 (100)

Complications resulted from various classes of drugs: Table 4 DRC due to various therapeutic categories of drugs.

Table4: Complications Observed Due To various Drug Classes

Drug	Hypersensitivity (%)	GI bleeding (%)	SJS (%)	Liver Disorder (%)	Neurological Disorder (%)	Misc. (%)	Total (%)
Analgesics	4 (6.35)	11 (17.46)	-	1 (1.58)	-	1 (1.58)	17 (26.98)
ATT	-	-	-	9 (14.28)	-	1 (1.58)	10 (15.87)
DANS	2 (3.17)	-	4 (6.35)		9 (14.28)		15 (23.81)
Antibacterial	5 (7.93)	-	3 (4.76)	-	-	3 (4.76)	11 (17.46)
Steroids	-	-	-	-	2 (3.17)	1 (1.58)	3 (4.76)
Miscellaneous	2 (3.17)	2 (3.17)	-	-	-	3 (4.76)	7 (11.12)
Total (%)	**13 (20.63)**	**13 (20.63)**	**7 (11.12)**	**10 (15.87)**	**11 (17.46)**	**9 (14.28)**	**63 (100)**

Occurrence of liver disorders in patients under Anti tubercular therapy (ATT) drugs: Table 5 shows the relationship between drug induced liver diseases in the study population

Table5: Relationship between liver disorders and ATT drugs

Liver disorders / ATT drugs	Yes	No
Yes	90%(9)	1.9%(1)
No	10%(1)	98.1%(52)
Total	**100%(10)**	**100%(53)**

*Chi-square= 48.91; p-value= 0.000

This implies the fact; ATT drugs were the major drugs to induce liver disorder than any other drugs. The statistical test reveals a significant relationship between these two attributes i.e. (p= 0.000).

Occurrence of Gastrointestinal (GI) bleeding inpatient under analgesics: Table 6 shows the Relationship between GI bleeding and analgesics.

Table 6: Relationship between GI Bleeding and Analgesics

GI Bleeding / Analgesics	Yes	No
Yes	84.6%(11)	12.0%(6)
No	15.4%(2)	88.0%(44)
Total	**100%(13)**	**100%(50)**

*Chi-square= 27.612; p-value= 0.000

The statistical test too shows the significant relationship between these two attributes (p=0.000).

In the present study, the incidence of hospitalization due to DRCs was found to be 0.4%. Our values were much lower than the values reported in other studies. A study by William et al reported 10% hospital admissions due to ADRs (Williamson, 1980). Another study by Wood et al reported values of 4% (Wood, 1980). The fewer incidence of hospital admissions due to ADR in our study could be attributed to lower rate of hospital admission in our study group than the ones reported in the literature.

We found the prevalence of DRC was more among the middle-aged patient (14-45 yrs) which accounts for (40.32) 64 % of the total ADRs and 0.258 % of the total incidence of ADRs. A study by Yosselson et al reported an incidence rate of 3.2% (Yosselsen, 1982). Another study by Mitchell et al reported a rate of 0.2% (Mitchell, 1988). Thus our values were in comparison with other reported studies.

Our study reported ADRs to be the major cause for DRCs accounting for 80.96% of the total DRCs. We also found other causes like overdose to be other important causes for DRCs accounting for 17.46% of total DRCs.

Our study reported hypersensitivity to be the major complication due to ADRs accounting for 20.6% of the total ADRs. A study reported 7% of hospital admissions due to ADRs to be related to hypersensitivity (Lakshmanan, 1986). The present value was found to be significantly higher than the reported by Lakshmanan, 1986.

Among the various category of drugs implicated for ADRs, we found analgesics were attributable to higher incidence of ADRs accounting for 26.98% of the total ADRs. And the other drugs implicated are ATT, DANS, antibacterial and steroids. A study reported diuretics, beta-blocker, and calcium-channel blockers to be the major contributors for ADRs in a cardiology clinic (Davidson, 1998). Another study reported cardiac drugs and anticoagulants to be the major contributors for ADRs (Cooke, 1985).

Pain is one of the commonest complains in any medical fields and analgesic bear the mainstay of pain management. Most of the analgesics being the Over The Counter (OTC) drug have more chances of being used irrationally. Often analgesics are urgently needed and mostly desired because patients are bothered more with the pain than the disease process. These are also the drugs, which are easily available and affordable by the patients. Alcohol can result the gastric mucosal barrier and can result the damage to the gastric mucosal barrier and can produce longitudinal tear in the gastrointestinal junction. Similarly older age is more susceptible to Non-Steroidal Anti-Inflammatory Drug (NSAID) induced gastrointestinal bleeding (Fauci, 1998). Proper instructions for the use and side effects should be mentioned while giving the medications. Inadequate counseling may result to such consequences.

ATT drugs related, hepatotoxicity was noted in nine patients accounting for 14.28% of the total DRCs. The basic mechanism behind the induction of hepatotoxicity due to ATT is due to the covalent binding of reactive metabolites of ATT drugs with hepatic macromolecule, which lead to hepatic necrosis.[18] Though, hepatitis with ATT is usually infrequent and unpredictable. It may occur at any time during or shortly after exposure to the drug and is immunological mediated. Often, the hepatitis is recognized to be mediated by toxic metabolites that damage the liver cell damages directly. Most of them result from different metabolic reactivity to the specific agents, host susceptibility which differs among individual. The occurrence of ATT induced complications in our study may have resulted due to the wide use of ATT drug which are easier to prescribe and easily accessible than preliminary examination. Failure to individualize the therapy may be another probable reason for precipitation of such complications.

Limitations: Study conducted comprised only limited number patients and thus becomes difficult to extrapolate the data. Our study also did not take into account the seasonal variation.

Conclusion: An ADR monitoring and reporting program can help to provide a measure of the quality of pharmaceutical care through identification of preventable ADRs and anticipatory surveillance for high- risk drugs patients, complement organizational risk-management activities and efforts to minimize liability, assess the safety of drug therapies, especially new ones, measure ADR incidence rates, over time, educate health professionals on drug effects and increase their level of awareness regarding ADRs, provide quality- assurance screening findings for use in drug –use evaluation programs. Overtime, an ongoing ADR monitoring and reporting program may help to measure the economic impact of ADRs prevented, as manifested through reduced hospitalization, efficient and economical drug use, and minimize organizational liability.

The study was the first of its kind in Nepal and evaluated the incidence of DRCs leading to hospitalizations. The study highlights the importance of monitoring ADRs as these can have a major impact in the cost of therapy, quality of health care and the quality of life of the patients. However, a further study encompassing the various dimensions of the healthcare including primary care is warranted in this area. The successful prevention of DRCs lies in the hands of the members of healthcare team in selecting appropriate drugs, doses and dosages and also in providing counseling to the patients regarding the prevention, detection and management of ADRs.

REFERENCES

1. Holland EG, Degruy FV, 1997. Drug-Induced Disorders. Am Fam Physician, 56 (7):1791.

2. Beard K, 1992. Adverse reactions as a cause of hospital admission in the aged. Drugs Aging, 2 (4): 356-67.

3. Lazarou J, Pomeranz BH, Corey PN, 1998. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA, 279: 1200-5.

4. Bernnan TA, Leape LL, Laird N, 1991. The nature of adverse events in hospitalized patients: the results of Harvard medical practice study II. N Engl J Med, 324: 377-87.

5. Lee A, Thomas SHL. Adverse drug reactions In: Clinical Pharmacy and Therapeutics. Walker R, Edwards C (eds), 3rd edition 2003. Churchill Livingstone, Edinburg, 33-46.

6. Noan BA, Brushwood DB, 2000. Adverse drug reactions in elderly patients: alternative approaches to post surveillance, J Health Law, 33(3): 383- 454.

7. Leppik IE, Lapora J, Loewonson R, 1985. Seasonal incidence of phenytoin allergy unrelated to plasma levels. Arch Neurol, 42: 120-2.

8. Anon: Press Release: FDA announces new alcohol warnings for pain relieves and fever reducers. United States Food and Drug Administration, U.S Department of Health and Human Services, Rockville, MD. October 21, 1998 (cited 10/22/98). Available from http//www.fda.gov.

9. Abebe W, 2002. Herbal medications: potential for adverse interactions with analgesic drugs. J Clin Pharm Ther, 27(6): 391-401.

10. Wong YL, 1993. Adverse effects of pharmaceutical excipients in drug therapy. Ann Acad Med Singapore, 22(1): 99-102.

11. Williamson J, Chopin JM, 1980. Adverse reactions to prescribed drugs in the elderly; a multicentre investigation, Age Ageing , 9: 73-80.

12. Wood SM, Turner P, Vere D, 1980. Clinical Pharmacology and general patient care in two teaching Hospitals, J R Soc Med , 73: 355-8.

13. Yosselsen-Superstine S, Weiss T, 1982. Drug-related problems causing admissions to a medical clinic, J Clin Hosp Pharm, 7: 195-203.

14. Mitchell AA, Lacouture PG, Sheehan JF, Kauffman RF, Shapiro S, 1988. Adverse drug reactions in children leading to hospital admission, Pediatrics, 82: 24-9.

15. Lakshmanan MC, Hershey CO, Breslau D, 1986. Hospital admissions caused by iatrogenic disease, Arch Intern Med,146: 1931-4.

16. Davidsen F, Haghfelt T, Gram LF, Brosen K, 1988. Adverse drug reactions and drug non-compliance as primary causes of admission to a cardiology department, Eur J Clin Pharmacol, 34: 83-6.

17. Cooke CI, Van Der Merwe W, Pudiflin DJ, 1985. Hospital admissions for adverse reaction to drugs and deliberate self-poisoning, S Afr Med J, 67: 770-2.

18. Fauci AS, Braunwald E, Issellbacher KJ, Wilson JD, Martin JB, Kasper DL, Hauser SL, Longo DL, 1998 (eds). Harrison's Principles of Internal Medicine, 14th edition, Mc Graw-Hill Companies, New York.