SciMedCentral

Journal of Pharmacology & Clinical Toxicology

Review Article

Profile of Suspect Adverse Drug Reactions in a Teaching Tertiary Care Hospital

Shubhatara Swamy[1], Bhanuprakash[2], Pratibha Nadig[1]*, Muralimohan[3] and Manjula Shetty[1]

[1]*Department of Pharmacology, Vydehi Institute of Medical Sciences and Research Centre, India*
[2]*Department of Dermatology, Vydehi Institute of Medical Sciences and Research Centre, India*
[3]*Department of Emergency Medicine, Vydehi Institute of Medical Sciences and Research Centre, India*

***Corresponding author**
Pratibha Nadig, Vydehi Institute of Medical Sciences and Research Centre, #18, Nallurahalli, Near BMTC 18th Bus Depot, EPIP Area, Whitefield, Bangalore 560066, Karnataka State, India, Tel: +91 80 28413382; Fax number: +91 80 28416199; Email: drpratibhanadig@yahoo.co.in

Submitted: 06 August 2013
Accepted: 23 August 2013
Published: 28 August 2013

Keywords
- Suspect adverse drug reactions
- Pharmacovigilance
- Causality assessment
- Cutaneous reactions

Abstract

Purpose: The present study was carried out to analyse the profile of suspect adverse drug reactions (ADRs) reported to the Pharmacovigilance unit. The primary objective was to identify the common drugs implicated and the pattern of the reactions, which would ensure a judicious prescription and further prevention.

Methods: An awareness building lecture on voluntary reporting of ADRs was conducted after which ADR forms were distributed to various departments. They were assessed for the type of reaction based on Rawlins and Thomson criteria; severity based on Hartwig's scale; seriousness as per Centre for Drugs Standards Control Organisation; expectedness as defined by International Conference on Harmonisation and causality based on Naranjo's algorhythm. The common group of offending class of drugs was also identified. The results were analysed using descriptive statistics.

Results: Out of 75 reactions 74 (98.67%) were type B and 1 reaction (1.33%) was type A. There were 5 unexpected reactions. Sixty four reactions (85.3%) were mild, 4 (5.33%) moderate and 7 (9.33%) were severe in nature. Seven (9.33%) out of 75 were considered serious as they required hospitalisation. The causality assessment for 154 drugs from 75 forms showed 118 (51%) to be possibly related, 36 (49%) as probably related and none were definitely related. The major group of drugs implicated was Antimicrobials followed by Non-steroidal anti-inflammatory drugs.

Conclusion: ADRs were mostly due to antimicrobials and Non-steroidal anti-inflammatory drugs. It is necessary to create more awareness to curb irrational polypharmacy which helps in prevention and an accurate diagnosis of the reactions.

INTRODUCTION

Adverse drug reactions (ADRs) are a great concern in therapeutics. An incidence of 5% to 35% is observed in all age groups among outpatients [1]. ADRs are the fourth leading cause of death ahead of pulmonary disease, diabetes, AIDS, pneumonia, accidents and automobile deaths. Serious ADRs account for 6.7% of all hospital admissions [2]. A study in South India showed that ADRs accounted for 0.7% of total admissions and 1.8% of resulted in death [3]. ADRs have an economic burden on the patients as well as on the health care establishment. It is estimated that a hospital spends an average of Rs.481/- per day in the management of ADRs [4].

Pharmacovigilance has evolved as a major discipline of science with a goal of understanding the various characteristics of ADRs like seriousness, severity, expectedness and contributing risk factors and their frequency. Pharmacovigilance as per World Health Organisation (WHO) is defined as 'the science and activities relating to the detection, assessment, understanding and prevention of adverse drugs reactions or any other drug related problems [5]. Monitoring the adverse drug reactions in any setting can be undertaken by several methods. Passive surveillance by voluntary reporting or stimulated reporting by physicians, active surveillance by prescription event monitoring and patient registries, epidemiological studies such as cohort and case control studies form some of the important methodologies used globally [6]. Most of the countries however

have adopted spontaneous or voluntary reporting as the most resourceful method to monitor ADRs because of its feasibility [7]. Spontaneous reporting system has led to the withdrawal of some of the blockbuster drugs like *Rofecoxib, Terfenadine* and *Cerivastatin* [8].

Pharmacovigilance is carried out in India by the sponsors as part of regulatory requirement and in collaboration with WHO as Pharmacovigilance Programme of India (PvPI). Medical college hospitals and some private hospitals work as peripheral centres under PvPI to collect the data on ADRs occurring in their hospitals, assess the causality and forward to the national centre through Vigiflow. The national centre will further process the reports and forward to the vigibase of the WHO Uppasala centre. Our hospital is recognised as one of the peripheral pharmacovigilance centre. The present study was carried out with the purpose of analysing the reactions further so as to identify the common drugs implicated in the causation of the ADRs and the pattern of there actions caused by them. The ultimate objective was to give a feedback to the prescribers that would ensure a judicious prescription and prevention of the reactions in future.

METHOD

This prospective non-interventional observational study was conducted over a period of 12 months from Jan 2010 - Dec 2010. Permission was obtained from the Head of the institution to conduct the study. An introductory lecture was organized in the academic society of the institute to orient the clinicians towards pharmacovigilance and spontaneous reporting system. The Central Drug Standard Control Organisation (CDSCO) suspect ADR forms (downloaded from CDSCO website[8]) were distributed to all the clinical departments personally by the pharmacovigilance co-ordinators. The form contained the patient details, drug details, the description of the reaction, concomitant medication, co-existing illness, any rechallenge, dechallenge etc.

On receiving information from the clinical departments, the members visited the hospital and interacted with the doctors to gather complete information on the ADRs. The suspected ADRs were carefully analysed and documented. Apart from this, regular visits were conducted by the unit members to collect the forms and follow up wherever possible.

Evaluation of the reports

The reports which had a minimum of the following information were used for analysis – Patient details, the suspect drug, reaction and the reporter details. The reactions were analyzed under the following categories

1). Type of reaction (based on Rawlins & Thomson criteria [9]):

- Type A: Augmented pharmacologic effects - dose dependent and predictable
    1. Intolerance
    2. Side Effects
- Type B: Bizarre effects (or idiosyncratic) - dose independent and unpredictable
- Type C: Chronic effects
- Type D: Delayed effects
- Type E: End-of-treatment effects
- Type F: Failure of therapy
- Type G: Genetic reactions

2). Severity – The severity of the reaction was determined based on the classification system of WHO [10] and system of Hartwig et al. [11]. Mild reactions were those that were self-limiting, resolved over time without treatment (antidote) and did not extend a patient's hospital stay. Moderate ADRs were defined as those that required therapeutic intervention and prolongation of the hospital stay by one day but that which resolved within 24 hours due to a change in drug therapy or the administration of a specific treatment to prevent further adverse outcomes. Severe ADRs were those that threatened patients' lives, caused disability, led to hospitalisation or prolonged hospital stays, required intensive medical care or led to death.

3). Seriousness: The reaction was deemed serious when the patient outcome was

a. death

b. life-threatening (real risk of dying)

c. hospitalization (initial or prolonged)

d. disability (significant, persistent or permanent congenital anomaly)

e. required intervention to prevent permanent impairment or damage [8]

4). The causality relationship with the drug was established using the Naranjo scale [12]. Accordingly the causality was categorised as definite, probable, possible or unrelated, depending on the scores.

5). Expectedness: An adverse reaction, the nature or severity of which was not consistent with the applicable product information was considered as unexpected reaction [13].

6). Suspected drugs associated with ADRs were also categorized based on pharmacological class.

The results were analysed using descriptive statistics and a feedback was sent to the clinical departments on the common drugs that caused the reactions and the type of reactions.

RESULTS

Eighty ADR forms were received by the pharmacovigilance unit from various clinical departments. Seventy-five out of eighty were utilized for analysis. The rest were rejected as they were incomplete in terms of reporters' signature, drug name, patient initials and the reaction. Seventy-five reactions per se were analysed for the type, expectedness, severity and seriousness.

Forty one (58.66%) suspect ADR forms had multiple drugs prescribed and more than one drug was suspected in the causation of the reaction. Therefore causality assessment was done for each of the suspect drug.

Demographic characteristics of patients with suspect ADRs

There were 56 (75%) patients who were above 18 years and

16 (21%) were less than 18 years of age. Data was unavailable for 3 (4%) patients. 44 (59%) were females and 31 (41%) were males.

Type of suspect ADRs

Out of 75 reactions 74 (98.67%) were type B and 1 reaction (1.33%) was type A as shown in (Table 1). The type A reaction observed was with Albendazole 400mg, given orally which produced hypotension. The patient was hospitalised and was recovering at the time of collection of the data.

Expectedness of suspect ADRs

As seen in the (Table 2) there were only 5 unexpected reactions (considered unexpected when the reactions were reported (i.e. as on June 2010). These were due to Gentamicin (intramuscular), Albendazole (oral tablets), Multivitamins (oral, Becosules syrup and Surbex T tablets) and Iron supplements (oral, Fefol tablets).

Severity of suspect ADRs

Sixty four reactions (85.3%) were mild, 4 (5.33%) moderate and 7 (9.33%) were severe in nature as shown in (Figure 1).

Seriousness of reactions

Seven (9.33%) out of 75 reactions were considered serious as they required or prolonged their hospitalisation (Figure 2). The remaining 68 (90.67%) were non-serious and treated on outpatient basis. There was no death due to ADRs. The serious reactions that were observed are shown in (Table 3).

Causality assessment

The causality was assessed for 154 drugs from 75 forms using Naranjo scale. Of these 118 (51%) were possibly related, 36 (49%) were probably related and none were definitely related (Figure 3).

Major classes of drugs implicated in suspect ADRs

The major group of drugs that caused the adverse events was Antimicrobials followed by Non- steroidal anti-inflammatory drugs (Table 4). The most common reactions in our study were cutaneous reactions. Higher percentages of ADRs were noted in patients on combination of drugs. Most commonly implicated group of antibiotics were Cephalosporins, Fluoroquinolones and Penicillins.

Table 1: Types of suspect ADRs classified as per Rawlins and Thomson criteria.

Category	No.	Percentage (%)
Type A (Augmented reaction)	1	1.33
Type B (Bizarre reaction)	74	98.67
Total	75	100

Table 2: Unexpected suspect ADRs observed.

Drug	Reaction
Gentamicin	Morbiliform eruption
Albendazole	Hypotension
Multivitamins (Becosules syrup) (Surbex T tablets)	Maculopapular rashes
Iron supplements	Steven Johnsons syndrome

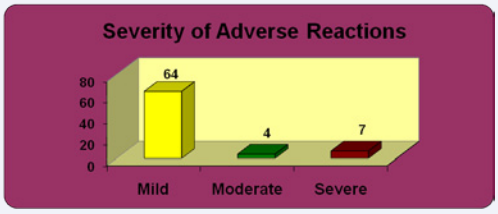

Figure 1 Severity of suspect ADRs.

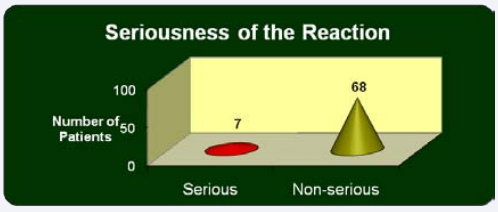

Figure 2 Seriousness of suspect ADRs.

Table 3: Suspect serious ADRs and the implicated drugs with dose and route of administration.

	Drug reaction	Drugs implicated with dose and route of administration	Condition indicated for
1	Morbiliform eruption	Tab. Phenytoin (100mg, PO)	Astrocytoma
2	Haematuria	Tab. Cefixime (*, PO) Tab. Nimesulide (*, PO)	Fever
3	Exanthematous pruritic papular rashes	Inj. Metronidazole (*, IV) Inj. Cefixime (*, IV) Tab. Tramadol (*, PO) Tab. Diclofenac + Serratiopeptidase (*, PO)	Post fissurectomy
4	ACDR with resolving erthroderma	Tab. Phenytoin (100mg, PO)	Not known
5	Hypotension	Tab. Albendazole (400mg, PO)	Not known
6	Steven Johnsons syndrome	Tab. Phenytoin LR 200 (200mg, PO) Tab. Ferrous sulphate + Folic acid (150mg, PO)	Not known
7	Erythematous kerototic pruritic lesion	Tab. Phenytoin (300mg, PO)	Generalised convulsions

*dose is mentioned when available from the suspect ADR forms

DISCUSSION

Adverse drug reaction monitoring is an essential aspect of therapeutics. However most of the time it is overlooked and not considered important. Even when observed, many would not document and report voluntarily. Establishing pharmacovigilance units in the hospitals has facilitated this activity to a great extent.

The number of reports we received were 80, which amounted to an incidence of 0.53% in our set up. In comparison with the study by Mandavi et al and Ramesh et al. [1,3] this can be considered as underreporting. It is a universal problem and many reasons are identified such as busy schedule of clinicians, lack of knowledge about the exact authority to report ADRs to, unavailability of

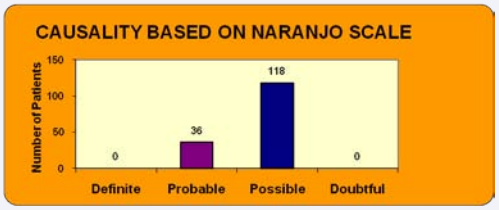

Figure 3 Causality assessment of suspect ADRs.

Table 4: Class of drugs implicated in suspect ADRs.

Class of Drug	No. of events	Percentage (%)
Antimicrobials agents	59	33.31
Antibiotics	56	36.36
Antimalarials	1	0.01
Anthelminthics	1	0.01
Antitubercular	1	0.01
Drugs acting on Cental Nervous System	50	32.46
Analgesics (Oipoids + NSAIDs)	32	20.77
Antiepileptic	18	11.68
Hormones	2	1.29
Corticosteroids	1	0.01
Other hormones	1	0.01
Cardiovascular drugs	2	1.29
Antihypertensives	2	1.29
Others	41	26.62
Total	154	100

ADR reporting forms, lack of incentives, reporting process being tedious and inadequate expertise [14,15]. Our verbal discussions with clinicians revealed similar reasons for underreporting in our institution.

The ultimate aim of spontaneous reporting is to generate data to see whether the reactions are attributable to the drug, if so in what percentage of population and among whom, and what are the risk factors involved etc. To arrive at these, the reports must have a quality data. Incomplete and incorrect entries would make the reports non-usable and thus some valuable information may be lost [16].

In our study we lost 5 reports out of 80 due to incomplete essential information. Further, most of the reports did not have other details like concomitant medication, indications for which they were used, batch number, expiry date etc, because of which most of them fell in the possible category of causality assessment.

The demographic analysis showed female gender predominance over males, which was similar to earlier study by Arulmani et al. [4]. As far as age was concerned, most of the reactions were in the adult group.

Majority of the reports that we received were from department of dermatology. They were either referred from the other clinical departments or came from direct consultation. Therefore the most commonly observed ADRs were cutaneous (Type-B) reactions. This finding is consistent with many studies which have reported a higher percentage of dermatological manifestations than others [17]. Another probable reason for predominant cutaneous reactions is the visibility because of which they are easily diagnosed as suspect drug reactions. On the contrary Type-A reactions are common but may not be reported as they are may have been overlooked.

In our study antibiotics, analgesics and antiepileptics were the most commonly implicated drug classes in causing suspect ADRs. This finding is consistent with the studies reported by Ding WY et al. [18], except that antiepileptic drugs were the second largest class of suspect drugs in their study. Antibiotics accounted for 33.31% of the suspect ADRs which seems to be low in comparison with the study by Padmaja et al. [19] who reported 42.4% among 1250 ADRs reported on an outpatient basis. This difference in our observations could be due to our smaller sample size.

There were seven serious drug reactions. Three reactions were seen with Phenytoin of which two were Steven Johnson's syndrome. All of them needed hospitalisation and were expected reactions.

With regards to causality assessment 51% were probably related and 49% were possibly related. None were definitely related. This value correlated with the fact that in majority of the cases there was polypharmacy. Hence alternate causes are always possible. Moreover many drugs cause cutaneous reactions. Therefore it was difficult to attribute the causality to a definite group of drugs.

CONCLUSION

In the present study most of the adverse drug reactions were due to antimicrobials and analgesics. The causality assessment revealed that all suspect ADRs fell under possible or probable category. The reporting rate appeared to be low. There is a need for increasing the knowledge and awareness to improve the reporting rate. Building awareness in rational drug prescriptions avoiding polypharmacy would help in preventing and in an appropriate diagnosis of a definite ADR.

ACKNOWLEDGEMENT

The authors are thankful to the management of Vydehi Institute of Medical Sciences and Research Centre, Bangalore, the Advisor - Dr. S. Kantha and the Principal for their encouragement and support during the conduct of the study.

Name(s) of sponser(s) of research with grant number: Vydehi Institute of Medical Sciences and Research Centre, Bangalore, India, VIMS & RC/EST/247/2009-10

CONFLICT OF INTEREST STATEMENT

There is no conflict of interest among all the authors.

REFERENCES

1. Mandavi, D'Cruz S, Sachdev A, Tiwari P. Adverse drug reactions & their risk factors among Indian ambulatory elderly patients. Indian J Med Res. 2012; 136: 404-10.

2. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions

in hospitalized patients: a meta-analysis of prospective studies. JAMA. 1998; 279: 1200-5.

3. Ramesh M, Pandit J, Parthasarathi G. Adverse drug reactions in a south Indian hospital--their severity and cost involved. Pharmacoepidemiol Drug Saf. 2003; 12: 687-92.
4. Arulmani R, Rajendran SD, Suresh B. Adverse drug reaction monitoring in a secondary care hospital in South India. Br J Clin Pharmacol. 2008; 65: 210-6.
5. WHO technical report. 2002.
6. Santosh KC, Tragulpiankit P. Pharmacovigilance: an overview. Mahidol University Journal of Pharmaceutical Science. 2011; 38: 1-7.
7. Härmark L, van Grootheest AC. Pharmacovigilance: methods, recent developments and future perspectives. Eur J Clin Pharmacol. 2008; 64: 743-52.
8. Central Drugs Standard Control Organization. Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India.
9. Rawlins MD, Thomson JW. Pathogenesis of adverse drug reactions. In *Textbook of Adverse Reactions*. Davies DM (ed). Oxford University Press: Oxford, 1977: 10
10. Glossary of terms used in Pharmacovigilance.
11. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. Am J Hosp Pharm. 1992; 49: 2229-32.
12. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981; 30: 239-45.
13. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use ich harmonised tripartite guideline;post-approval safety data management: definitions and standards for expedited reporting;e2d -Current Step 4 version;dated 12 November 2003
14. Kamtane AR, Jayawardhani V. Knowledge, attitude and perception of physicians towards adverse drug reaction (adr) reporting: a pharmacoepidemiological study. Asian Journal of Pharmaceutical and Clinical Research. 2012; 5: 210-214.
15. Gupta P, Udupa A. Adverse drug reaction reporting and pharmacovigilance: knowledge, attitudes and perceptions amongst resident doctors. J Pharm Sci & Res. 2011; 3: 1064-1069.
16. Johansson ML, Hägg S, Wallerstedt SM. Impact of information letters on the reporting rate of adverse drug reactions and the quality of the reports: a randomized controlled study. BMC Clin Pharmacol. 2011; 11: 14.
17. Jose J, Rao PG. Pattern of adverse drug reactions notified by spontaneous reporting in an Indian tertiary care teaching hospital. Pharmacol Res. 2006; 54: 226-33.
18. Ding WY, Lee CK, Choon SE. Cutaneous adverse drug reactions seen in a tertiary hospital in Johor, Malaysia. Int J Dermatol. 2010; 49: 834-41.
19. Padmaja U, Adhikari P, Pereira P. A prospective analysis of adverse drug reactions in a south indian hospital. Online J Health Allied Scs. 2009; 8: 12.

Cite this article

Swamy S, Bhanuprakash, Nadig P, Muralimohan, Shetty M (2013) Profile of Suspect Adverse Drug Reactions in a Teaching Tertiary Care Hospital. J Pharmacol Clin Toxicol 1(1): 1005.