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Incidence of Adverse Drug Reactions in a Tertiary Care Hospital: A Systematic Review and Meta-Analysis of Prospective Studies

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Abstract

To study the incidence of adverse drug reactions in a tertiary care hospital and to determine the drugs which cause adverse drug reactions, the age group and sex commonly affected in outpatients and inpatients. A systematic review of studies on ADRs in hospitalized patients, inpatients and outpatients, on ADRs causing hospital admissions were performed. Studies were identified through a search of the MEDLINE and EMBASE databases. The inclusion criteria required that the population was not selected for particular conditions or drug exposure and prospective monitoring was used for identifying ADRs. Data were analysed by a random-effects model. A total number of 50 patients with adverse drug reactions (ADRs) were reported in the present study. Maximum number of adverse drug reactions were observed with NSAIDs. Out of 50 patients, 16 developed ADRs with different NSAIDs, which were 32%. 26% of patients had adverse drug reaction with antibiotics, which included 13 patients. 4 cases with anti-tubercular drug (8%), 3 cases with anticancer drugs (6%), one case each with anti-covulsant, antiviral, anti-diabetic and antihypertensive drug (2% each), and 10 patients developed ADRs with herbal drugs which was 20%. The results shown that ADRs in patients are a significant public health issue. The accuracy of prescription reporting as well as clinical information from studies was a rarity, making it difficult for healthcare practitioners to implement evidence based preventive strategies. Further, methodologically sound drug surveillance studies are necessary for an effective promotion of a safer use of drugs.

Keywords: adverse drug reactions, patient, meta-analysis, prospective studies, systematic review.

INTRODUCTION

According to the world health organization an adverse drug reaction is defined as any noxious, unintended, and undesired effect of drug, which occurs at doses used in humans for prophylaxis,

diagnosis, or therapy [1]. This includes reaction due to overdose, predictable side-effects, and unanticipated adverse manifestations. The safety of drug prescribing has become a highly visible topic in adult medicine, due in part to research suggesting that there are important ADRs caused by commonly used medications [2]. Patients constitute a vulnerable group with regard to rational drug prescribing since many new drugs are released onto the market without the benefit of even limited experience [3]. This deficiency causes practitioner to often prescribe drugs in an 'off-label' manner, thereby increasing the risk of drug toxicity [4].

Adverse effects may be local or systemic, where a medication has caused adverse effects through the systemic effects, although they are administered locally as eye drops, since a fraction escapes to the systemic circulation [5]. As more drugs are marketed and as more individuals take multiple drugs, the occurrence of adverse drug reaction will probably continue to increase. Therefore, better approaches must be devised for reporting and assessment and management of individuals who present with drug induced diseases [6]. The incidence of adverse drug reaction varies from 6-15%[8] to 30% [7] with at least 90 million courses of drug treatment given yearly in the USA [8]. The reported percentage of patients who develops an adverse drug reaction during hospitalization varies markedly in different studies from 1.5% to 44% [9]. Although in most studies the incidence is about 10 to 20% [10] about 3 to 8% of hospital admissions are a consequence of adverse drug reactions [11, 12].

A large number of new drugs are launched every year. Further, there is limited information on the market penetration of new drugs and on their rational and safe prescribing. Studies of adverse drug reactions have been reported rarely in India attempts to monitor ADRs have been made only during the past one decade. Still there is need for a national policy and concerted efforts by dedicated workers to identify which drugs and safe or not safe for our population. This study was designed to report the incidence of hospital inpatients and outpatients with adverse drug reactions.

MATERIALS AND METHODS

Identification of relevant literature

The English and foreign-language medical literature was searched using the Medline (from January 1966 to May 2000) and Embase (from January 1988 to May 2000) databases. The search strategy employed the following keywords: ('adverse drug reaction reporting system' or 'drug therapy/adverse effects' or 'pharmaceutical preparations/adverse effects') and 'prospective studies'. The references of the retrieved studies and of published reviews on ADRs in patients found via a manual search of various journals were examined in order to identify additional appropriate studies. The following criteria were used for considering studies in the review: the patients studied were not selected for particular conditions or specific drug exposures, prospective monitoring was used to identify ADRs, and sufficient information was reported to calculate their incidence.

Data abstraction

The present study was started in the month of November 2007 and completed in the month of April 2008. It was conducted in Osmaina General Hospital, Hyderabad.

The inpatients and outpatients with adverse drug reactions were included in the study. Complete details of the cases with present and past history of the drug intake, past history of allergic reactions, previous drug reactions, type of drug reactions, investigations done and the treatment given to the patients were recorded in the case record form.

Statistical Analysis: Data was expressed as number of cases and percentage of cases involved in various ADRs, as shown in table 1 and figure 1.

Data synthesis

We used a random-effects model to perform the analysis in order to take into account the heterogeneity of the various studies [13]. Briefly, the measured incidence of each study is considered to be a random variable with a total variance given by the sum of a within-study term and unknown between-study term (accounting for heterogeneity between studies). Separated pooled incidences were obtained for ADRs that occurred in hospitalized patient, in patient admitted to the hospital due to ADRs, and in general outpatients. This covariate was chosen as it was the only available information reported in most studies in the hospital setting.

RESULTS

A total number of 50 patients with adverse drug reactions (ADRs) were reported in the present study. The demographic data of these patients are presented in the Table-3, were 16 males and 34 females included. The age of males ranged from 12-80 years and females 12-68 years. 43 inpatients and 7 outpatients were included in the study. The duration of study was for 5 months.

Number of adverse drug reactions associated with drugs:

Maximum number of adverse drug reactions were observed with NSAIDs. Out of 50 patients, 16 developed ADRs with different NSAIDs which were 32%. 26% of patients had adverse drug reaction with antibiotics, which included 13 patients. 4 cases with anti-tubercular drug (8%), 3 cases with anticancer drugs (6%), one case each with anti-covulsant, antiviral, anti-diabetic and antihypertensive drug (2% each), and 10 patients developed ADRs with herbal drugs which was 20%.

Table 1. The number of cases and percentage of adverse drug reactions with patients are as follows

Sl. No.	Adverse drug reactions	Number of cases	Percentage
1	Cutaneous ADRs	31	62%
2	Hepatotoxicity	07	14%
3	Nephrotoxicity	04	08%
4	Gastrointestinal ADRs	05	10%
5	Blood dyscrasias	02	04%
6	Anaphylaxis	01	02%
		50	**100%**

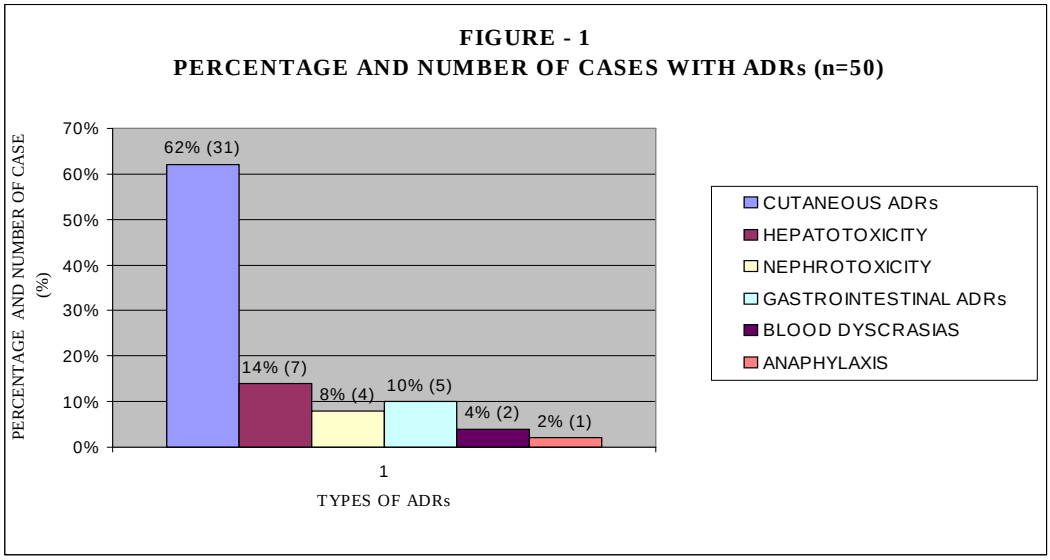

Fig. 1 Percentage and number of cases with adverse drug reaction

Adverse drug reactions with different drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs)

A total of 4 cases of ADRs were observed with Ibuprofen. 2 patients developed urticarial rash. It was observed that 4 cases with Nimesuldie, each presented with purpura, pemphigus vulgaris, Steven Johnson Syndrome and exanthematous reaction. Aspirin induced hematemesis was observed in 2 patients and malena in 2 patients and one case of gastritis was reported with aspirin intake. Two cases of urticaria and one case of hepatitis was noted with oral intake of Diclofenac sodium. Urticaria was seen with Mefenamic acid and hepatomegaly along with Jaundice with Acetaminophen.

Antibiotics

Fluoroquinolones

Adverse drug reactions were observed with Ofloxacin, Ciprofloxacin, Sparfloxacin and Norfloxacin. Cutaneous drug reactions were observed with these drugs. Fixed drug eruption and erythema mutltiforme was seen with Ofloxacin in each patient. It was observed that Ciprofloxacin, induced papular urticaria, Norfloxcion induced pemphigus vulgaris and Sparfloxacion induced eczematous reaction in each case.

Sulfonamides

Steven Johnson Syndrome was observed in one patient with Co-trimoxazole and one patient had erythema multiforme after Trimethoprim ingestion.

Beta Lactam antibiotics

Ampicillin induced pemphigus vulgaris was seen in one patient, Amoxicillin induced eczematous rash was observed. In one patient erythematous eruption was developed due to Cefotaxime on oral administration.

Erythromycin: Pustular dermatitis with erythromycin was seen in one patient.

Tetracycline: It produced Steven Johnson Syndrome in one patient.

Anti-tubercular Drugs
Isoniazid and Rifampicin were the anti-tubercular drugs which produced ADRs. Isoniazid produced jaundice in 2 patients and one patient had thrombocytopenic purpura. One patient on Rifampicin and Isoniazid combination developed hepatic failure.

Anticancer drugs
One patient developed bone marrow depression with Methotrexate treatment. Cyclophosphamide produced pemphigus vulgaris in one patient and Chlorambucil induced purpura was observed in one patient.

Anticonvulsants
One patient presented with jaundice, who was on phenytoin sodium.

Antiviral Drugs :
Lamivudine induced gastritis was seen in one case.

Anti-diabetic Drugs :
It was observed that Steven Johnson syndrome in one case, who was on insulin.

Antihypertensive agents :
Nephropathy was seen in one patient, who was on Enalapril.

Herbal drugs :
Ten cases of ADRs were reported due to intake of herbal medicines. 2 patients presented with pemphigus vulgaris, one patient had lupus nephritis, one patient developed hematamesis and malena, one patient with tubular nephritis, one with glomerulonephritis, two cases of urticaria, one case of hepatitis and one case presented with exfoliative dermatitis.

Table 2. Age group with adverse drug reactions (n=50)

AGE GROUP	NUMBER OF CASES
10-20	10 Cases
21-30	13 Cases
31-40	10 Cases
41-50	08 Cases
51-60	05 Cases
61-70	03 Cases
71-80	01 Case

All the cases were treated satisfactorily and no deaths were reported.

All the adverse drug reactions with individual drugs are shown in Table-4 and 6.
Patients with severe type of reactions who were admitted in the hospital were 43 (Table 3), which included fixed drug eruption 2, pemphigus vulgaris 6, erythematous reaction 1, exanthematous reaction 1, Steven Johnson Syndrome 4, urticaria 3, eczematous reaction 1, pustular dermatitis 1, lupus erythema multiforme 2. Purpura 2, hepatotoxicity 7, nephrotoxicity 4, gastrointestinal ADRs 5, blood dyscrasias 2, anaphylactic reaction 1.

7 patients with adverse drug reactions were reported in outpatient clinic which included urticaria 5, eczematous reaction 1, exfoliative dermatitis 1, (Table-3).
Out of fifty cases females were 34 (68%) and males were 16 (32%), (Table 3).

Table 3. Demographic data (n=50)

CHARACTERISTICS	NUMBER	PERCENTAGE
Males	16	32%
Females	34	68 %
Age (years)	12-80	-
Inpatients	43	86%
Outpatients	07	14%

Table 4. Group of drugs invovled in adverse drug reactions (n=50)

Sl. No	Drugs	Number of Cases	Total	Percentage %
1.	**NSAIDs :**			
	a) Ibuprofen	4		
	b) Nimesulide	4		
	c) Diclofenac sodium	3	16	32%
	d) Aspirin	3		
	e) Acetaminophen	1		
	f) Mefenamic acid	1		
2.	**Antibiotics :**			
	a) Co-trimoxazole	1		
	b) Trimethoprim	1		
	c) Ofloxacin	2		
	d) Ciprofloxacin	1		
	e) Sparfloxacin	1		
	f) Norfloxacin	1	13	26%
	g) Cefotaxime	1		
	h) Procaine penicillin	1		
	i) Ampicillin	1		
	j) Amoxicillin	1		
	k) Erythromycin	1		
	l) Tetracycline	1		
3.	**Anti tubercular drugs :**			
	a) Isoniazid	3	4	8%
	b) Rifampicin	1		
4.	**Anti cancer drugs :**			
	a) Methotrexate	1		
	b) Cyclophosphamide	1	3	6%
	c) Chlorambucil	1		
5.	**Anti convulsants :**			
	Phenytoin sodium	1	1	2%

6.	**Anti viral drugs :** Lamivudine	1	1	2%
7.	**Anti diabetic drugs :** Insulin	1	1	2%
8.	**Anti hypertensive agents :** Enalapril	1	1	2%
9.	**Herbal drugs**	10	10	20%

Table 5a. Percentage of adverse drug reactions (n=50)

Sl. No	ADVERSE DRUG REACTION	DRUG INVOVLED	NO. OF CASES	TOTAL NO. OF CASES	PERCEN TAGE %	TOTAL %
1. A)	**CUTANEOUS ADRS:** Fixed drug eruption	a) Ibuprofen b) Ofloxacin	1 1	2	4%	62 %
B)	Pemphigus vulgaris	a) Nimesulide b) Norfloxacin c) Cyclophosphamide d) Ampicillin e) Herbal drugs	1 1 1 1 2	6	12%	
C)	Erythematous reaction	Cefotaxime	1	1	2%	
D)	Exanthematous reaction	Nimesulide	1	1	2%	
E)	Steven Johnson Syndrome	a) Nimesulide b) Insulin c) Co- trimoxazole d) Tetracycline	1 1 1 1	4	8%	
F)	Urticaria	a) Ibuprofen b) Diclofenac sodium c) Mefenamic acid d) Ciprofloxacin e) Herbal drugs	2 2 1 1 2	8	16%	
G)	Eczematous reaction	a) Amoxicillin b) Sparfloxacin	1 1	2	4%	
H)	Pustular dermatitis	Erythromycin	1	1	2%	
I)	Exfoliative dermatitis	Herbal drugs	1	1	2%	
J)	Lupus erythematosus	Ibuprofen	1	1	2%	
K)	Erythema multiforme	Trimethoprim Ofloxacin	1 1	2	4%	
L)	Purpura	Nimesulide Chlorambucil	1 1	2	4%	

Table 5 b. Percentage of adverse drug reactions (n=50)

Sl. No	Adverse drug reaction	Drug Involved	Number of Cases	Total No of cases	Percentage %	Total %
1. A)	**Hepatotoxicity :** Jaundice	a) Isoniazid b) Phenytoin	2 1	3	6%	14%
B)	Hepatomegaly with jaundice	Acetaminophen	1	1	2%	
C)	Hepatitis	a) Diclofenac b) Herbal drug	1 1	2	4%	
D)	Hepatic failure	Rifampicin	1	1	2%	
2. A)	**Nephrotoxicity :** Glomerulonephritis	Herbal drug	1	1	2%	8%
B)	Tubular nephritis	Herbal drug	1	1	2%	
C)	Lupus nephritis	Herbal drug	1	1	2%	
D)	Nephropathy	Herbal drug	1	1	2%	
3. A)	**Gastrointestinal ADRs :** Gastritis	Lamivudine	1	1	2%	10%
B)	Heamtemesis and malena	a) Aspirin b) Herbal drug	1 1	2	4%	
C)	Gastritis and malena	Aspirin	1	1	2%	
D)	Hematemesis	Aspirin	1	1	2%	
4. A)	**Blood dyscrasias :** Bone marrow depression	Methotrexate	1	1	2%	4%
B)	Thrombocytopenic purpura	Isoniazid			2%	
5.	**Anaphylaxis**	Procaine penicillin	1	1	2%	2%

Table 6. Adverse reactions with individual drug (n=50)

Sl. No	DRUG	Adverse Drug reaction	Number of Cases
1.	Ibuprofen	Fixed drug eruption Urticaria Lupus erythematosus	1 2 1
2.	Nimesulide	Purpura Pemphigus vulgaris Steven Johnson Syndrome Exanthematous reaction	1 1 1 1
3.	Diclofenac sodium	Hepatitis Urticaria	1 2
4.	Aspirin	Gastritis and malena Hematemesis and malena Hematemesis	1 1 1
5.	Acetaminophen	Hepatomegaly with jaundice	1
6.	Mefenamic acid	Urticaria	1
7.	Co-trimoxazole	Steven Johnson Syndrome	1

8.	Trimethoprim	Erythema multiforme	1
9.	Ofloxacin	Fixed drug eruption Erythema multiforme	1 1
10.	Ciprorofloxacin	Urticaria	1
11.	Sparfloxacin	Eczematous reaction	1
12.	Norfloxacin	Pemphigus vulgaris	1
13.	Cefotaxime	Eryghematour reaction	1
14.	Procaine penicillin	Anaphylaxis	1
15.	Ampicillin	Pemphigus vulgaris	1
16.	Amoxicillin	Eczematous reaction	1
17.	Erythromycin	Pustular dermatitis	1
18.	Tetracycline	Steven Johnson Syndrome	1
19.	Isoniazid	Jaundice Thrombocytopenic purpura	2 1
20.	Rifampicin	Hepatic failure	1
21.	Methotrexate	Bone marrow depression	1
22.	Cyclophosphamide	Pemphigus vulgaris	1
23.	Chlorambucil	Purpura	1
24.	Phenytoin sodium	Jaundice	1
25.	Lamivudine	Gastritis	1
26.	Insulin	Steven Johnson Syndrome	1
27.	Enalapril	Nephropathy	1
28.	Herbal drugs	Urticaria Pemphigus vulgaris Hematemesis and malena Glomerulonephritis Tubulonephritis Lupus nephritis Hepatitis Exfoliative dermatitis	2 2 1 1 1 1 1 1

Table 7. Life- threatening adverse drug reactions

SL. NO	ADVERSE DRUG REACTION	NUMBER OF CASES
1.	Nimesulide induced Steven Johnson Syndrome	1
2.	Co-trimoxazole induced Steven Johnson Syndrome	1
3.	Insulin induced Steven Johnson Syndrome	1
4.	Tetracycline induced Steven Johnson Syndrome	1
5.	Herbal drug induced Exfoliative dermatitis	1
6.	Cyclophosphamide induced Pemphigus vulgaris	1
7.	Procaine penicillin induced Anaphylactic reaction	1
8.	Herbal drug induced Lupus nephritis	1

DISCUSSION

Adverse drug reactions contribute significantly to patient's morbidity and mortality and are significant public health concern [14, 15].

In the present study majority of patients affected by ADRs were from adult population (21-60 years) which was 72%. Previous study conducted by Joshua Lisha et. al. reported 72% of ADRs in adult population [16], which was similar to this study (Table 2).

Women have been reported to be at a greater risk for ADRs (68%) in this study. Where as in the previous study reported that 74.1% of ADRs in women population [17] (Table 3).

The most common organ system Associated with ADRs was skin, which was 62% in this study. A previous North Indian study reported cutaneous drug reactions are responsible for the majority of ADRs in hospitalized patients [18]. Rash was the clinical manifestation of skin reaction reported in this study. Several studies reported that rash was frequently occurred skin reactions [19] (Table 1, Figure 1).

The frequency of ADRs in hospitalized patients in this study was 3.5% which is similar to previous studies, which showed 3.4-3.7% of ADRs in hospitalized patients [20]. In another study conducted previously, reported that consequences of ADRs were 3-8% of hospital admissions [21], supporting this study.

In this study we observed that occurrence of life-threatening ADRs was 16% (Table-7), which seems to be higher when compared to that cited in previously published report, which was 10% [22].

In the present study, NSAIDs, antimicrobials, herbal and anti-tubercular agents were the most commonly implicated drug, which probably reflects their widespread use.

In this study, administration of NSAIDs showed 6% of gastrointestinal reactions (Gastritis, Hematemesis and Malena), whereas in the previous study it was 5% [23].

The study conducted previously reported that anti-tubercular drug-induced hepatotoxicity was found to be 8% [24]. Similarly in this study we observed that hepatotoxicity with isoniazid and rifampicin (anti-tubercular drugs) was 8%.

Two out of 50 cases of blood dyscrasias were reported in this study accounting for 4%, whereas study conducted in Sweden showed that hematological complications were about 10% of all reports to the ADR committee [25]. Whereas in this hospital, incidence of blood dyscrasias was less when compared to Sweden study.

Anaphylactic reaction due to penicillin was seen in one patient out of 50 cases (2%). It has been reported that up to 27 million people (0.7% to 10%) are allergic to penicillin administration. Therefore the incidence rate of allergic reaction to penicillin in this study is in consistent with the previous report given by Boston collaborative drug surveillance program [26].

The present study showed that incidence of total ADRs in this hospital was 4.1%, which was comparable with previous studies reported. Their studies showed 1.5 - 44% and 3 - 8% of total ADRs in hospital.

Total inpatients with ADRs in this hospital were 86% and the outpatient cases reported with ADRs were 14% (Table 3). As it is a referral hospital, the numbers of cases were referred from various district and peripheral health centers, therefore we have encountered more number of severe ADRs, which required admission.

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