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Original Article:

A Prospective Analysis of Adverse Drug Reactions in a South Indian Hospital

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Abstract:
Adverse drug reactions are a great cause of concern to the medical profession, the patients and the pharmaceutical industry. However ADR reporting and monitoring is yet to catch up in India. Hence we undertook a study to record and analyze adverse reactions among all patients admitted to the medical wards of a tertiary care. Centre patients admitted to all medical wards over one year were assessed for ADRs throughout their admission. Suspected ADRs were recorded and analyzed for i) the type of reaction ii) severity iii) Consequence on treatment that is if the drug was continued, or stopped, or needed to be treated with other drugs, iv) Physiological system involved and the v) group of the drugs associated with ADRs. Among 1250 patients admitted during the study period, 250 adverse events were observed. Majority (76.8%) were of mild type, 66% were severe requiring intensive care and 3 patients died. Antimicrobials were responsible for maximum (42.4%) ADRs followed by drugs acting on CNS (20%). When we analyzed the systems affected, CNS side effects were more common in our study. While in many other studies Cardiovascular and gastrointestinal side effects were the most common. Combination of drugs was responsible for a large percentage of ADRs. Inadvertent use of antipsychotics with sedatives led to respiratory failure in 4 patients of which 1 died. Contaminated IV fluids are suspected to be the cause of death in another fatal ADR. In conclusion there is a need for vigilant ADR monitoring to be done by all doctors to prevent morbidity and mortality from ADRs.
Key Words: Adverse drug reactions, Monitoring, Antimicrobials, Combination of drugs, Hospital

Introduction:

There is general agreement that drugs prescribed for disease are often themselves the cause of a serious amount of disease (adverse reactions) ranging from mere inconvenience to permanent disability and death. Since drugs are intended to relieve suffering, patients find it particularly offensive that they can also cause disease.

It is estimated that adverse reactions cause 2–3 % of consultations in general practice, upto 3% of admissions to intensive care units and 0.3% of general hospital admissions are due to adverse drug reactions (ADR).[1] A recent study done in Sweden has implicated ADRs as the 7th most common cause of death.[2] Another study involving 19,000 admissions has shown that 6.5% of patient admissions were related to an ADR.[3] Data from older studies on ADRs occurring in in-patients have suggested that 10-20% of patients experience ADRs in hospital.[4]However these studies are decades old and with an increase in life expectancy and development in medicine over the years, there is a need for more data on the ADR in hospital in-patients.

Though ADRs are of great concern to the general public, the medical profession, the pharmaceutical industry and the regulatory authorities, the concept of ADR reporting is still new in India. There are very few centres in India to monitor ADRs and hardly any detailed ADR surveys done in India are published.[8–12] Hence a study was undertaken to record and analyze all adverse reactions among hospitalized patients in the medical wards of a tertiary care hospital in Mangalore, a South Indian city.

Patients and Methods:

A total of 1250 patients admitted to the medical wards of Kasturba Medical College Hospital, Attavar, Mangalore, for a period of 1 year were observed for possible ADRs, as per W.H.O. definition. W.H.O. has defined ADR as a noxious or unintended response to a drug which occurs at doses normally used in humans for prophylaxis, diagnosis or treatment of a disease or for modifying the physiological function.[13] However the term adverse event is now frequently used to describe any untoward medical occurrence that may be present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with the treatment.[14] ADRs were identified by 2 physicians and confirmed by a clinical pharmacologist. When there were doubts/disagreements, such cases were not included. ADRs that occurred outside the hospital and got admitted in our hospital were also included. Those who were identified to have ADRs were examined and the details recorded in a proforma, where details of the drugs taken, observed reactions, measures taken for untoward reactions, investigations and response to measures were recorded.

The results were analyzed under the following headings:

1. Type A or Type B reaction[1]
2. Severity
3. Consequence of ADR
4. Types of reactions based on the system involved.
5. Groups of drugs commonly associated with ADR
6. Type of reactions and drugs commonly associated with it.

1. **Type A or augmented reactions** are those that will occur in everyone if enough of the drug is given because they are due to excess of normal, predictable, dose related pharmacodynamic effects of a drug.

Type B or bizarre reactions are those that are not part of normal pharmacology of the drug, are not dose related and care due to unusual attributes of the patient interacting with the drug. The class includes idiosyncrasies and immunological processes and amount for most fatalities.

2. **Severity of ADR** – Mild adverse reactions were defined as those which did not by itself require prolongation of hospitalization and could be managed by simple measures, moderate were those ADRs which needed prolongation of hospital stay of the patient for treatment of the same and severe were life threatening ADRs.

3. **Consequences of ADRs** were recorded under the following headings -

1. The patient continued the drug
2. The dose had to be reduced
3. The drug had to be stopped/withdrawn
4. Another or more drugs were needed to treat an adverse event.

4. **Systems involved** – Reactions were classified according to the system involved i.e., percentage of involvement of different systems. Eg. Cardiovascular system, central nervous system

5. **Group of the offending drug** – Drugs were classified according to groups and frequency of ADRs noted in each group.

6. **Details of types of reactions** – Type of reaction noted and the drugs commonly associated with the same were also recorded.

Results:

A total of 250 adverse events were observed and recorded during the study period.

Type of adverse event – Table 1 shows the Types of reactions

Table 1: Analysis Of Adverse Reactions

Category	No	Percentage
Type A (Augmented reactions)	80	32%
Type B (Bizarre reactions)	170	68%
Total	**250**	**100%**

Severity (Table 2): We found a large fraction of ADRs (76.8%) to be of mild type while 17.2% of the reactions were of moderate type requiring prolongation of hospital stay of the patient for the treatment of the event. Six percent of the reactions were severe requiring intensive care and 3 patients (1.2%) died as a consequence of these events. Details of moderate and severe reactions are mentioned in Table 3 and 4 respectively.

Table 2: Analysis Of Adverse Reactions Based On The Severity

ADE Severity	No	Percentage
Mild	192	76.8%
Moderate	43	17.2%
Severe		
Those requiring intensive care	12	4.8%
Death due to ADR	3	1.2%
Total	**250**	**100%**

Table 3: Moderate Reactions That Needed Prolonged Hospitalization

Types of reaction	Offending drug	Number
I Neurological		
a. Extrapyramidal reactions	Haloperidol	2
	Chloroquine + metoclopramide*	4
b. Convulsions	Prochlorperazine	1
	Chloroquine	3
c. Psychosis	Lithium	1
	Theophylline*+ ciprofloxacin	1
	Lignocaine IV	1
	Chloroquine	4
	Corticosteroids	1
	Levodopa* + trihexiphenidyl	2
	Ranitidine	1
	Ciprofloxacin	2
Total		**23**
II Cardio vascular		
a. AV Block	Quinine	1
b. Q-Tc prolongation	Quinine	1
c. Ventricular bigemini	Digoxin	1
d. Multiple ectopics	Theophylline*+ salbutamol	3
e. Unstable angina	Pentoxyphylline	1
Total		**7**
III Gastro intestinal		
a. GI Haemorrhage	Aspirin * + ibuprofen*	1
	Aspirin	2
b. Toxic hepatitis	INH * + rifampicin*+ pyrazinamide*	3
IV Dermatological		
Exfoliative dermatitis	Phenytoin	2
V Respiratory		
Pulmonary tuberculosis	Long term corticosteroids	1
VI Endocrine		
Hypoglycemia	Sulphonylurea	2
	Quinine	1
Severe Hyperglycemia	Long term corticosteroids	1
Gynacomastia	Spironolactone	2
* probable offending drug		

Table 4: Analysis Of Severe Reactions (Life Threatening)

Types of reaction	Offending drugs	Number
Haematological		
Aplasia	Carbamazepine	1
	Busulphan	1
Massive haemorrhage	Warfarin * + ibuprofen	1
	Prednisolone * + diclofenac*	1
Respiratory failure	Haloperidol + lorazepam*	1
	Diazepam	2
	Haloperidol + diazepam*	1
Acute Renal Failure	Gentamicin	1
	Naproxen	1
Acute Pancreatitis	Etoposide	1
Cardiac arrhythmias	Theophylline* + norfloxacin	1
	Theophylline* + salbutamol	1
Angioneurotic oedema	Diclofenac	1
Anaphylaxis	Contaminated IV fluid	1
Stevens Johnson syndrome	Sulfonamide, Haloperidol + lorazepam	1
	Total	**16**
* probable offending drug		

Details of ADR death:

Case 1: Elderly female of 70 years was prescribed corticosteroids for radiation pneumonitis which she developed following treatment of carcinoma breast. She was initially given a high dose of 60 mg/day prednisolone which was tapered to a maintenance dose of 10 mg/day. She developed acute abdominal pain and relatives gave diclofenac 1 tab thrice a day on day 1 and 2 tablets thrice a day on day 2. She died of massive upper gastrointestinal haemorrhage.

Case 2: A young girl (18 yrs) was admitted for ibuprofen (for chondritis costo) induced gastritis and persistent vomiting. Intravenous fluids were started, and the patient developed stridor, hypotension and suddenly died. Autopsy did not reveal any other cause of death. Presumed cause of death was intravenous fluid induced anaphylaxis, as same batch of fluids was found to be contaminated with fungi.

Case 3: An elderly male of 70 with COPD developed restlessness and hallucinations following intravenous ciprofloxacin for lower respiratory infection. He was sedated with diazepam (10 mg). The patient developed severe type II respiratory failure.

Consequence of ADR: Table 5 shows the effect of ADR on the treatment of the primary disease.

Table 5: Consequence of ADR on The Treatment of Primary Disease

Consequence	No.	Percentage
Patient continued the drug	62	24.8%
Dose had to be reduced	56	22.4%
Drug had to be stopped	122	48.8%
ADR developed after stopping the drug	10	4.0
Total	**250**	**100%**
ADR needed treatment with other drugs	**75**	**30%**

Classes of drugs: When we analyzed the classes of drugs responsible for adverse events in the order of their frequency, we found that antimicrobial agents including antimalarials were the drugs which caused maximum number of adverse effects (Table 6). Anticancer drug related effects were only 4% because we have a separate unit for treatment of cancers. Among the hormones, most frequent offending agents were corticosteroids.

Table 6: Adverse Events According to Class of Drug Involved

Drug class	No of events	Weighted Percentage
Antimicrobial agents	**106**	**42.4%**
Antimalarials	70	
Antibiotics	23	
Antitubercular drugs	13	
Drugs acting on central nervous system	**50**	**20%**
Antipsychotics	18	
Analgesics	14	
Antiseizure	8	
Sedatives	7	
Antiparkinsonian	3	
Hormones	**31**	**12.4%**
Corticosteroids	24	
Other hormones	7	
Cardiovascular drugs	**20**	**8%**
Antihypertensives	13	
Antianginal	5	
Antiarrhythmics	1	
Digoxin	1	
Others		
Respiratory system	18	7.2%
Diuretics	7	2.8%
Water for injection	6	2.4%
Anticancer drugs	4	1.6%
Anticoagulants	4	1.6%
Miscellaneous	4	1.6%
Total	**250**	**100%**

Systems involved: Table 7 shows the systems affected and the number of patients affected. Table 8 shows the type of reaction under each system and the offending drugs that were associated with the same.

Table 8: System wise Classification Of 250 ADRs With The Possible Offending Drugs	
I Central Nervous System	
a) Headache	Nitrates, chloroquine
b) Insomnia	Chloroquine, trihexyphenidyl, prednisolone
c) Psychosis	Chloroquine, levodopa, trihexyphenidyl, prednisolone, ranitidine, ciprofloxacin & methyldopa
d) Depression	Chloroquine, reserpine & methyldopa
e) Convulsions	Chloroquine, levodopa, lignocaine, theophylline
f) Respiratory depression	Diazepam, chloropromazine, haloperidol, lorazepam
g) Ptosis	Diazepam
h) Dysarthria	Diazepam, chloropromazine
i) Extrapyramidal Reactions	Chloroquine, metoclopromide, haloperidol, chloropromazine
j) Ataxia, nystagmus	Carbanazepine
k) tingling, numbness	Enalapril
II Cardiovascular System	
a. Angina	Pentoxyphylline
b. Arrhythmias	Digoxin, theophylline, salbutamol, quinine, chloroquine
c. AV block	Quinine
d. Oedema	Nifedipine, prednisolone
e. Hypotension	Enalapril
f. Hypertension	Corticosteroids
III Gastro – intestinal system	
a. Gastro intestinal haemorrhage	Aspirin, dicofenac, ibuprofen, warfarin, prednisolone
b. Nausea, Vomiting, dyspepsia	Cotrimoxazole, erythromycin, pyrazinamide, Chloroquine, griseofulvin, rifampicin, ramipril, theophylline, diclofenac, prednisolone
c) Hepatitis	INH, rifampicin, pyrazinamide, ticlopidine
d) Acute Pancreatitis	Etoposide
e) Diarrhoea	Amoxycilline, warfarin
f) Loss of appetite	Tinidazole
g) Dry mouth	Imipramine
h) Gingival hyperplasia	Phenytoin
i) Oral ulcers	Diclofenac
IV Renal	
a. Dysuria	Trihexyphenidyl
b. Nephropathy	Diclofenac, gentamicin
c. Incontinence & Polyuria	Lithium
V Dermatological	
a) Pruritus	Erythromycin, spironolactone, Ampicillin, Ibuprofen, Ciprofloxacin, vitamin injection, phenolphthalein, salbutamol,cotrimoxazole, metronidazole, INH, rifampicin, nifedipine, insulin, cloxacillin, Chloroquine, doxycycline, theophylline
b) Rashes	Erythromycin, Ibuprofen, Ampicillin, paracetamol, Ciprofloxacin, theophylline, ozothine, Chloroquine, primaquine, cotrimoxazole
c) Pigmentation	Busulphan
d) Acne	Prednisolone
e) Erythema Multiformae	Sulpha, Haloperidol, Chlorpromazine, Lithium, carbanazepine
f) Exfoliative dermatitis	Phenytoin, Phenobarbitone, Doxycycline, Sulpha
VI Haematological	
Pancytopenia	Busulphan, carbanazepine
Petechiae & purpura	Rifampicin, Prednisolone
VII Musculoskeletal System	
a. Cramps	Triamterene, Thiazides, Chloroquine
b. Myopathy	Corticosteroids, chloroquine
c) Arthralgia	Pyrazinamide
d) Muscle tremors	Salbutamol, theophylline
VII Multisystem involvement	
a. Anaphylaxis	Penicillin, Ozothine, Intravenous fluid
b. Angio – oedema	Ciprofloxacin, metronidazole
c. Febrile reactions	Water for injection

Previously unreported ADRs

1. Etoposide induced pancreatitis: An adult male (35 yrs) suffering from seminoma testis was treated with etoposide as part of a multidrug regimen. With the first dose of etoposide, patient developed acute pancreatitis. Etoposide was stopped and the patient recovered. But, etoposide was repeated as part of the regimen following which pancreatitis developed again. This established the cause - effect relationship beyond reasonable doubt as 'definite' (rechallenge). The drug was never repeated in the patient. The case has been reported[15].

2. IV fluids induced anaphylaxis: Though reactions to intravenous fluids have been mentioned in the literature, to the best of our knowledge, no cases of intravenous fluid induced anaphylaxis have been reported. The current practices of using delicate containers make them more susceptible to damage and lead to contamination. A case has been described above.

Discussion:

Adverse drug reactions are a common occurrence, but are often not recognized. Even if they are recognized they are under-reported as many physicians are unaware that clinically important ADRs should be reported to ADRs monitoring centres. In our series of 1250 hospitalized patients we found a high incidence of ADR 16.66% of which 1.2% were fatal ADRs. In a meta analysis of all prospective studies of ADRs in US hospitals[16] by Lazarou et al an overall incidence of 15.1% ADR was detected of which 6.7% were serious ADRs with a fatal ADR incidence of 0.32%. Our results are comparable.

The majority of our reactions were Type B reactions (68%) which indicate that most of our reactions were inevitable and unavoidable in contrast to the meta analysis by Lazarou et al[16], where 76.2% were Type A reactions. The cause for this discrepancy may be due to inclusion of large number of reactions to antimalarials and other antimicrobials (42.4%) in our set up.

Majority of our patients had mild reactions while 23.2% of cases had moderate to severe reactions of which 6% had serious reactions and of them 1.2% were fatal. Various other studies have quoted an incidence of serious ADRs to be 0 - 20% with a fatality rate of 0 – 0.8%. Table 9 shows various studies of ADRs on the incidence and severity and their comparison with the present study. A pilot study of 125 in-patients done in UK showed that 19% of patients suffered from ADRs with patients spending 6.5 days longer in hospital than those without ADRs.[17] However many of the studies have included only patients admitted to the hospitals for ADR or patients who developed ADR after admission to the hospital. Our study has included both the groups.

It is interesting to note that 30% of ADRs had to be treated with another drug adding to the cost of therapy and prolonging hospitalization. Cassen et al[18] have proved in a study that attributable lengths of stay and costs of hospitalization for ADRs are substantial and they have also concluded that it is responsible for 2 fold increased risk of death. Bates et al[19] in an article have estimated that the annual costs attributable to all ADE for a 700 bed teaching hospital is 5.6 million dollars.

Regarding class of drugs associated with ADRs antimicrobials rank high in the list as they are the most commonly prescribed drugs in our set up. Similar observation was noted in an Indian study.[2] In a study by Caranasos[20] et al, antimicrobials were the second most common cause of ADRs while non – narcotic analgesics topped the list. Kanjanarat et al[21] noted cardiovascular drugs to be causative in 17.9% of ADRs while Lakshmanan et al[22] in a study of hospital admissions due to iatrogenic illness, found antihypertensives to be responsible for most of the iatrogenic admissions. However the latter study included moderate to severe reactions only and our study has included mild side effects also. Steel et al[23] also have found low percentage of antibiotic related iatrogenic illness. Bates et al[24] in a study of 247 patients found 30% of ADRs to be due to analgesics, 24% due to antibiotics, 8% due to sedatives and 7% due to antineoplastic drugs. Davies et al in UK[25], have found the most frequent ADR causative drugs relative to usage to be opioid analgesics, anticoagulants, fibriolytics, systemic glucocorticoids, diuretics and antibiotics. However, these differences seen in different places could also be due to the variation in drug usage and disease prevalence in different places.

Table 9: Comparative Studies on ADRs in Patients While in Hospital

Authors	Study size	Incidence of ADRs %		
		All severities	Serious	Fatal
Davies et al 2009	3322	15.8	15.2	0.4
Bates et al 1995	379	5.3	0.8	0
Bates et al 1995	4031	4.4	1.5	0 – 0.8
Bates et al 1993	420	3.6	1.9	0
Steel at al 1981	815	14.8	2.8	-
Mitchell et al 1979	1669	16.8	-	-
Our series	1250	20	0.96	0.24

When we analyzed the systems affected most of them were CNS side effects (23.1%) which is much lower than 77.2% reported in a systematic review of ADRs by Thomsen et al[26] This is in contrast to previous studies where gastrointestinal side effects were more frequent as in the study by Natalie et al.[27] However they too noted that neuromuscular problem was quite frequent with an incidence of 22.6% whereas Caranasos[20] et al found 22.2% cardiovascular ADRs and 18.5% gastrointestinal ADRs with only 11.1% neurologic ADRs in a study of 189 ADRs. This discrepancy may be due to inclusion of large number of antimalarials which produced CNS side effects.

Among moderate to severe reactions, combinations of drugs (drug interactions) were responsible for a large percentage of ADRs. 41.1% of ADRs in severe reactions, 29% of cases in moderate reactions and 66.6% of fatal reactions were all due to combination of drugs. One important observation was that of inadvertent use of antipsychotics and sedatives for patients with respiratory failure in 4 cases of which one died. As patients with respiratory failure may present with psychotic symptoms one should be careful about sedating a patient with preexisting respiratory failure. Drug-drug interactions were linked to 59% of ADRs in a study by Davies et al.[25]Polypharmacy was implicated by them to be the cause in a large percentage of cases where incidence of ADR was higher in patients receiving higher number of drugs compared to those receiving fewer drugs.

It is important to note that commonly used drugs such as chloroquin can produce serious neuropsychiatric problems such as extrapyramidal reactions, convulsions and psychosis as seen in 11 of our patients. If this fact is not considered, these patients may end up with unnecessary investigations such as lumbar puncture, EEG and a CT scan.

Our study has included reactions to water for injections and IV fluids. Although it cannot be considered as a true ADR, it can be considered as an adverse drug event. Intravenous fluids have been associated with reactions such as rigors and rarely anaphylaxis. In one of our fatal cases this is suspected, because an IV fluid bottle of the same company was found to have overt fungal growth in a few bottles.

We also found a case of etoposide induced pancreatitis[15] which was unknown previously.

In conclusion, ADR monitoring has to be carried out by all the doctors, as the pattern of ADR may vary from place to place and time to time. By early recognition of these reactions, necessary action can be taken to prevent mortality and morbidity from such reactions.

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