Pattern of Adverse Drug Reactions of Antimicrobial Agents in a Tertiary Care Teaching Hospital of Tripura: A Prospective Study

Prithul Bhattacharjee[1], Sarthak Vats[2], Lakshman Das[3], Ranjib Ghosh[4], Sayan Bhattacharjee[5]

ABSTRACT

Introduction: ADR monitoring and reporting activity is in its infancy in India. India rates below 1% in pharmacovigilance as against the world rate of 5%. India is the fourth largest producer of pharmaceuticals in the world. So there is an immense need to improve the pharmacovigilance system to protect the Indian population. This study is aimed to identify ADRs of antimicrobial agents and assess their pattern.

Material and methods: The reports of ADRs were recorded as per the standard guidelines fixed by pharmacovigilance programme of India (PvPI). Naranjo ADR probability scale was used to assess the causality of suspected ADRs. Severity of ADRs was identified using modified Hartwig's criteria. Types of ADRs were identified using Rawlins and Thompson classification.

Results: A total 84 ADRs were reported from 70 patients. Out of 84 ADRs, the most were related to gastrointestinal system (45.23%), followed by skin and appendages disorders (36.90%). Of 70 patients 56 had one ADR, 14 suffered from two ADRs, and none suffered from more than two ADRs. Based on modified Hartwig severity scale, 85.71% reactions were mild, 12.86% were moderate and 1.43% were severe.

Conclusions: The present study shows ADRs are commonly encountered at this tertiary health care set up. Many ADRs are life threatening type B reactions, but the higher incidence of type A reactions means that these can be avoided.

Keywords: Patient Safety, Pharmacovigilance, Causality.

INTRODUCTION

Drugs are the most common medical intervention, primarily used to relieve suffering. But it has been recognized long ago that drug themselves can prove fatal, as the saying rightly goes "Drugs Are Double Edged Weapon". Drugs prescribed for diseases are often themselves the cause of adverse reactions ranging from mere inconvenience to permanent disability and death.

The WHO defines Adverse Drug Reactions (ADRs) as "any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function".[1] The ADRs affect the patient recovery as well as the economy of health care. This has been the basis of starting of international drug monitoring program by WHO.[2]

Antibiotics belong to different classes such as penicillins, cephalosporins, sulfonamides, and aminoglycosides, and they vary in respect of their mechanism of actions and adverse effects. Antibiotics are used commonly in routine practice for treatment and prophylaxis of various disease conditions.[3] Over half of all hospitalized patients are treated with antimicrobial agents and their use account for 20–50% of drug expenditures in hospitals. More than 70% of ICU patients receive antibiotics for therapy or prophylaxis, with much of this use being empiric and over half of the recipients receiving multiple agents. The total costs associated with antibiotics are not only related to antibiotic use itself, but also to co-medication and adverse drug events.

In Darchy's report, antibiotics accounted for 11% of iatrogenic disease. Classen states that, although adverse events seem to occur in a small proportion of antibiotic courses, the frequency of antibiotic use makes them account for 23% of all adverse events recorded.[6,4]

ADRs monitoring is still in its infancy in India and reporting is scarce. North East Indian region comprised of eight (8) states with varied tribal communities and ethnicities. However from this region still there is underreporting of ADRs. Although ADRs can occur to any class of drug, antimicrobial agents (AMAs) are one of the most common causative agent.[5] Over half of all hospitalized patients are treated with AMAs and their use account for 20-50% of drug expenditure in hospital.[4]

Thus the aim of this study was to record and analyse the pattern ADRs of AMAs in a tertiary care teaching hospital of Tripura.

MATERIAL AND METHODS

A prospective study was carried out at Tripura Medical College & Dr. BRAM Teaching Hospital, a tertiary care teaching hospital in Agartala, Tripura, for two (2) months from May 2018 - July 2018 at inpatients setting. Permission from Institutional Ethical committee of the hospital was obtained prior to the initiation of study. All the "suspected ADR reporting forms" of Indian Pharmacopoeia Commission (IPC)[7] were filled up by health professionals in Inpatients department (IPD). The contact number and e-mail

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Id of author were circulated among health professional to facilitate reporting of ADRs. For each patient the form was filled with regard to

- Age of patient
- Gender of patient
- Number of drug prescribed
- Duration of treatment
- Number of ailment(s), the patient was suffering from
- Causality of the ADRs
- Severity of the identified ADR

The study included all patients with AMAs related ADRs among the admitted patients in general medicine ward.

Sample size: 70 patients with 84 ADRs

Inclusion criteria: All the suspected ADRs, caused by AMAs either due to selfmedication or prescribed by physician were taken in the study.

Exclusion criteria:

1. The patients receiving alternative system of medicine such as Ayurveda, Homeopathy, Siddha, Unani (AYUSH) etc. were excluded from the study.
2. All mentally retarded, drug addicted and unconscious patients were also be excluded from the study.
3. Patients admitted due to alcohol or drug abuse, a suicide attempt or admission planned more than 24 hours in advanced were excluded.

A duly explained and informed consent was taken from the patient before participation in the study. The causality assessment of the ADRs was done using Naranjo ADR probability scale.[8]

Scoring of the suspected ADRs was done by using a set of questions of Naranjo's algorithm. Score of >9 were graded as definite, score 5-8 as probable, score 1-4 as possible and score 0 as doubtful. Severity of the identified ADRs was assessed at different levels, ranging between 1 and 7 using modified Hartwig's criteria.[9] Mild ADRs belonged to levels 1 and 2, moderate ADRs belonged to level 3 and 4 and severe ADRs were level 5 and above.

STATISTICAL ANALYSIS

Profile of patients like age, gender, duration of treatment, the responsible drug(s) for ADRs with causality assessment and severity of the identified ADRs are represented as percentage. Odds ratio was calculated to assess the relationship between profile of patient and common system wise ADRs. Statistical significance was determined at 95% level of confidence.

RESULTS

Types of ADRs with their numbers and suspected drug/ drugs are shown in table 1. Total 84 ADRs were reported in 70 patients. Out of 84 ADRs, the most were related to gastrointestinal system (45.23%), followed by skin and appendages disorders (36.90%). Of 70 patients 56 had one ADR, 14 suffered from two ADRs, and none suffered from more than two ADRs.

The ADRs related to body as whole-general body disorders were 7.14% and central and peripheral nervous system

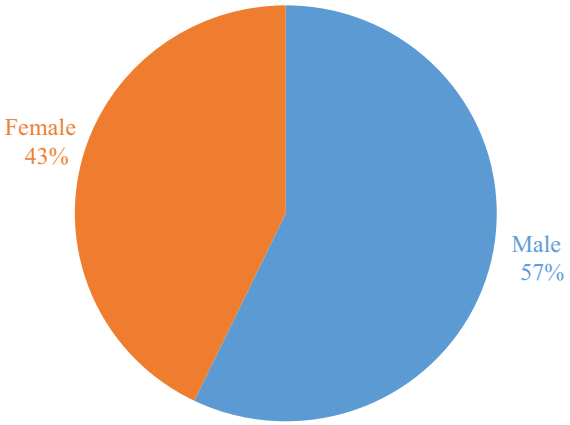

Figure-1: Division of ADRs based on sex of patient

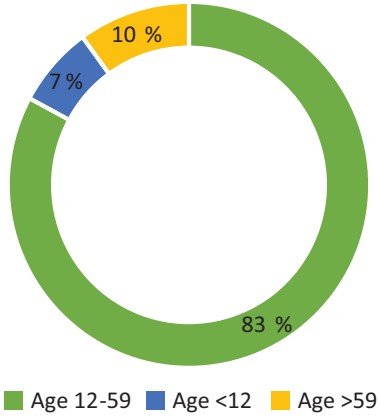

Figure-2: Division of ADRs based on age of patient

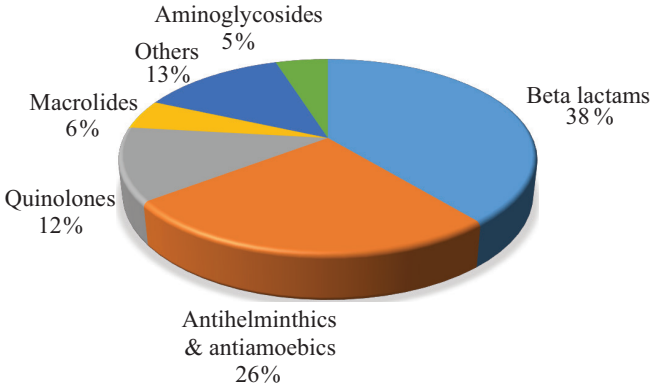

Figure-3: Therapeutic classes of antimicrobials implicated to cause ADRs

disorders were 5.92%. ADRs related to other systems (musculoskeletal system disorders, respiratory system disorders) were 4.76%. Profile of patients suffering from ADRs (N=70) is shown in table 2 and determinants of various types of ADRs among study subjects are shown in table 3. There was preponderance of ADRs in males as compared to females (57.84% vs 42.85%) depicted in figure 1. Out of 70 patients, majority of the patients (82.86%) were between 12-59 years, median age group being 21-39 years, whereas patients above 59 years were 10%, oldest patient being 82 years old, and patients below 12 years of age were 7.14%, youngest patient being 4 months old (figure 2). The association of females in developing general body disorders

Reaction/event	Number (n=84)	Drugs involved
Skin & appendages Disorder	**N=31(36.90%)**	
Generalised itching	12	Ciprofloxacin(1), Cefuroxime(1), Ceftriaxone(6), Doxycycline(1), Vancomycin(1) Cefoperazone+sulbactam(1), Cefuroxime+linezolid(1)
Skin irritation	**2**	Amikacin(1), mupirocin(1)
Fixed drug Eruption	**5**	Metronidazole(3), Ofloxacin(1), Ciprofloxacin(1)
Rashes	**11**	Amikacin(2), ampicillin(1), Fusidate sodium(1), ceftriaxone(1), Piperacillin+tazobactam(1), Azithromycin(1), Cefuroxime+linezolid(1), Cefoperazone+sulbactam(1),
		Azathioprine (1), Cefotaxime+sulbactam(1)
Toxic epidermal Necrolysis	**1**	Dapsone(1)
Gastro-Intestinal Disorders	**N=38 (45.23%)**	
Loose motion	5	Amoxicillin+clavulinic Acid(2), linezolid(1), Cefotaxime(1), Azithromycin(1)
Nausea	**7**	Ceftriaxone(1), Vancomycin(1), Amoxicillin+clavulinic Acid(1), faropenem(1), Albendazol(3)
Vomiting	**8**	Albendazole(5), Faropenem(1), ofloxacin(1), ceftriaxone(1)
Dyspepsia	1	Azithromycin(1)
Diarrhoea	5	Cefpodoxime(1), Amoxicillin+clavulinic Acid(1), ampicillin(1), Cloxacillin(1), Norfloxacin(1)
Mettalic taste	2	Norfloxacin(1), ciprofloxacin(1)
Bitter taste	3	Cefexime(1), albendazole(1), azithromycin(1)
Stomach ache	5	Albendazole(5)
Decreased appetite	1	Ceftriaxone(1)
Increased thirst	1	Linezolid(1)
CNS & PNS Disorders	**N=5 (5.95%)**	
Dizziness	1	Levofloxacin(1)
Shivering	1	Doxycycline(1)
Light headedness	1	Ofloxacin(1)
Vertigo	2	Albendazole(2)
Respiratory System disorders	**N=3 (3.57%)**	
Breathing difficulty	1	Albendazole(1)
Hoarseness of Voice	**1**	Amoxicillin+clavulinic Acid(1)
Dry throat	**1**	Amoxicillin+clavulinic Acid(1)
Musculoskeletal System disorders	**N=1 (1.19%)**	
Muscle spasm	1	Vancomycin(1)
Generalised body Disorders	**N=6 (7.14%)**	
Generalized weakness	3	Albendazole(2), azithromycin(1)
Burning sensation	1	Levofloxacin(1)
Swelling	2	Cefuperazone+sulbactam(1), amikacin(1)

Table-1: Types of adrs with their numbers (n=84) and suspected drug/drugs.

Characterstics	Criteria	N (%)
Age (in years)	<12	5 (7.14%)
	12-59	58 (82.85%)
	>59	7 (10%)
Gender	Male	40 (57.14%)
	Female	30 (42.85%)
Causality	Unlikely	0
	Probable	37 (52.86%)
	Possible	33 (47.14%)
	Certain	0
Duration of treatment (in days)	<5 days	56(80%)
	>5 days	14(20%)
Severity of ADRs	Mild Moderate Severe	60 (85.71%) 09 (12.86%) 01 (1.43%)

Table-2: Profile of patients suffering from ADRs (n=70)

Types of ADRs (N:84) Characterstics		Total	Skin and appendages (N=31)	OR (P value)	GI disorder (N=38)	OR (P value)	Others (N=15)	OR (P value)
Age(in years)	12-59 <12 & >59	58 12	24 (77.41%) 07 (22.58%)	0.50 (0.287)	33 (86.84%) 05 (13.16%)	1.85 (0.339)	12 (80.0%) 03 (20.0%)	0.78 (0.741)
Gender	Male Female	40 30	21 (67.74%) 10 (32.26%)	1.45 (0.442)	18 (47.37%) 20 (52.63%)	0.41 (0.074)	13(86.67%) 02 (13.33%)	6.74 (0.018)
Duration of treatment	<5 days >5 days	56 14	27 (87.09%) 04 (12.90%)	2.33 (0.193)	33 (86.84%) 05 (13.18%)	2.58 (0.126)	11 (73.33%) 04 (26.66%)	0.61 (0.469)
Causality	Score 0-5 Score 5-9	33 37	09 (29.03%) 22 (70.97%)	0.26 (0.008)	25 (65.79%) 13 (34.21%)	5.77 (0.001)	05 (33.33%) 10 (66.67%)	0.48 (0.232)
Severity	Mild Moderate & Severe	60 10	27 (87.09%) 04 (12.90%)	1.23 (0.769)	33 (86.84%) 05 (13.16%)	1.22 (0.769)	13 (86.67%) 02 (13.33%)	1.10 (0.905)

Table-3: Determinants of various types of ADRs among study subjects.

was found statistically significant (p=0.018). 79.48% patients developed ADRs within 5 days of treatment while 20.52% patients developed ADRs after 5 days of treatment. The ADRs were more common in the group of patients receiving treatment for less than 5 days. The antimicrobial class affected with ADRs are shown in figure 3 which revealed that Beta Lactams (cephalosporins (62.50%), penicillins (31.25%), carbapenemes (6.25%)) were the most accounted antibiotic class 32 (38.09%), followed by Antihelminthics and Antiamoebics (Albendazole (86.36%), Nitroimidazole (13.63%)) 22 (26.20%), others (including glycopeptides, tetracyclines, sulphonamides, oxazolidinones, fusidate sod., mupirocin, etc) 11 (13.10%), Quinolones 10 (11.90%), Macrolides 5 (5.95%), Aminoglycosides 4 (4.76%). When analysed on Naranjo ADR probability scale, 0% ADRs were unlikely (score 0), 47.14% ADRs were possible (score 0-4), 52.86% ADRs were probable (score 5-8) and 0% ADRs were certain (score >9). The association of the skin and appendages related ADRs with the causality scoring of 5-9 was highly significant (p=0.008), and association of GI related ADRs with causality scoring 5-9 was also found to be highly significant (p=0.001). Based on modified Hartwig severity scale, 85.71% reactions were mild, 12.86% were moderate and 1.43% were severe.

DISCUSSION

Antimicrobial agents are used for treatment and prophylaxis of various infectious conditions and are considered as safer drugs when used rationally. But, like all other drugs, they also show some Adverse Drug Reactions in various patient conditions. This study tried to find out the pattern of Adverse Drug Reactions by AMAs in patients admitted to a tertiary care hospital in the state of Tripura. Antibiotics were second most accounted drug class causing adverse drug reactions in another study conducted by Hussain et al[10] our study although showed a relatively low incidence of ADRs involving AMAs, with 82 adverse drug reactions in 70 patients admitted in General medicine ward of either sex over a period of two months, this could be attributed to better awareness for ADRs in our hospital, or could be because most patients suffering from mild ADRs take over the counter drugs for them and thus reporting decreases.

In our study majority of reported cases were males (57.14%), which is consistent with findings of Bhattacharjee P et al[11] (56.84%) and Shamna M et al[13] (53.06%), but inconsistent with study done by Ratan J. Lihite et al[12] (46.11%) this could be due to majority of the admitted patients were males with more antibiotic use during the study period. Analysis of age wise distribution showed predominance of patients aging between 13 and 59 (82.85%), with geriatric patients (10%), and children (7.14%), probable cause for the finding is that it is likely that this population is attending hospital more frequently and is a major population receiving drug therapy,

Ratan J. Lihite et al[12] also found majority of patients from the same age group.

The majority of adverse drug reaction were mainly affecting the GIT (42.23%), followed by skin and appendages (36.90%), the study of Shamna M et al[13] also found the predominance of gastrointestinal system followed by skin and appendage associated ADR, another study by Md Misbah et al[10] show the predominance of cutaneous manifestations. Remaining ADRs affected general body as whole, musculoskeletal system, CNS, PNS and respiratory system. The beta lactams are the most commonly used antimicrobial agents, thus reported ADRs were mostly from this group(38%), among beta lactams cephalosporins were associated with most adverse drug reactions, followed by penicillins and carbapenems, following beta lactams were antihelminthics and antiamoebics (26%), consisting majorly of albendazol, followed by nitroimidazoles, other associated drugs were from classes, miscellenous (tetracyclines, sulphonamides, glycopeptides, fusidate sod., oxazolidinone etc), quinolones, macrolides, aminoglycosides. M. shamma et al[13] and Stavreva et al[6] also said cephalosporins were the most associated AMA causing ADRs.

Assesment using Naranjo algorithm showed majority of reactions were probable(score 5-9), followed by possible (score 0-4), substantiating studies by M. Shamma et al[13] and Srivastava S. et al.[14] On modified hartwig severity scale most of the reactions were mild, followed by moderate and only one severe ADR (toxic epidermal necrolysis), Bhattacharjee P. et al[11] also presented similar facts in his study. Majority of the patient (80%) developed ADR within 5 days of treatment.

CONCLUSION

The study concluded that spontaneous reporting of ADRs in this part of the nation is still less and more awareness is needed to be spread. Most of the ADRs were mild in nature and easily preventable. Although the time duration of the conducted was less and there were certain limitations, still this study will definitely give important insights into the pattern of adverse drug reactions to commonly used AMAs in a tertiary care teaching hospital of north eastern state of Tripura and may help in promoting rational use of AMAs and to increase awareness for further pharmacovigilance studies.

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