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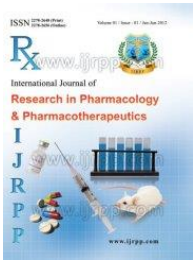

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Pattern of adverse drug reactions reported at a tertiary care teaching hospital in north east India: a retrospective observational study conducted under pharmacology department

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ABSTRACT

Background

Adverse Drug Reactions (ADRs) are commonly encountered at hospitals where poly pharmacy is practiced due to increased chances of drug interactions. Nowadays there is growing interest in reporting ADRs. Yet, there is a paucity of data regarding adverse drug reaction monitoring in India.

Aim

The present study was done to analyze all the reported ADRs at Tripura Medical College & Dr. BRAM Teaching Hospital (TMC).

Materials & Methods

A retrospective, observational study of all the reported cases of ADRs that occurred in both Outpatients Departments (OPD)&In patients Departments(IPD) at TMC in last 18 months (Jan 2017 to June 2018) are included in the study. All the ADRs that were reported by different OPDs & IPDs were recorded in Suspected Adverse Drug Reaction Reporting Forms of Indian Pharmacopoeia Commission (IPC). The reports were recorded as per the standard guidelines fixed by Pharmacovigilance Programme of India (PvPI). WHO-UMC scale was used to assess the causality of suspected ADRs.

Results/observations

A total of 204 ADRs were reported from 177 patients. Out of 177 patients, 30 patients were admitted in IPD with different ADRs, 55 ADR cases were treated in OPD and 82 patients developed ADRs during their hospital stay with other ailments. Adult male patients were mostly affected. Commonest form of manifestation was skin & appendages disorders, second common is gastrointestinal system disorders followed by psychiatric& nervous system

disorders. Maximum cases had mild reactions that recovered after discontinuation of medications, two patients had disability and nine patients developed life threatening ADRs that needed intensive care with prolonged hospital stay.

Conclusion

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: ADR, Causality, Incidence

INTRODUCTION

Adverse drug reactions (ADRs) are a major cause of morbidity. ADRs related hospitalizations have consistently increased which has caused an economic burden to the developing country like India. ADRs are common in elderly population. [1] In USA, more than 90% of adults aged 65 yr and older use one medication per week and 10-25% experience an ADR. These ADRs are responsible for 3.4 -7.0 % of hospital admissions. [2] of all the factors that are most consistently associated with adverse drug reactions, poly pharmacy is considered to be the most important. Studies from overseas as well as India have demonstrated that polypharmacy is prevalent and associated with increased potential for adverse drug reactions, inappropriate prescription and drug interactions. [3]

ADR monitoring and reporting activity is in its infancy in India. India rates below 1% in pharmacovigilance as against the world rate of 5%. [4] India is the fourth largest producer of pharmaceuticals in the world. There are more than 6000 licensed drug manufacturers and more than 60000 branded formulations . [5] It is also emerging as a clinical trials hub. Many new drugs are being introduced in the country, so there is a immense need to improve the pharmacovigilance system to protect the Indian population from potential harm that may be caused by some of the drugs. [6] The important reason of less pharmacovigilance activity is lack of awareness and lack of interest of healthcare professionals in ADR reporting and documentation. Therefore, this study was aimed to identify ADRs and assess their causality, incidence and severity.

MATERIALS AND METHODS

A retrospective data analysis was carried out at Tripura Medical College & Dr. BRAM Teaching Hospital (TMC) in last 18 months (Jan 2017 to June 2018) from different departments. All the Suspected Adverse Drug Reaction Reporting Forms of Indian Pharmacopoeia Commission (IPC) were filled up by health care professionals in both Outpatients Departments (OPD) &In patients Departments (IPD). For each patient the form was completed with regard to patient age, gender, diagnosis, past medications, currently prescribed drugs, their brand names, daily doses, treatment duration, indications for each drug, laboratory investigation reports.

Identification of adverse drug reactions

Suspected ADRs were assessed for causality, severity using WHO-UMC scale. [7] The degree of association of an ADR with a drug was done which involves assigning score to set of questions. The total score for a particular ADR was calculated and the association was termed into one of these categories - definite (score >9), probable (score 5-8), possible (score 1-4) or doubtful (score 0). Severity was identified using modified Hartwig's criteria which involve seven severity levels. [8] Severities of the identified ADRs was assessed at different levels, ranging between 1 and 7. Levels 1 and 2 indicated mild , 3 and 4 considered as moderate and level 5 and above as severe ADRs . The potential risk factors assessed were age, sex, number of medications, number of diagnoses and duration of treatment. ADRs were characterized using Rawlins and Thompson classification. [9]

STATISTICAL ANALYSIS

The results are represented as mean ± SEM and percentages as applicable, age, diagnosis, number of medications and duration of treatments were variable for determination of risk factors. Odds ratio was calculated to assess the most common risk factors for ADRs. Statistical significance was determined at 95 per cent level of confidence. The data were analyzed using Sigma Stat package (Ver. 3.5).

RESULTS

Incidence of ADRs

A total of 204 ADRs were reported from 177 patients .135 patients suffered only one ADR, 20patients suffered two ADRs and 22 patients experienced three or more than three ADRs. The incidence rates of ADRs was 21% while incidence of patients affected due to ADR was 19 %. Out of 177 patients 30 patients were admitted due to development of ADRs, while 82 patients developed ADRs during hospital stay, 165 patients did not require admission following development of adverse drug reactions. Therefore the incidence of hospitalization due to ADRs was 16.94 % while the incidence of ADRs in hospitalized patients was 46.32%.

The average age of patients was 48.28 ± 0.11 yr. Of the 177 patients, 122 patients belonged to the age group 12-59 yrs while 40 patients belonged to the age group 60-75 yrs and the remaining 15 were less than 12 yrs of age. Data showed preponderance of ADRs in male subjects as compared with females .Incidence of ADRs was found to be higher in patients aged more than 40 years of age compared to patients aged < 40years of age. This difference was found to be statistically significant ($P < 0.05$).

It was found that approximately 69 per cent of the patients suffered from two or more diseases. On an average, each patient had 2.01±0.01 diagnoses; 41 per cent of patients were diagnosed as having 2 co-morbidities; It was found that 35.59percent of the patients suffered from infectious disease followed by digestive system disorders -26.55percent, 14.12 percent of patients suffered from neurological &psychiatric disorder and cardiovascular, endocrine, nutritional, metabolic diseases accounted for 33.74 per cent. The average number of medications prescribed was 6.45±0.04. The distribution of medication followed the normal Gaussian distribution. Over half of the patients (57.9%) received more than five medications concurrently.

Types of ADRs

When categorized on the basis of Rawlins and Thompson classification for the type of ADRs , majority of ADRs were Type A (144 - 81%) , whereas Type B accounted for only 33(19%) of ADRs .There was no significant association between Type A or Type B reaction and patient's characteristics , that is age, gender , and number of comorbid conditions .

Severity of ADRs

Based on modified Hartwig severity scale, 35 reactions (17.15%) were categorized as mild, 156 ADRs (76.47%) were moderate type and only 13 ADRs (6.37%) were severe in nature. Mild and severe reactions were more common in males, whereas moderate reactions were significantly more common in females. Moderate reactions were common in both the age groups. Moderate and severe reactions were significantly more common in patients with more than two comorbid conditions ($P<0.01$). All types of ADRs were common in patients taking more than five drugs concurrently.

Using logistic regression analysis, it was found that patients of more advanced age (over 60 yr) were at significant risk for ADRs as compared to the patients of age group 13-59 yr. In this study, patients with multiple diseases, multiple medications and longer duration of treatment were more likely to have ADRs.

Causality of ADRs

When analyzed on WHO-UMC scale 88.6 per cent of the ADRs were probable (n=182) with a score of 5-8. Only 2 were definite (with score equal or over 9) and 20 ADRs (9.8%) were possible type with score range of 1-4.The probable reactions were more common in males as compared with females, however the difference was statistically non-significant. Probable reactions were common in patients with age less than 60 years, whereas possible reactions were significantly more common in patients above 60 yrs of age. Moreover, both probable and possible reactions were common in patients with more than two comorbid conditions.

Commonly reported ADRs

The total number of ADRs was 204 in 177 patients. The most commonly identified ADRs were nausea/vomiting, generalized itching, fever, fixed drug eruption, maculopapular rash (Table I). The other ADRs were Steven Johnson syndrome, extrapyramidal syndrome, dystonia, headache, tremor, convulsion, oedema, loose stool, pain abdomen, hepatitis, myopathy, dyspnea, hypotension retention of urine.

Drugs involved in ADRs

The most common offending class of drug was the antimicrobial drugs, followed by Japanese encephalitis vaccine and drugs used to treat psychiatric &neurological disorders (57.5% >12.7% >10%).

Management and outcomes

The offending drug was withdrawn in 99 reported cases (48.5%), whereas 180 cases (88.23%) required an additional treatment for management of ADR .Dose was altered in 25 cases (12.25%).35 cases (17.15%) required no additional treatment or change in dose of offending drug. Total number of interventions done (220) was different from the total number of ADRs reported (204), because in many cases more than one intervention was done for management of a single ADR.

Of all the reported ADRs, 83 ADRs were serious in nature that is they either required or prolonged hospitalization or caused permanent disability or resulted in death. In the present study 30 patients were admitted due to ADR while ADRs prolonged hospital stay in 33 patients and two patients died due to development of ADR. Of 177 reported patients 143 patients (70.09%) recovered fully whereas 15 patients (7.35%) were still continuing the medication for the ADR sequel and 44 patients (21.56%) were recovering. Overall only two reactions (0.98%) due to Japanese encephalitis vaccine proved fatal.

DISCUSSION

Adverse drug reaction is defined as a response to a drug which is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for modification of physiological function. [10] Importance of ADR monitoring can be understood from the fact that Medical council of India has recommended to establish Pharmacovigilance committee in every teaching hospital. [11]

Adverse drug reactions and non-compliance are important causes of hospital admissions. Other studies reported high proportion (30.4%) of hospital admissions were ADRs related among elderly patients. [12] In the present study, 30 patients required hospitalization to manage the condition. The possible reason for these differences may be differences in ADRs reporting and documentation and use of broad definition of ADRs. It is known that frail elderly patients appear to be particularly at risk of ADRs. Incidence of ADRs may vary from place to place and even within a country because of difference in prescribing patterns. [13]

Predisposing factors like age, gender, comorbidity, number of drugs taken and length of stay in the hospital have been reported as significant risk factors for the development of ADRs. [14, 15] on multivariate analysis, the present study revealed that advanced age and female gender were the independent risk factors for development of ADRs.

Age is an important risk factor for ADRs and incidence of ADRs increases steadily with age. This is due to pharmacokinetic and pharmacodynamic changes which along with impairment of homeostatic mechanisms and the effect of coexisting disease, contribute to a significant increase in the incidence of ADRs. Another reason for increased incidence of ADRs is increased consumption of medicines. [16] Present study confirmed that polypharmacy and comorbidity played a significant role in causation of ADRs.

Earlier studies have also reported a higher incidence of of ADRs in females. [17] The difference may be due to different rate of drug metabolism. Even after correction made for lean body mass and body surface area , significant gender difference do exist in drug metabolism. [18] Other major pharmacokinetic differences between the genders that can affect appearance of ADRs are lower body weight and glomerular filtration rate and a high percentage of body fat in women compared with men. [19]

In the present study two reactions were categorized as certain. It was observed that possible reactions were more commonly reported in elderly as compared with probable. The reason might be comorbidity leading to polypharmacy as more drugs were being used, so an ADR cannot be attributed to a single drug. A high incidence of Type A reactions in comparison with Type B reactions (81% vs 19%) indicate that majority of ADRs were preventable.

CONCLUSION

Although present study has some limitations as it is a retrospective analytical study, still this study would definitely give an insight into the pattern of

ADRs in a tertiary care center and may help to increase awareness for further pharmacovigilance studies.

Manifestations of the ADRs

Reaction/Event	Drugs involved	No of cases (%)
Skin and appendages disorder		
Urticaria	Ceftriaxone + tazobactum, Norfloxacin , Piperacillin+tazobactum,Japanese encephalitis vaccine	4
Steven-Johnson syndrome	Sulphasalazine , phenytoin , paracetamol , antitubercular drugs , norfloxacin, ofloxacin+ornidazole	9
Maculopapular rash	Ceftriaxone + tazobactum , spiramycin , amoxycillin& clavulanic acid , ertapenem, calcium+ vitamin D3, ursodeoxycholicacid ,lamotrigine , dehydroepialdosterone	12
Fixed drug eruption	Paracetamol , ofloxacin + ornidazole,ketorolac ,fluconazole ,norfloxacin ,diclofenac sodium	14
Angioedema	Diclofenac , piperacillin	2
Generalised itching	Cefoperazone+sulbactum,ceftriaxone,moxifloxacin hydrochloride , amoxycillin+clavulanic acid,rabeprazolesodium,azithromycin ,cefuroxime ,ofloxacin , cefotaxime+sulbactum ,amikacin ,ofloxacin+ornidazole ,clindamycin ,piperacillin+tazobactum	20
Blister	Vancomycin	1
Skin hyperpigmentation	Amlodipine + atenolol	1
Blackish discolouration of skin	Isoniazid, rifampicin , pyrazinamide, ethambutol	1
Gastro-intestinal system disorders		
Nausea, Vomiting	Isoniazid,rifampicin ,ethambutol,streptomycin , carboprost , ceftriaxone , lithium , ertapenam,eracobal ,imipenem ,cyclophosphamide,epirubicin ,fluorouracil, japanese encephalitis vaccine , cefuroxime,amikacin ,dextran infusion	41
Loose stool	Clindamycin,fluoxetine ,isoniazid,ethambutol,terbinafine hydrochloride , ceftriaxone sodium	6
Pain abdomen	Trimethoprim + sulphamethoxazole , Japanese encephalitis vaccine	5
Constipation	Ornidazole	1
Metallic taste	Satronidazole	1
Decreased appetite	Cisplatin , paclitaxel , carboplatin , fluorouracil	4
Dysphagia	Cisplatin	1

Liver and biliary system disorders		
Hepatitis	ATT	4
Psychiatric disorders		
Nightmares	Mirtazepine	1
Central and peripheral nervous system disorders		
Neurologic disorder	Imipenem + cilastatin , risperidone	2
Headache,	Pregabalin , methylcobalamin + etodolac & paracetamol,japanese encephalitis vaccine ,amikacin ,fluvoxamine	5
Ringing in ears		
Numbness	Lignocaine + adrenaline	1
Akathisia	Amisulpride , quetiapine , iloperidone	3
Convulsion	Ertapenem,japanese encephalitis vaccine	4
Tremor	Haloperidol	1
Dystonia	Risperidone + trihexyphenidyl , haloperidol	2
Extrapyramidal Syndrome	Haloperidol ,aripiprazole ,amisulpride , olanzapine , divalproex sodium , risperidone	7
Dizziness	Ceftriaxone	1
Sluggishness of movements	Risperidone	1
Muskulo-skeletal system disorder		
Joint pain	ATT	1
Myopathy	Fenofibrate + pitavastatin , promethazine teoclate	2
Leg pain	Cyclophosphamide , Epirubicin	1
Cardiovascular disorders		
Hypotension	Iron sucrose , netilmicin	2

Eye disorders		
Conjunctival hemorrhage	Vitamin B complex	1
Body as a whole-general disorders		
Syncope vasovagal	Polystarch	1
`	olanzapine	1
Chest pain		
Chest tightness	Iron sucrose	2
Burning sensation		
(CNS)	Dextran infusion	1
Oedema legs	Aceclofenac , rifaximin , acetaminophen , s- amlodipine , aceclofenac	6
Oedema generalised	Piroxicum	1
Fever		
	Japanese encephalitis vaccine	20
Generalised weakness		
	Cyclophosphamide , epirubicin	2
Discomfort in throat		
URINARY SYSTEM DISORDER	Chlorpromazine / trihexyphenidyl	1
Urinary retention		
ENDOCRINE DISORDER		
	Nortryptline hydrochloride	1
Diabetes mellitus		
		1
	Aripiprazole	
Respiratory system disorder		
Dyspnea	Olanzapine , misoprostol	3
Throat pain	Ofloxacin + ornidazole	1
		1
Cough and cold	Japanese encephalitis vaccine	
TOTAL		204

Risk factors associated with adverse drug reactions (ADRs)

Variable	Total no.of patients	Number of ADR	Odds ratio 95%confidence level	P value
All	177	204		
Age (yr)				
12- 59 yrs	122	138	1(reference)	
60-75yrs	40	45	1.3(1.02- 1.6)	0.03
<12yrs	15	21	1.7(1.21- 2.37)	0.001
No.of medication				
<6	82	83	1(reference)	
6-10	90	100	1.4(1.10-1.75)	0.005
>10	5	21	1.8(1.26-2.50)	0.001
Duration of treatment(days)				
<10days	102	89	1(reference)	
>10days	75	115	2.28 (1.6- 3.4)	0.00
No.of diagnosis				
Single	28	44	1(reference)	
Double	122	125	1.80(1.37-2.39)	0.00
Multiple	27	35	2.03(1.52-2.73)	0.00
Gender				
Male	85	93	1(reference)	
Female	92	111	1.09(0.88- 1.35)	0.41

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