Original Research Article

Study of Pharmacovigilance in the Department of Medicine in tertiary care hospital

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Abstract

Objectives: This studywas to assess the clinical pattern and spectrum of ADRs reported in department of medicine, the assessment of ADRs by various scales, and to compare between patient reporting and HCP reporting of ADRs in terms of causality, severity, preventability factors and its impact on emotional, social and occupational life. **Methods:**Clinical evaluation and scrutiny of data was done to assess pattern, extent, severity and duration of the reactions, to detect any predisposing or underlying disease/pathological factors, and to assess any other organ/ system involvement as a part of the drug reaction. The pattern of reported ADRs was analyzed for their clinical types, and causative drugs. The causality of the reactions was assessed by WHO-UMC and Naranjo's causality assessment scale (Annexure-5), severity of ADR using Modified Hartwig scale and preventability assessed by using Modified Schumock and Thornton scale. Regular awareness and motivational programme for the patients to report any suspected ADR to our pharmacovigilance unit was conducted.**Results:**Data was analyzed by using SPSS version 13 software. The data was analyzed using descriptive statistics namely mean and standard deviation for quantitative variables and the association between two different discrete variables was assessed using chi-square test. P-value was taken less than or equal to 0.05 ($p \leq 0.05$) for significant differences.**Conclusion:**The clinical spectrum of ADRs reported from the more common mild reactions like skin rashes, itching, nausea and vomiting to moderately severe reactions prolonging the hospital stay of the patients resulting in decrease in physical quality of life. No fatalities due to ADR were reported. The predominant causative agents were antimicrobials drugs, antiretroviral drugs, NSAIDs and antihypertensive drugs. Majority of ADRs were probable in causality assessment, moderate in severity and probably preventable. Majority of ADRs were reported by HCP ,while direct reporting of ADR by patients were negligible. Comparison of ADR reporting between HCP and patient revealed similarity in qualitative analysis in terms of presenting complaints, drug causing pattern and preventability of ADR. In contrast to HCP, patient reporting of ADR had very elaborative narration and highlighted more about emotional and occupational impact of ADR on patient's life.

Keywords: ADRs, clinical symptoms, antimicrobial drugs, HCP, age group

Introduction

Adverse drug reaction (ADR) is a major worldwide public health problem. It is an inevitable consequence of drug therapy, as no pharmacotherapeutic agent is completely safe (free from unwanted and unintended effects).The fact that medicines are not absolutely safe and have the potential to cause adverse reactions is known since a long time. Sir Claude Bernard states ''Everything is poisonous, nothing is poisonous, it is all a matter of dose' 'Hence poison when used in small doses can be utilized as medicines and medicines when used in large doses may turn in to poison**.** Drugs prescribed for disease are often themselves the cause of serious number of adverse reactions ranging from mere inconvenience to permanent disability and death. According to DJP Barker, ''There are three actions of a drug: The one you want, the one you don't want, and the one you don't know about [1].ADR contributes to the burden of drug related patient morbidity and mortality adding to the cost of patient health care. They are common and often preventable cause of hospital admission. Data on ADRs are poor and inadequate though they were implicated as 7th commonest cause of death[2] and up to 57% of ADRs are unrecognized by attending physiciansin 2012 [3]. The recent epidemiological studies have estimated that adverse drug reactions are the fourth to sixth leading causes of death [4]. While, the incidence of ADR in Indian population ranges between 1.8-25.1%[5]. The median incidence of ADR on hospital Admission and ADR developed during hospitalization were 2.85% and 6.34%, respectively [6]. Spontaneous reporting system (SRS) by health care professionals (HCP), a common method of ADR reporting serves as the backbone for pharmacovigilance. The main drawback of SRS by HCP is under reporting and selective reporting. This canlead to false conclusion about drug risk. Therefore, including patients as reporters of ADR may increase its early detection and reporting and provide useful added source of information as patients are found to perceive ADRs more rapidly and clearly, than HCP [7]The pharmacovigilance system is responsible for continuous drug safety evaluation after-market authorization. This is facilitated by several phases, such as data collection and management, signal detection, safety-issue assessment and decision-making [8,9]. Objective of this study prospective observational study was to assess the clinical pattern and spectrum of ADRs reported in department of medicine, the assessment of ADRs by various scales, and to compare between patient reporting and HCP reporting of ADRs in terms of causality, severity, preventability factors and its impact on emotional, social and occupational life.

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Methodology

This present study was conducted in **o**utpatients and inpatients of Department of Medicine,Katihar Medical College and Hospital, Katihar,Bihar, India during a period from June 2015, to August 2016. Entire subjects signed an informed consent approved by institutional

ethical committee of KMCH was sought.A total of 100 consecutive cases attending the medicine OPD and inpatient admitted to Katihar Medical College and Hospital with suspected ADRs were enrolled.

Inclusion criteria

All subjects of above 18 years of age from both gender with suspected ADRs.

Willingness to give written informed consent and available for follow-up, if any.

Exclusion criteria

Patients with drug reaction due to deliberate or unintentional over dosage.

ADR due to medicines of alternate systems like Ayurveda, Homeopathy, Unani.

Drug reaction occurring due to prescribing and dispensing error.

Mentally retarded or unconscious patients.

Reactions due to blood and blood products.

Procedure: Before initiation of the study, an awareness programme on the importance of ADR reporting by HCP was conducted in medicine department. Data of spontaneously reported ADRs by healthcare professionals was collected through the hospital ADR reporting form made available at medicine wards and OPD.For each patient with suspected ADR, a detailed history including drug history, personal history, family history, present and past medical history, and history of previous drug allergy were documented, any untoward event was labeled as adverse drug reaction after discussion with the treating physician.A through clinical evaluation and scrutiny of data was done to assess pattern, extent, severity and duration of the reactions, to detect any predisposing or underlying disease /pathological factors, and to assess any other organ/ system involvement as a part of the drug reaction. The causality of the reactions was assessed by WHO-UMC and Naranjo's causality assessment scale, severity of ADR using Modified Hartwig scale and preventability assessed by using Modified Schumock and Thornton scale.Regular awareness and motivational programme for the patients to report any suspected ADR to our pharmacovigilance unit was conducted. They were motivated to report the suspected ADRs verbally or through distributing ADR form.Comparison between spontaneous reporting by healthcare professionals and patient direct reporting of adverse drug reactions was assessed in terms of response rate, pattern of ADR reported, causality, severity and preventability assessment. Social, emotional, occupational impact factors and ADRs narrative elaboration scores were compared. Signal detection noted if any.

Follow-up: Follow up was done for severe reactions to assess the clinical progress.

Statistical analysis

Data was analyzed by using SPSS version 13 software. Chi-square test was applied. P-value was taken less than or equal to 0.05 for significant differences.

Results & discussion

Table 1:Organ system affected

Organ system	Female		male		Total	
	n	%	n	%	n	%
Skin	41	39	25	39	66	39
Cardiovascular system	18	14	4	6	22	13
Gastrointestinal system	15	17	10	15	25	14
Musculoskeletal	5	5	7	11	12	7
CNS	2	2	3	5	5	3
Metabolic	3	3	2	3	5	3
Hepatobiliary system	1	1	2	3	3	2
Ophthalmology	1	1	4	6	5	3
Genitourinary system	2	2	4	6	6	4
Others	17	16	3	6	20	12
Total	105	100	64	100	169	100

Table 2:Suspected therapeutic classes of drugs

Class of drugs causing ADR	Female		male		Total	
	n	%	n	%	n	%
Antimicrobials	33	47	7	23	40	40
Antiretroviral agents	7	11	5	16	12	12
Antihypertensives & diuretics	2	6	1	3	3	3
NSAIDS	5	7	2	6	7	7
Oral hypoglycemic agents	2	3	2	6	4	4
Antiepileptics	2	3	2	6	4	4
Corticosteroids	2	3	4	13	6	6
Bronchodilators	1	1	0	0	1	1
Opioid analgesics	1	1	1	3	2	2
Hypolipidemic agents	0	0	1	3	1	1
Antiemetics	1	1	12	6	3	3
Anticancer	2	3	1	3	3	3
Antihistaminics	1	1	0	0	1	1
Anticholinergics	2	3	0	0	2	2
Anxiolytics	0	0	0	3	1	1
Antipsychotics	1	1	1	0	1	1
Antidepressants	1	1	0	3	2	2
Haematinics	2	3	0	0	2	2
Vitamin A analogues	1	1	0	0	1	2
Others	3	4	2	6	5	5
Total	69	100	31	100	100	100

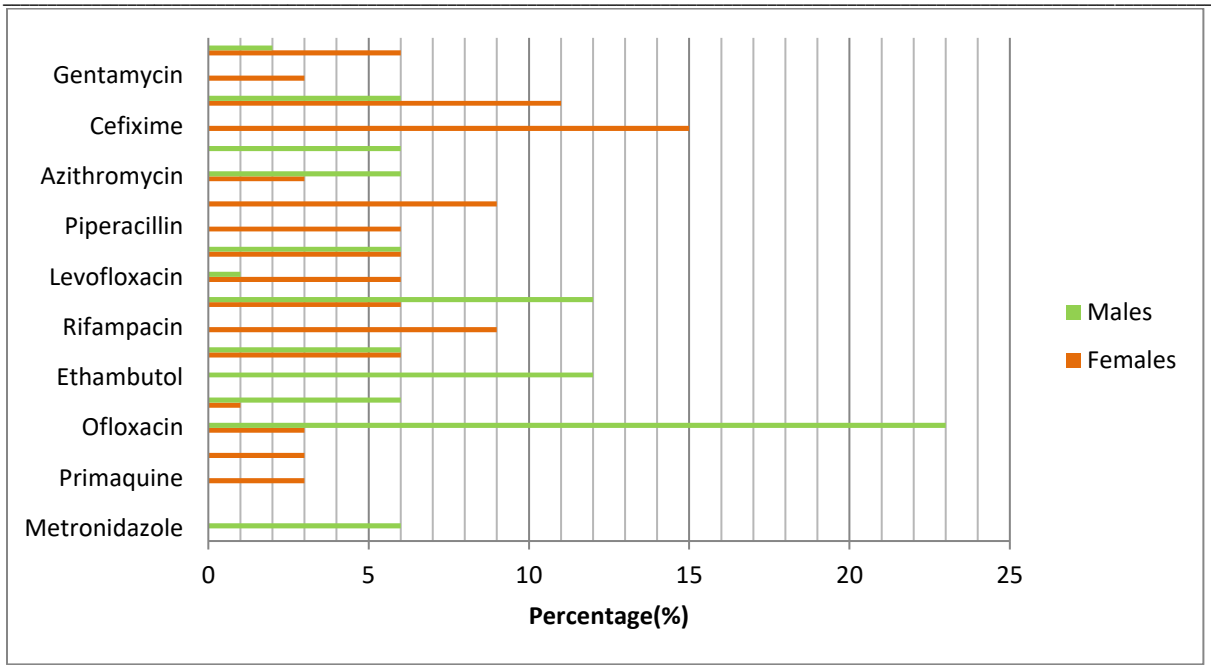

Fig 1: Antimicrobial agents

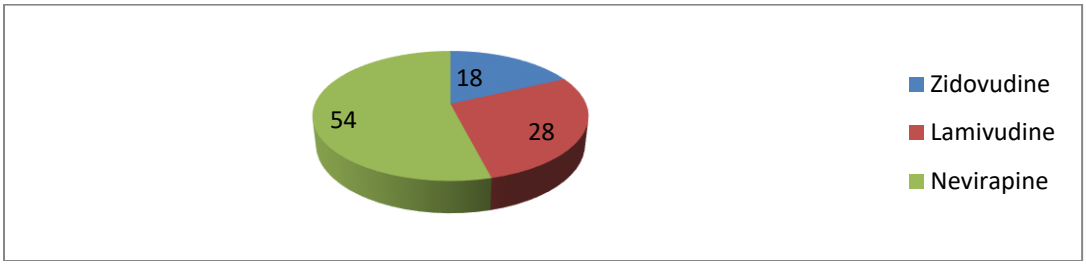

Fig 2: Antiretrovirals

Table 3: Comparison of presenting complaints

	HCP		patient		p-value
	n	%	n	%	
Skin rashes	38	22	5	21	0.4210
Itching	38	22	3	13	0.5240
Nausea &vomitting	14	8	0	0	0.141
Headache	2	1	0	0	0.4236
Abdominal discomfort	5	3	3	13	0.0003
Diarrhoea	3	2	1	4	0.01267
Constipation	1	1	0	0	0.06710
Sleep disturbances	1	1	0	0	0.5730
Obesity	3	2	0	0	0.328
Lab abnormalities	5	3	0	0	0.2130
Breathlessness	9	5	0	0	0.371
Giddiness	11	6	2	9	0.4766
Swelling of legs	10	6	0	0	0.8146
Myalgia	3	2	3	13	0.5347
Tremors of hand	6	3	0	0	0.5470
Yellow sclera	5	3	1	4	0.538
Others	18	10	5	23	0.3705
Total	172	100	23	100	

Table 4: Comparison of causality

Causality	HCP		Patient		Total	χ^2	p-value
	n	%	n	%		16.981	<0.001
Certain	0	0	1	10	1		
Probable	52	58	7	70	59		
Possible	38	42	2	20	40		
Total	90	100	10	100	100		

Table 5: Comparison of preventability

Preventabilty	HCP		Patient		Total	χ^2	p-value
	n	%	n	%		4.100	0.116
Definitely preventable	13	14	1	10	14		
Probably preventable	66	73	9	90	75		
Not preventable	11	13	0	0	11		
Total	90	100	10	100	100		

Results

Result of this study shows the frequency of age and gender distribution of the study subjects, their mean age was 39.42±10.46 years (32.04±11.01 for males and 40.06±14.32 for females) the mean age difference between the gender was not statistically significant (p>0.05), the eldest being 93 years and the youngest subject being 18 years of age. Majority of the study subjects were in the age group of 26-40 years (36%) which is in accordance with previous study the reason being attributed to increased incidence of diseases like diabetes, hypertension leading to increased usage of medicines, increased visit to the hospital for regular checkup associated with increased complaints of drug related adverse events [10]. This group was followed by 34% of subjects aged between 41-60 years, 16% of subjects between 18-25 years, 11.2% of subjects between 61-80 years and 3% of subjects were more than 80 years of age.In gender distribution, majority of the study subjects were females(69%) indicating higher incidence of ADR in females which is not in consistence with earlier documented reports [10].Result of this study shows the status of study subjects assessed based on Modified Kuppuswamy Scale [11].

Majority of the subjects (43%) were from lower middle followed by 20% from upper lower, 17% from upper class and 15% were from upper middle socioeconomic status. 5% of the ADR were reported from the lower class indicating probable lack of awareness of ADR reporting in this group. Presenting ADR complaints with gender distribution.

The commonest complaints were skin pruritis (21%), which is in concordance with previous studies[12] followed by skin rash in 19% of subjects, others 10%, Giddiness, nausea and vomiting were complained by 9% of the subjects, Breathlessnesswere complained by 6% of subjects. Pain abdomen in 4%, pedal oedema complained by 4% of subjects. Diarrhea, Myalgia, tremors of hands, was seen in 3% of study subjects. Obesity, Laboratory abnormalities like asymptomatic elevation of liver transaminase enzymes like SGOT, SGPT, discoloration of sclera in 2% of subject. Headache, sleep disturbances, constipation was seen in 1% of study subjects. There was considerable overlapping of presenting complaints. The gender related differences in presenting complaints were not statistically significant. Organ system affected due to ADRs with gender distribution. The commonest organ system involved in ADRs was skin accounting for 39% of total ADR which is consistent with previous studies that dermatological manifestation of ADR are common [13]. Antihypertensives and diuretics in 7%, corticosteroids in 6%, others in 5%, antiepileptics and Oral hypoglycemic agents, induced ADR in 4% of study subjects. NSAIDs, antiemetic, anticancer agents caused ADR in 3% of study subjects, followed by opioid analgesic, anticholinergics antidepressants, and haematinics in 2% of study subjects. Bronchodilators, hypolipidemic agents, antihistaminics, anxiolytics, antipsychotics and vitamin A analogue each were responsible for 1% of reported ADRs. The gender related difference in suspected therapeutic class of drugs causing ADR was not statistically significant.Antimicrobial drug was caused ADR with its incidence.

Among antimicrobials, ceftriaxone,ofloxacine(headache,myalgia and skin rash) was responsible for majority (10%) of adverse effects (skin rashes, itching, pain abdomen, giddiness) which is similar to earlier study,[14] probably it is the most common antibiotic prescribed in our hospital setting. levofloxacin (myalgia, skin rash and itching) each caused 8% of ADR among antimicrobial group, Streptomycin, Isoniazid also accounted for 8% study subject followed by clarithromycin, amoxicillin (was responsible for pain abdomen, diarrhea, skin rashes and pruritus), rifampacin(skin rash ,ithching,and pain abdomen) pyrazinamide(skin rash and itching),ethambutol (skin rash,itching) in 6% of study subjects, azithromycin(skin rash and pruritis) and piperacillin(skin rash, itching, nausea and vomiting) related ADR in 4% of study subjects, cefuroxime,gentamycin(skin rash and pruritis), aztreonam, dapsone, primaquine and metronidazole related ADR in 2% of study population. Antiretroviral drug causing ADRs with its incidence. Among antiretroviral therapy (ART), Nevirapine caused skin rashes, itching and mouth ulcers in 54% (n=6) of subjects which is responsible for majority of ADR in study subjects on ART drugs , followed by Lamivudine which was responsible for peripheral neuropathy in 28% (n=3) of study subjects on ART. Lastly zidovudine accounts for in 18% (n=2) of adverse effects like anemia, nausea, vomiting and skin rashes among the study subject group on ART in contrast to previous studies [15].

Antiepileptic drugs (n=6) caused ADR. Among antiepileptics, phenytoin sodium caused adverse effects in three subjects (yellowish discolouration eyes, skin rash and itching) followed by carbamazepine (n=2), causing instability of gait, skin rashes and itching which was in accordance with many previous studies with reason attributed that phenytoin and carbamazepine being frontline antiepileptic are commonly prescribed [16]. Sodium valproate caused skin rash, itching, pancytopenia in one study subject.

Antihypertensive drug wascaused ADRs (n=6) in 6 patients. Amlodipine caused pedal oedema in three cases which is consistent with previous study quoting that among antihypertensive CCBs were found to be most frequently associated with ADRs [17]. Enalapril induced cough was seen in similar number of three cases in study subject.Bronchodilators was caused ADR (n=4), salbutamol caused tremors of hand (n=2) and terbutaline caused skin rash in two study subjects.

Among antihistaminic, chlorpheniramine maleate (n=1),Pheniramine maleate (n=1) caused adverse effect of dryness of mouth, giddiness.

Each atorvastatin and rosuvastatin caused myalgia as adverse effect in one study subject. Among antiemetic causing ADR, metoclopramide caused features of extra pyramidal system like stiffness of upper limbs in one study subject, skin rash and itching was seen with domperidone (n=1). Atropine induced delirium and dicyclomine induced dryness of mouth was seen in one study subject each. Isotretinoin, a vitamin A analogue induced myalgia was reported in two subjects. Hematinic oral ferrous sulphate caused upper abdominal pain was reported in two subjects. Among anticancer drugs causing ADR, methotrexate induced hepatic cirrhosis was reported in one and cyclophosphamide caused black discolorations of palm in one subject. Alprazolam and tramadol induced vomiting was reported in one case each.ADRs with respect to WHO causality assessment was performed. Majority (65%) of the reported ADRs were evaluated as being probable, followed by 24% as being possible and 11% of cases were evaluated as being certain. The above findings were found to be similar with previous studies [18]. The cases assessed as certain ADR were amoxicillin induced skin rashes and itching, IV ceftriaxone induced generalized urticaria and paracetamol induced swelling of lips and generalized urticaria ,5 cases of ofloxacin induced rash and itching and 3 cases of tazobactum induced diarrhea, in these cases there was appearance of ADR following accidental rechallenge and recovery from ADR was noted on drug DE challenge.

ADRs was assessed according to Naranjo' s probability scale. Majority (54%) of ADR were evaluated as being probable similar to previous studies, [19,20] 44% as being possible and 2% of ADRs belonged to definite category.Assessment of severity of ADR based on modified Hartwig scale. Majority of ADRs (59%) were categorized as moderately severe which was consistent with the findings of previous studies,[21,22] 38% were of mild severity and 5% of cases were evaluated as severe. No fatalities due to ADR were recorded in the study.

Emotional impact of ADR was reported with drugs like atropine (delirium, confusion), prednisolone (depression, disturbed thoughts), ciprofloxacin, ofloxacin (anxiousness), chlordiazepoxide (low mood, confusion) in patient ADR reporting.Mean age of the study subject is 39.42 ±10.46 years with female preponderance which is in contrast with previous studies [23].The predominant pattern of ADR noted were skin rashes with itching which in accordance with earlier studies [24]. The common organ system involved was skin similar to previous studies,[24] however, in some studies gastrointestinal system was commonly involved [25]. Majority of the ADRs were from HCP as compared negligible reporting by patient, indicating better awareness among HCP about pharmacovigilance. Majority of patient self-reporting of ADR were from upper socio-economic status indicating better awareness about ADR in contrast to HCP reported ADR containing majority of study subjects from lower middle socioeconomic status.The predominant presenting complaint both in HCP and patient reported ADR were dermatological like skin rashes and itching showing that skin is one of the major target organs for ADR. The commonly implicated causative class of drug in both patient and HCP reporting of ADR were antimicrobial agents. Among antimicrobials, in HCP reporting ceftriaxone and ofloxacin were the leading causative drug where as in patient reporting it was amoxicillin.Majority of the reactions reported by patient were mild in severity, in contrast majority of ADR reported by HCP were moderate. Comparisons between HCP reporting and patient direct reporting also revealed that majority of ADR in both groups were probably preventable. Majority of ADR reported by HCP had no narration or had scanty narration, in contrast to patient direct reporting which had very elaborate narration of ADR. Patient who did direct reporting of ADR highlighted more about emotional and occupational impact of ADR in their life than the ADRs reported by HCP [26,27].

Conclusion

The clinical spectrum of ADRs reported from the more common mild reactions like skin rashes, itching, nausea and vomiting to moderately severe reactions prolonging the hospital stay of the patients resulting in decrease in physical quality of life. No fatalities due to ADR were reported. The predominant causative agents were antimicrobials drugs, antiretroviral drugs, NSAIDs and antihypertensive drugs. Majority of ADRs were probable in causality assessment, moderate in severity and probably preventable. Majority of ADRs were reported by HCP ,while direct reporting of ADR by patients were negligible. Comparison of ADR reporting between HCP and patient revealed similarity in qualitative analysis in terms of presenting complaints, drug causing pattern and preventability of ADR. In contrast to HCP, patient reporting of ADR had very elaborative narration and highlighted more about emotional and occupational impact of ADR on patient's life.

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