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A Prospective Study on Adverse Drug Reactions in a Tertiary Care South Indian Hospital

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ABSTRACT

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Background: ADRs have a major impact on public health, reducing patients' quality of life and imposing a considerable financial burden on the health care systems. **Objectives:** The main objectives were to analyze the pattern and extent of occurrence of ADRs in the hospital, identify co-morbidities, past and present illness, assess causality and identify the offending drugs, assess the severity and preventability of adverse drug reactions. **Methods:** Prospective, observational, spontaneous, reporting study with both active and passive methods. **Results:** A prospective observational spontaneous reporting study was carried out from January 2009 to August 2012. A total of 950 ADRs were accepted from the reported total of 1227 ADRs. Female patients experienced more number of ADRs when compared to male patients. Fever was the most commonly observed reason for admission. Maculopapular skin rashes were the commonly observed ADR in the study population. Amoxicillin and Clavulanic acid combination implicated more number of ADRs in the antibiotic category than others. Sixty one percent of the ADRs were moderate in severity followed by minor and severe ADRs. Most of reactions in the study population were managed by withdrawing the offending drug and rechallenge was performed in few subjects. Most of ADRs in the study were definitely preventable (40%) and were predictable in nature. Eighty percent of the reactions were probably related to the offending drugs, 758 reactions in the likely to cause ADRs. Twenty five percent of the ADRs were treated symptomatically in the study population.

Keywords: Adverse drug reactions, Pharmacovigilance, Spontaneous reporting, Allergic reactions, Observational study

INTRODUCTION

Adverse drug reactions (ADRs) cause considerable morbidity and mortality worldwide and in many cases are avoidable. ADRs have a major impact on public health; reducing patients' quality of life and imposing a considerable financial burden on the health care systems at a time when many health care systems are under considerable financial strain.[1] ADRs are a recognized hazard of drug therapy. Although some ADRs are minor and resolve without sequelae, others can cause permanent disability or death, and contribute to the incidence of adverse drug reactions, resulting in increasing health care costs.[2]

ADRs monitoring and reporting activity is in its infancy in India. ADRs reporting programs in an institutional basis can support the settings up of a sound pharmacovigilance system in the country. Further, hospital based ADRs programs can provide valuable information about potential problems in drug usage in an institution. Throughout the world, most of the ADRs monitoring programs rely on physician initiated (voluntary reporting) and have been partially successful. Under-reporting has been the biggest challenge in voluntary reporting method/ spontaneous ADRs reporting and it is prevalent even in developed countries with a long history of functional ADRs reporting system.[3] This may be due to several reasons like increase in workload, perception that reporting will not result in any improvement and lack of knowledge that an adverse event has occurred and fear of exposing oneself to litigation.[4] A method that could be employed to tackle this problem in a hospital set-up is to increase awareness about an existing system and the advantages of ADRs reporting.[3]

Therefore, it is important to motivate health care professionals to understand their role and responsibility in the detection, management, documentation, reporting of ADRs and all essential activities for optimizing patient safety. Thus, the program may contribute to decrease morbidity, mortality, and length of stay, health care costs and liability associated with ADRs. The main objectives of the current prospective observational spontaneous reporting study was to analyze the pattern and extent of occurrence of ADRs in the hospital, to identify the co-morbidities, past and present illness, to assess causality and to identify the offending drugs and to assess the severity and preventability of adverse drug reactions.

METHODOLOGY

Study site: The study was carried out at 800 beds Kovai Medical Center and Hospital, where all facilities under one roof were available with wide range of specialties.

Study design: Prospective, observational, spontaneous,

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reporting study with both active and passive methods: **a) Active method:** Pharmacist actively looking for suspected ADRs; **b) Passive method:** Stimulating prescriber to report suspected ADRs

Study period: The study was carried out for a period of three year and eight months between January 2009 and August 2012. Ethical committee clearance was obtained from the KMCH Ethics Committee to carry out the study in the hospital patients (Ref. No: EC/AP/103/09-2009).

Inclusion criteria: Inpatients, those who were exposed to any adverse drug reactions in the hospital and those who were admitted for the treatment of adverse drug reaction (i.e. reason for admission was ADRs) were included in the study.

Exclusion criteria: Patients who develop an ADR due to accidental or intentional poisoning, ADR due to fresh blood or blood products, ADR due to over dose, patients with drugs abuse and intoxication were excluded from the study.

ADRs notification and documentation form: Separate ADRs notification and documentation form was designed which consists of all relevant data including patient's demographic details, all drugs the patients received prior to onset of reaction, their route of administration, respective dosage, frequency, date of onset of reaction and the patient's allergy status to drugs and foods, ADRs management, details of reporter, etc. This form was made available in all nursing stations of the hospital and the out-patient areas for easy access to all healthcare professionals. It has two fold advantages; primarily to serve as an official medium of reporting back to the healthcare professional with necessary information pertaining to the suspected ADRs reported. Secondly, it acts as a method to encourage their continuous reporting of suspected ADRs.

Data collection and assessment of causality, severity and preventability

When a suspected drug was reported and met the inclusion and exclusion criteria, data on that particular suspected drug and reaction was collected and documented in a suitably designed ADR documentation form. Data for the study were collected from patient's case sheet, treatment chart, investigation reports, and personal interview with patient/patient's attendant, personal interview with reporting persons / clinicians. The collected data were transferred to the specially designed ADRs documentation form for evaluation.

Assessment of Causality: The extent of relationship between suspected ADR and the drug therapy was assessed using the WHO Probability assessment scale. It was further classified into Certain, Probable/likely, Possible, Unlikely, Conditional/unclassified and Un-assessable/unclassifiable. The causality relationship between a drug and suspected reaction was established by using the Naranjo's causality assessment scale[5], further the causal relation were classified into Definite, probable, possible, and unlikely.

Assessment of Severity: Severity of the reaction was assessed by using the Modified Hartwig and Siegel Severity assessment scale[6] and the severity is broadly categorized in to "mild", "moderate" and "severe" for each ADR.

Assessment of Preventability: All the reported ADRs were assessed for their preventability using the modified criteria of Schumock and Thornton's by Lau, et al.[7] and were categorized into "Definitely preventable", 'probably preventable" and "not preventable".

Preparation and Issue of Alert card: All the patients who were admitted to the hospital due to an ADR were provided, where applicable with an ALERT CARD, so as to prevent the future occurrence of similar ADRs in the patient. All the reported and evaluated suspected ADRs were documented in a suitably designed form and a feedback to each reporter was given using a THANK YOU note. The total cost of treatment was calculated by using cost of therapy, bed and room charge, extra number of days in hospital, prescriber fee, monitoring and laboratory studies, emergency department charge if any, etc.

Data Analysis, Interpretation and results

The collected data were analyzed for its appropriateness and suitability and interpretation was made for the collected data. Statistical analysis was performed with SPSS software, version17.0. P-values <0.05 were considered to be statistically significant. From the data analysis, results were obtained and conclusion was drawn.

RESULTS

In the current prospective observational spontaneous reporting study, 1227 Adverse Drug Reactions (ADRs) were reported but only 950 ADRs were accepted. About 277 ADRs were not accepted due of lack of information and some reactions were not categorized as ADRs. The gender distribution shown that 408 (33.25%) ADRs cases were male and 819 (66.75%) cases were female patients in the reported ADRs population. 313 (32.95%) were male patients and 637 (67.05%) were female patients in the accepted ADRs population.

Among the 1227 reported ADRs, 1196 (97.47%) were reported from In-patients and 31 (2.53%) were from out-patients. Among the 950 accepted ADRs cases, 928 (97.68%) were from In-patients and 22 (2.32%) were from out-patients. Allergic status of the accepted ADRs study population shown 13.68 (n=130) percent female and 8.84 (n=84) percent male were known case of allergic patients; about 53.37 (n=507) percent female and 24.11 (n=229) percent male were not

having any type of allergic history. In the overall accepted ADRs study population, only 22.53 (n=214) percent were found to be known allergic patients, majority of patients (77.47%; n=736) were found to be not a known allergic cases.

Suspected ADRs were observed in all department of the hospital but mostly in dermatology (28.63%; n=272) and General medicine (24.32%; n=231), followed by Neurology (7.89%; n=75), pulmonology (5.05%; n=48), diabetology (4.74%; n=45), gastroenterology (4.42%; n=42), nephrology (3.79%; n=36), gynecology (3.79%; n=36) and slim clinic (3.37%; n=32), etc. The department wise distributions of ADRs were described in table 1. Fever was the major and most commonly observed reason for admission in suspected ADRs population, which is observed in around 6.42 (n=61) percent of patients, which is followed by cough (n=42; 4.42%), general weakness (n=41, 4.32%), rashes (n=39; 4.11%), itching (n=39; 4.11%), allergic rhinitis (n=37; 3.89%), abdominal pain and giddiness were commonly found in each of 33 (3.47%) patients, followed by others.

Study on past medical history of study population was carried out, which revealed that diabetes mellitus was the major medical problem in around 61 (6.42%) patients and fever in around 47 (4.95%), hypertension in 46 (4.84%), atherosclerosis in 42 (4.42%), breathlessness in 39 (4.11%) patients. Stroke was past medical status in 38 (4.0%) patients followed by gastritis in 37 (3.89), fracture in 31 (3.26%), Ischemic Heart Disease (IHD), sinusitis and Chronic Renal Failure (CRF) in around each 28 (2.95%) patients, Acute Renal Failure (ARF) in 26 (2.74%), respiratory failure in 25 (2.63%) of the study population. 24 (2.53%) patients each had appendicitis, viral pyrexia and diabetes with hypertension, and others.

Therapy or medications used for the management of previous or past illness called as past medication history. In our study, the most commonly found drug as past medication was Paracetamol in around 58 (6.11%) patients, Amlodipine in 39 (4.11%) patients, Pantoprazole in 37 (3.89%), Zolpidem in 35 (3.68%), Atenolol in 34 (3.58%) patients. Glibenclamide and Metformin combination was given for 34 (3.58%) patients, Insulin with Metformin in 32 (3.37%), Ramipril and Ibuprofen each in 30 (3.16%) patients. Atorvastatin along with Ezetimibe used in 29 (3.05%) patients, Alprazolam in 27(2.84%), Atenolol with Amlodipine combination in 27(2.84%), Rabeprazole in 24(2.53%), Atorvastatin in 23(2.42%), Aspirin in 22(2.32%) and Aspirin with Clopidogrel in 21 (2.21%) patients.

Insulin, Rosuvastatin and Ciprofloxacin were prescribed for 19 (2.0%) patients each; Methotrexate and Chloroquine in 18 (1.89%) patient each, Clopidogrel in 16 (1.68%) patients, Streptokinase in 15 (1.58%), Tenofibrate in 13 (1.37%) of the study population. Ten (1.05%) of the study population received Heparin, Probenecid, Thyroxin sodium and Cisplatin as past medication. 8 (0.84%) Vincristine and 7 (0.74%) patient received Digoxin. Glipizide, Phenytoin sodium, Sodium valproate, Isoniazid, Piroxicam, Haloperidol, and Azathioprine were prescribed as past medication in each of 6 (0.63%) patients in the study population, etc.

Table 1: Department wise distribution of ADRs (n=950)

Name of the Department	Female		Male		Total	
	Number	Percent	Number	Percent	Number	Percent
Dermatology	150	15.79	122	12.84	272	28.63
General medicine	173	18.21	58	6.11	231	24.32
Neurology	54	5.68	21	2.21	7	57.89
Pulmonology	36	3.79	12	1.26	48	5.05
Diabetology	27	2.84	18	1.89	45	4.74
Gastroenterology	23	2.42	19	2.00	42	4.42
Nephrology	22	2.32	14	1.47	36	3.79
Gynecology	36	3.79	0	0.00	36	3.79
Slim clinic	16	1.68	16	1.68	32	3.37
Cardiology	22	2.32	8	0.84	30	3.16
Oncology	18	1.89	7	0.74	25	2.63
Dentistry	20	2.11	4	0.42	24	2.53
ENT	15	1.58	8	0.84	23	2.42
Orthopedics	9	0.95	4	0.42	13	1.37
Psychiatry	10	1.05	1	0.11	11	1.16
Pediatric & neonatology	6	0.63	1	0.11	7	0.74
Total	637	67.05	313	32.95	950	100.00

Diagnosis of disease in the accepted ADRs study population indicates medical condition or the health of patients. In this study, diabetes was major disease condition diagnosed in around 10 (n=95) percent of the study subjects, followed by fever (n=59; 6.21%), portal hypertension (n=57; 6.00%), peptic ulcer (n=50; 5.26%), asthma (n=44; 4.63%), acute renal failure (n=39; 4.11%) and hypertension (n=35; 3.68%).

Chronic obstructive pulmonary disorder (COPD) and epilepsy were diagnosed in each of 34 (3.58%) patients, chronic renal failure in 32 patients (3.37%); myocardial infarction and tuberculosis were in each of 31 (3.26%) patients; migraine, sleep apnea and carcinoma were observed in 30 (3.16%) patients each; acute pharyngitis in 29 (3.05%) patients; Diabetes with atherosclerosis found in 29 (3.05%) patients; diabetes+hypertension+atherosclerosis was observed in 27 (2.84%) patients; diabetes along with hypertension was diagnosed in around 25 (2.63%) patients, followed by atherosclerosis, angina pectoris, gastro-esophageal reflux disease (GERD) etc.

Status of admission in to the hospital shown that around 168 (17.68%) patient was admitted for treatment of ADRs which includes 103 (10.84%) female and 65 (6.84%) male patients, but a total of 782 (82.32%) patients experienced ADRs during their hospital stay when they were in the treatment of their clinical or diseased condition, which includes 534 (56.21%) female and 248 (26.11%) male patients.

Study on organ or system affected by the suspected ADRs revealed that a total of 9 systems were affected, among these skin and appendages was most badly affected in around 373 (39.26%) patients, gastrointestinal system in 304 (32.0%) patients. The other systems affected were endocrine system (n=71; 7.47%), central nervous system (n= 50; 5.26%), cardiovascular system (n=48; 5.05%), excretory system (n=33; 3.47%), hematological system (n=30; 3.16%), respiratory system (n=25; %) and skeletal system in 5 (0.53) patients. The detailed system wise ADRs were included in the table 2.

Each and every patient reported only one ADR (n=950) and none of the patients reported more than one ADR. Classification of suspected / accepted ADRs revealed that majority of ADRs in the study population were fall in the category of Type-A (Augmented and predictable) and it was around 548 (57.68%) ADRs, in this 357 (37.58%) ADRs were in female and 191 (20.11%) ADRs were in male patients. Type-B (Bizarre and unpredictable) ADRs were around 268 (30.11%), among this 206 (21.68) ADRs were in female and 80 (8.42%) ADRs were in male patients. In Type-C ADRs, 15 (1.58%) were found in female and 11 (1.16%) ADRs in male patients with a total of 26 (2.74%) ADRs. Among 20 (2.11%) Type-D ADRs, 11 (1.16%) ADRs were observed in female and 9 (0.95%) were in male patients, followed by Type-E ADRs, Type- F ADRs and others. The types of ADRs were included in table 3.

Maculopapular skin rashes was the most commonly reported and accepted Adverse Drug Reactions (ADRs), it was seen in 93 (9.79%) patients, followed by Severe gastric irritation (n=67; 7.05%), Exfoliative dermatitis (n=59; 6.21%), Acute urticaria (n=46; 4.84%), Hyper-pigmentation (n=38; 4.00%), Oral ulcer (n=35; 3.68%), Fixed drug eruption (n=33; 3.47%), Nausea and Vomiting (n=32; 3.37%), and Toxic epidermal necrolysis (TEN) (n=30; 3.16%). Abdominal pain and Elevation of liver enzyme were seen in each of 26 (2.74%) patients; Diarrhoea and Anemia also observed in each of 23 (2.42%) patients. Hypoglycemia and dysuria were reported by 22 (2.32%) each of the study population. Twenty one (2.21%) patients were found with morbiliform skin eruption, 20 (2.11%) patients with Steven Johnson syndrome, 20 (2.11%) patients with dyspepsia, 19 (2.0%) with erythroderma and 19 (2.0%) with acute

Table 2: Report of organ / system affected by the ADRs (n=950)

Name of the Organ/System	Female		Male		Total	
	Number	Percent	Number	Percent	Number	Percent
Skin and appendages	246	25.89	127	13.37	373	39.26
Gastrointestinal system	208	21.89	96	10.11	304	32.00
Endocrine system	49	5.16	22	2.32	71	7.47
Central nervous system	36	3.79	14	1.47	50	5.26
Cardiovascular system	28	2.95	20	2.11	48	5.05
Excretory system	21	2.21	12	1.26	33	3.47
Hematological system	22	2.32	8	0.84	30	3.16
Respiratory system	16	1.68	9	0.95	25	2.63
Skeletal system	4	0.42	1	0.11	5	0.53
Others	7	0.74	4	0.42	11	1.16
Total	637	67.05	313	32.95	950	100.00

hepatitis, 18 (1.89%) with drowsiness, 17 (1.79%) with dyspnoea, and 16 (1.68%) patients with head ache.

Constipation, sore throat and hyperglycemia were observed in each of 15 (1.58%) patients, followed by dry mouth and hyperuricemia in each of 14 (1.47%) patients, glossitis and arterial hypertension were in each of 12 (1.26%) patients. 10 (1.05%) patients were found with orthostatic hypotension and 9 (0.95%) each with systemic lupus erythematosus, arterial hypotension and hypokalemia. 8 (0.84%) reported with orthopnoea, 7 (0.74) each reported with extra-pyramidal symptoms and urinary retention, etc. The details of reactions were included in the table 4.

The drugs implicated in producing Adverse Drug Reactions (ADRs) were studied extensively and described that a total of 81 different drugs implicated 950 ADRs. Among the implicated drugs antibiotics produced more number of ADRs it was around 212 (22.32%), in this antibiotics category Amoxicillin and Clavulanic acid combination produced 46 ADRs followed by Ciprofloxacin 32, Moxifloxacin 26, Cloxacillin 18, Levofloxacin 11, Cefuroxime 9, Cefoperazone 8, Ceftriaxone 7, Cephalexin 7, Ampicillin 7, Penicillin 6, Doxycyline 5, Erythromycin 5, Vancomycin 3, and Bleomycin 3. Gentamycin, Imipenem, Metronidazole, and Piperacillin with Tazobactam each produced one ADR.

One hundred and thirty one (13.79%) ADRs were produced by Non-steroidal Anti-Inflammatory Drugs (NSAIDs), in this Aspirin produced majority of ADRs (n=35), followed by Paracetamol 27, Diclofenac sodium 21, Naproxen 18, Indomethacin 12, Celecoxib 7, Ibuprofen 7 and Nimesulide 4 ADRs. Cardiovascular drugs implicated 9.47 (n=90) percent of ADRs, in this category Carvedilol produced 31 ADRs followed by Amlodipine 27, Nifedipine 16, Verapamil 10, and Diltiazem 6 ADRs. Corticosteroids implicated 86 (9.05%) ADRs, in which Dexamethazone produced 30 ADRs, Hydrocortisone 27, Prednisolone 14, Fluticasone 12 and Solumedrol 3 ADRs. A total of 72 suspected ADRs were implicated by antineoplastic drugs; Vincristine 19, Vinblastine 13, Methotrexate 11, 6-Mercaptopurine 10, Carboplatin 7, Doxorubicin 6 and Paclitaxel 6 ADRs. 53(5.58%) ADRs were implicated by antidiabetic agents; Insulin 22, Metformin 14, Glipizide 9 and Gliclazide 8 ADRs. In the lipid lowering agents, Atorvastatin implicated 23 ADRs, Fenofibrate 14, Rosuvastatin 8, and Ezetimibe 4, with a total of 49 (5.16%) ADRs by lipid lowering agents. Anticonvulsants produced 45 (4.74%) ADRs; Carbamazepine 24, Phenytoin 16, Oxcarbazepine 4 and Topiramate produced one ADRs. Ranitidine, Omeprazole and Rabeprazole were the antiulcer or antisecretory agents which implicated 15, 11 and 8 ADRs respectively and a total of 34 (3.58%) ADRs were produced by these drugs. Dapsone, Sulphonamides and Sulfamethoxazole with Trimethoprim implicated 15, 7 and 4 ADRs respectively with a total of 26 (2.74%) ADRs. Local anesthetics like Xylocaine and Gesicaine produced 15 and 8 ADRs respectively with a total 23 (2.42%) ADRs. Antiemetics implicated 19 (2.0%) ADRs in which Ondansetron implicated 11 and Phenergan implicated 8 ADRs, etc. The drugs which implicated ADRs were included in the table 5.

Severity of suspected ADRs were assessed with modified Hartwig and Siegel Severity assessment scale, revealed that majority of suspected ADRs were moderate (n=583; 61.37%), in which 440 (46.32%) were observed in female patients and 143 (15.05%) in male patients. Mild ADRs were found to be 308 (32.42%), in this 158 (16.63%) were detected from female patients and 150 (15.79%) from male patients, followed by severe ADRs, it was around 55 (5.79%), among this 36 (3.79%) were from female and 19 (2.0%) were from male patients. 4 (0.42%) lethal effects were observed in the study patients, among this 3 (0.32%) from female and 1 (0.11%) from male patients.

Causality assessment was used to describe the causal relationship between offending drugs and the reaction and it

Table 3: Classification of suspected/ accepted ADRs in the study population (n=950)

Type of ADR's	Female		Male		Total	
	Number	Percent	Number	Percent	Number	Percent
Type - A	357	37.58	191	20.11	548	57.68
Type - B	206	21.68	80	8.42	286	30.11
Type - C	15	1.58	11	1.16	26	2.74
Type - D	11	1.16	9	0.95	20	2.11
Type - E	10	1.05	7	0.74	17	1.79
Type - F	5	0.53	3	0.32	8	0.84
Type - G	2	0.21	1	0.11	3	0.32
Type - H	23	2.42	9	0.95	32	3.37
Type - U	8	0.84	2	0.21	10	1.05
Total	637	67.05	313	32.95	950	100.00

Table 4: List of Suspected /Accepted ADRs in the study population (n=950)

Description of ADRs	Female		Male		Total	
	Number	Percent	Number	Percent	Number	Percent
Maculopapular skin rashes	64	6.74	29	3.05	9	39.79
Severe gastric irritation	48	5.05	19	2.00	67	7.05
Exfoliative dermatitis	42	4.42	17	1.79	59	6.21
Acute urticaria	29	3.05	17	1.79	46	4.84
Hyper-pigmentation	24	2.53	14	1.47	38	4.00
Oral ulcer	25	2.63	10	1.05	35	3.68
Fixed drug eruption	19	2.00	14	1.47	33	3.47
Nausea and Vomiting	25	2.63	7	0.74	32	3.37
Toxic Epidermal Necrolysis (TEN)	17	1.79	13	1.37	30	3.16
Abdominal pain	15	1.58	11	1.16	26	2.74
Elevation of liver enzyme	18	1.89	8	0.84	26	2.74
Diarrhea	15	1.58	8	0.84	23	2.42
Anemia	17	1.79	6	0.63	23	2.42
Hypoglycemia	15	1.58	7	0.74	22	2.32
Dysuria	15	1.58	7	0.74	22	2.32
Morbiliform skin eruption	13	1.37	8	0.84	21	2.21
Steven Johnson Syndrome	12	1.26	8	0.84	20	2.11
Dyspepsia	16	1.68	4	0.42	20	2.11
Erythroderma	15	1.58	4	0.42	19	2.00
Acute hepatitis	12	1.26	7	0.74	19	2.00
Drowsiness	13	1.37	5	0.53	18	1.89
Dyspnoea	11	1.16	6	0.63	17	1.79
Headache	11	1.16	5	0.53	16	1.68
Constipation	7	0.74	8	0.84	15	1.58
Sore throat	7	0.74	8	0.84	15	1.58
Hyperglycemia	10	1.05	5	0.53	15	1.58
Dry mouth	11	1.16	3	0.32	14	1.47
Hyperuricemia	9	0.95	5	0.53	14	1.47
Glossitis	9	0.95	3	0.32	12	1.26
Arterial hypertension	5	0.53	7	0.74	12	1.26
Hyperkalemia	8	0.84	3	0.32	11	1.16
Orthostatic hypotension	7	0.74	3	0.32	10	1.05
Systemic lupus erythematous	8	0.8	4	10.11	9	0.95
Arterial hypotension	6	0.63	3	0.32	9	0.95
Hypokalemia	7	0.74	2	0.21	9	0.95
Orthopnea	5	0.53	3	0.32	8	0.84
Extra pyramidal symptoms	6	0.6	3	10.11	7	0.74
Urinary retention	3	0.32	4	0.42	7	0.74
Convulsions	4	0.42	2	0.21	6	0.63
Tachyarrhythmia's	3	0.32	3	0.32	6	0.63
Bradycardia	4	0.42	2	0.21	6	0.63
Thrombocytopenia	4	0.42	2	0.21	6	0.63
Acne form eruption	3	0.32	2	0.21	5	0.53
Tachycardia	3	0.32	2	0.21	5	0.53
Hematuria	3	0.32	1	0.11	4	0.42
Steroid psychosis	2	0.21	1	0.11	3	0.32
Myalgia	2	0.21	1	0.11	3	0.32
Rhabdomyolysis	2	0.21	0	0.00	2	0.21
Unusual Cough	1	0.11	1	0.11	2	0.21
Alopecia	1	0.11	1	0.11	2	0.21
Scarlatiniform eruption	1	0.11	1	0.11	2	0.21
Ataxia	1	0.11	1	0.11	2	0.21
Agranulocytosis	1	0.11	0	0.00	1	0.11
Hirsutism	1	0.11	0	0.00	1	0.11
Lichenified plaques	1	0.11	0	0.00	1	0.11
Myopia	1	0.11	0	0.00	1	0.11
Total	637	67.05	313	32.95	9501	00.00

Table 5: List of drugs implicated in ADRs and frequency of reactions (n=950)

Class of drug(s)	Name of the drug	Number	Percent
Antibiotics (212; 22.32%)			
	Amoxicillin/Clavulanic acid	46	4.84
	Ciprofloxacin	32	3.37
	Moxifloxacin	26	2.74
	Cloxacillin	18	1.89
	Ofloxacin	15	1.58
	Levofloxacin	11	1.16
	Cefuroxime	9	0.95
	Cefoperazone	8	0.84
	Ceftriaxone	7	0.74
	Cephalexin	7	0.74
	Ampicillin	7	0.74
	Penicillin	6	0.63
	Doxicyclin	5	0.53
	Erythromycin	5	0.53
	Vancomycin	3	0.32
	Bleomycin	3	0.32
	Gentamycin	1	0.11
	Imipenem	1	0.11
	Metronidazole	1	0.11
	Piperacillin/Tazobactam	1	0.11
NSAIDs (131; 13.79%)			
	Aspirin	35	3.68
	Paracetamol	27	2.84
	Diclofenac sodium	21	2.21
	Naproxen	18	1.89
	Indomethacin	12	1.26
	Celecoxib	7	0.74
	Ibuprofen	7	0.74
	Nimesulide	4	0.42
Cardiovascular drugs (90; 9.47%)			
	Carvedilol	31	3.26
	Amlodipine	27	2.84
	Nifedipine	16	1.68
	Verapamil	10	1.05
	Diltiazem	6	0.63
Corticosteroids (86; 9.05%)			
	Dexamethazone	30	3.16
	Hydrocortizone	27	2.84
	Prednisolone	14	1.47
	Fluticasone	12	1.26
	Solumedrol	3	0.32
Antineoplastic drugs (72; 7.58%)			
	Vincristine	19	2.00
	Vinblastine	13	1.37
	Methotrexate	11	1.16
	6-Mercaptopurine	10	1.05
	Carboplatin	7	0.74
	Doxorubicin	6	0.63
	Paclitaxel	6	0.63
Antidiabetic agents (53; 5.58%)			
	Insulin	22	2.32
	Metformin	14	1.47
	Glipizide	9	0.95
	Gliclazide	8	0.84
Lipid lowering agents (49; 5.16%)			
	Atorvastatin	23	2.42
	Fenofibrate	14	1.47
	Rosuvastatin	8	0.84
	Ezetimibe	4	0.42
Anticonvulsants (45; 4.74%)			
	Carbamazepine	24	2.53
	Phenytoin	16	1.68
	Oxcarbazepine	4	0.42
	Topiramate	1	0.11
Antiulcer or antisecretory agents (34; 3.58%)			
	Ranitidine	15	1.58
	Omeprazole	11	1.16
	Rabeprazole	8	0.84
Antileprotic and sulpha drugs (26; 2.74%)			
	Dapsone	15	1.58
	Sulphonamides	7	0.74
	Sulfamethoxazole/trimethoprim	4	0.42
Local anaesthetics (23; 2.42%)			
	Xylocaine	15	1.58
	Gesicaine	8	0.84
Antiemetics (19; 2.0%)			
	Ondansetron	11	1.16
	Phenargan	8	0.84
Opioid analgesics (19; 2.0%)			
	Fentanyl	8	0.84
	Dextropropoxyphene	6	0.63
	Tramadol	5	0.53
Antitubercular drugs (19; 2.0%)			
	Isoniazid	12	1.26
	Rifampicin	7	0.74
Antidiarrhoeal (18; 1.89%)			
	Loperamide	11	1.16
	Bisacodyl	7	0.74
Antiplatelet aggregating agents (17; 1.79%)			
	Clopidogrel	17	1.79
	Anticoagulants (9; 0.95%)		
	Heparin90.95		
Antiparkinsonian agents (5; 0.53%)			
	Cabergoline	5	0.53
Antimalarial (4; 0.42%)			
	Chloroquine	4	0.42
Antihistamines (4; 0.42%)			
	Cetirizine	4	0.42
Miscellaneous (15; 1.58%)			
	Folic acid	03	0.32
	Unknown	12	1.26
	Total	950	100.00

was done with Naranjo's causality assessment scale and shown that 20 (2.11%) ADRs were definitely related to drugs, 759 (79.89%) ADRs were probably related to drugs, 165 (17.37%) ADRs were possibility related to drugs and 6(0.63%) ADRs were unlikely related to drugs.

Probability of the suspected ADRs were assessed with WHO probability assessment scale and revealed that 22 ADRs were certain, 758 ADRs were probable or likely, 160 ADRs were possible, 5 ADRs were unlikely, 5 ADRs were un-assessable or unclassifiable and none of the ADRs was conditional or unclassified.

Preventability of the suspected ADRs were assessed with Schmock and Thornton criterion modified by Lau, et al. and showed that 384 (40.42%) ADRs were definitely preventable, among this 256 (26.95%) ADRs were present in female and 128 (13.47) in male patients; probably preventable ADRs were 294 (30.95%) in which 198 (20.84%) ADRs were identified in female and 96 (10.11%) ADRs in male patients; 272 (28.63) ADRs were identified as not-preventable and it was observed in 183 (19.26) female and 89 (9.37) male patients.

Management of ADRs in the study population shown that, in 89.89 (n=854) percent patients the offending drug was withdrawn it includes 60.21 (n=572) percent female and 29.68 (n=282) percent male patients; dose was altered in 10.11 (n=96) percent of the patients including of 6.84 (n=65) percent female and 3.26 (n=31) percent male patients.

Regarding the treatment given for patients after experiencing an ADR; a total of 264 patients received treatment in this 150 (15.79%) were female and 114 (12.0%) were male patients. Symptomatic treatment was given in 236 (24.84%) patients including 138 (14.53%) female and 98 (10.32%) male patients; specific treatment was given to 28 (2.95%) patients, it includes 12 (1.26%) female and 16 (1.68%) male patients. The outcome ADRs management was studied and shown that 948 (99.79%) patients were recovered, among this 637(67.05) patients were female and 311 (32.74) were male patients; 2 (0.21%) patients experienced a fatal reaction and these 2 patients were male.

Dechallenge and Rechallenge was observed in the study population; in around 927 (97.58%) patients dechallenge was done, which includes 620 (65.26%) female and 307 (32.32%) male patients; rechallenge was performed in only 23 (2.42%) patients which includes 17 (1.79%) female and 6 (0.63%) male patients. Assessment on outcome of dechallenge was carried out and revealed that from 927 (97.58%) dechallenged patients, 925 (97.37%) patients were completely recovered with an recovery percentage of 99.78 and 2 (0.21%) male patients experienced fatal reaction. The suspected reaction has not reappeared in the study population. Assessment on outcome of rechallenge was carried out in 23 (2.42%) patients and revealed that 20 (2.11%) patients were completely recovered and the suspected reaction did not reappear after administering the offending drug(s). But in 3 (0.32%) patients with rechallenge, the reaction reappeared and they were female.

Pathophysiological conditions were found as predisposing factor in 255 (26.84%) patients, amount of drug administered in 215 (22.63%) patients, previous history of allergy in 197(20.74%), diseased circumstances in 107 (11.26%) patients, race or genetics in 25 (2.63%), Pregnancy in 24(2.53%) patients. Polypharmacy was the important factor to cause ADRs in many of the study population, the same was observed in our study also in predisposing factors of ADRs. The study on number of drugs per prescription revealed that only one (0.11%) patient received single medications and most of the patients received more than one medication. 21(2.21%) patients received 2 drugs, 102 (10.74%) patients received 3 drugs, and 76 (8.0%)patients received 4 drugs.

Majority of patients (n=184; 19.37%) received 5 drugs, 155(16.32%) patients received 6 drugs, 127 (13.37%) patients received 7 drugs and 82 (8.63%) patients received 8 drugs. 9 drugs were found in 18 (1.89%) of the prescription, 10 drugs in 24 (2.53%) prescriptions, 11 drugs in 63 (6.63%) prescription, 12 drugs in 34 (3.58%) prescriptions and 13 drugs in 24 (2.53%) prescriptions. Fourteen drugs were prescribed in 14 (1.47%) patients, 15 drugs were prescribed in 16 (1.68%) patients and 9 (0.95%) patients were prescribed with more than 15 drugs. The average drug prescribed per patient was found to be 6.80±0.63 drugs, and shown a significant correlation with results.

DISCUSSION

A total of 950 ADRs were accepted from the 1227 reported ADRs, 97.68 percent of ADRs were reported from In-patient department and 2.32 percent ADRs were reported from out-patient department. This finding was similar to an Indian study population showed that 73(76.04%) ADRs were reported from inpatient department and 23 (23.96%) ADRs were from outpatient department.[8]

A total of 219 (23.05%) patient with suspected ADRs found between the age group of 41 and 50 years. Hundred and sixty eight (17.68%) patient with ADRs observed in the age between 51 and 60 years; in the age group of 61 to 70 years, a total of 204 (21.47%) patients were found to have any one suspected ADRs. This observations were consistent with many studies, patients admitted with ADRs were significantly older than patients without ADRs (65-83 years).[9] An Indian study found adult predominance (70%) over the pediatric (16%) and geriatric (14%) population.[10] Geriatric patients reported more number (24; 56%) of ADRs than others.[11] This

may be due to the fact that most adult patients who were receiving multiple drugs therapy and also presented with other co-morbidities such as diabetes, hypertension and atherosclerosis etc.

In this study, female patients were more prone to have allergic history ((n=130; 13.68%) when compared to male ((n=84; 8.84%). This may be due to the poor immune status and less tolerability against disease(s) in female patients. Suspected ADRs were observed in all department of the hospital but mostly in dermatology (28.63%; n=272) and General medicine (24.32%; n=231), followed by neurology (7.89%; n=75), pulmonology (5.05%; n=48), diabetology (4.74%; n=45) etc. This is the facts due to all cutaneous reactions were admitted in the dermatology department and wide use of medications in the general medicine department. This findings were similar to a study with maximum number of ADRs were reported from the skin 35.13% followed by GIT 29.72% and then from CNS 18.91%.[12] Medicine department had reported the highest percentage of ADRs (42%) followed by the dermatology department (39%).[10] But in another study maximum number of ADRs reported from general medicine department (19; 42.22%) followed by cardiology (11; 24.4%) and other departments.[11]

Fever was the major and most commonly observed reason for admission in 61 patients, followed by cough (n=42; 4.42%), general weakness (n=41, 4.32%), and others. Diabetes mellitus was the major medical problem as past medical history in around 61 (6.42%) patients, hypertension in 46 (4.84%), etc. Past medical history of patients plays a major role in the development of adverse drug reactions, since they were using many medications for management of diseases and all the diseases were inter-related with one another.

Polypharmacy for the management of disease(s) prone to initiate the development of suspected ADRs in the study population. We observed the polypharmacy in many cases and most of them were developed with any one adverse drug reactions.

Diabetes was the major disease condition diagnosed in around 10 (n=95) percent of subjects, followed by fever (n=59; 6.21%), portal hypertension (n=57; 6.00%), peptic ulcer (n=50; 5.26%), asthma (n=44; 4.63%), acute renal failure (n=39; 4.11%) and hypertension (n=35; 3.68%). This may be due to the changes in life style of the study population and changes in food behavior; most of the study population likes to have carbohydrate food frequently than other food items. This also may be one of reason for developing diabetes and their associated complications. Our findings were contrast to a study showed that the most common principal diagnoses among inpatients admission was agranulocytosis (9.44%) followed by heart failure (3.64%).[13]

Around 168 (17.68%) patient were admitted for the treatment of ADRs and a total of 782 (82.32%) patients were experienced ADRs during their hospital stay when they were in the treatment of their clinical or diseased condition. This observation was similar to the findings of a study in that ADRs leading to hospital admission were recorded in 47 (7.8%) out of 600 patients.[14] This may be due to the utilization of any over the counter medications or polypharmacy or self medications of the patients for their simple ailments leads to the development of ADRs.

In this current study, skin and appendages was most badly affected in around 373 (39.26%) patients, gastrointestinal system in 304 (32.0%) patients. This observation was similar to many other studies the system most commonly affected by an ADR was the dermatology (62%) followed by the gastrointestinal (12%) system.[10] Most common system associated with ADRs were skin, GIT and CNS.[12] The most commonly affected organ system associated with ADRs in our study was the skin (52,5%).[15] Reactions affecting the skin, gastrointestinal tract and central nervous system were the most often reported and together accounted for 62.8% of all reactions.[16] Skin and appendage are the main parts of body to have cutaneous drug reactions, photo sensitivity reactions, fixed drug eruption, etc. Mostly drugs were disintegrated, distributed, metabolized and absorbed through gastrointestinal system, so the system is frequently exposed to all chemicals and drugs, leads to the development of gastrointestinal symptoms.

Majority of ADRs in the study population were fall in the category of Type-A (Augmented and predictable) and it was around 548 (57.68%) ADRs and Type-B (Bizarre and unpredictable) ADRs were around 268 (30.11%). These findings were consistent with many other studies most of the ADRs in the study were classified as Type A (n-1161, 95%).[9] The majority (91%) of ADRs can be assigned to type A ADRs which are preventable.[14] All the ADRs observed were Type-B, and were unrelated to dosage.[17] Of the reported ADRs Type A reactions (34; 75.55%) were common compared to Type B reactions (11; 24.44%).[11] Type A reactions were more common in the study because they were dose related, predictable, high morbidity, low mortality and respond to dose reduction.

Maculopapular skin rashes (n=93; 9.79%) was the most commonly reported and accepted ADRs in the study population, followed by Severe gastric irritation (n=67; 7.05%), Exfoliative dermatitis (n=59; 6.21%), etc. These findings were consistent with a many other studies in that the most commonly reported reactions were rashes (32%) followed by itching or pruritis (11%), edema (6%) and urticaria (5%).[10] 11.3% (n=21) were cutaneous eruptions,

11.3% (n=21) were hyperglycemia and gastrointestinal abnormalities in 25.3% (n=47) patients in another study.[18] Most common morphologic varieties of the reactions were urticaria (27.19%), fixed drug rashes (25.16%) and macular and morbiliform eruptions (25.16%).[19] Most common ADRs were gastrointestinal in nature (52.5%); abdominal discomfort (37.7%), vomiting (1%), nausea (9.8%); alopecia 4.9%.[20] In one study 48 hospitalized patients reported nausea, diarrhea and head ache during the anticancer therapy.[21]

A total of 81 different drugs implicated 950 ADRs in the study population. But in one study they reported a total of 194 ADRs resulted from the use of 70 different drugs.[18] Among the implicated drugs antibiotics produced more number of ADRs, in this Amoxicillin and Clavulanic acid combination produced 46 ADRs followed by Ciprofloxacin 32, Moxifloxacin 26, Cloxacillin 18, etc. The offending drugs and the reactions were similar to various other studies, a retrospective study reported Urticaria developed in two patients, one who received Piperacillin/Tazobactam and one who was treated with Imipenem.[17] Asymptomatic liver function disturbances were seen in one patient who received Cefepime therapy. Two out of four who received Piperacillin/Tazobactam developed severe neutropenia during their 2-4 weeks therapy. The drug most commonly implicated with ADRs was antibiotics (24%) followed by anti-tubercular drugs (23%).[10]

Antibiotics were the most frequent cause of ADRs with 219 (38.8%) patients experiencing an ADR associated with this drug class.[15] The therapeutic group most frequently suspected of causing ADR comprised anti-infective drugs and vaccines.[16] Amoxicillin and Clavulanic acid association was most frequently reported, and among the reactions reported for this antibiotics. Among antimicrobials, the most common drugs were Cotrimoxazole (15%) and Fluoroquinolones (15%) while Phenytoin (67%) and Carbamazepine (20%) were the commonest antiepileptics.[22] Antibiotics were the treatment group that precipitated the most ADRs (16.3%), opiates (18; 9.1%), corticosteroids (11; 5.6%).[18] One hundred and thirty one (13.79%) ADRs were produced by Non-steroidal Anti-Inflammatory Drugs (NSAIDs), in this Aspirin produced majority of ADRs (n=35), followed by Paracetamol 27, Diclofenac sodium 21, Naproxen 18, Indomethacin 12, Celecoxib 7, Ibuprofen 7 and Nimesulide 4 ADRs. This observation was consistent with a study, Non steroidal anti-inflammatory drugs and diuretics were most commonly implicated, Aspirin was the most common drug implicated in 18% of admissions.[9]

In the cardiovascular drugs, Carvedilol produced 31 ADRs followed by Amlodipine 27, Nifedipine 16, Verapamil 10, and Diltiazem 6 ADRs. Hyperkalemia as one of the reasons for hospital admission was related to administration of angiotensin converting enzyme inhibitors or potassium sparing diuretics or their combination.[14] Diuretics produced more number ADRs (10; 22.22%) followed by antibiotics (8: 17.77%).[11] Anticonvulsants produced 45 (4.74%) ADRs; Carbamazepine 24, Phenytoin 16, Oxcarbazepine 4 and Topiramate produced one ADRs. These observations were similar to a study, the most common offending drugs were Carbamazepine (16.23%), Phenytoin (15.15%) and Cotrimoxazole (13.53%).[19] Bleeding related to Warfarin overdosing as an ADR causing hospitalization was reported only in seven patients.[14] Similar findings were noted in our study also that antiplatelet aggregating agents like Clopidogrel produced 17 (1.79%) ADRs, anticoagulants like Heparin produced 9 (0.95%) ADRs.

In the current study, majority of the suspected ADRs were moderate (n=583; 61.37%), followed by mild (n=308; 32.42%) and severe (n=55; 5.79%). These observations were consistent with other studies, the severity of ADRs was either moderate (urticaria, abnormal LFT) or severe (neutropenia).[17] Most of the ADRs (96.5%) were moderately severe while 3 cases were severe in nature and were preventable.[22] At least one in five patients was admitted to the hospital due to the severe ADRs and a small portion (0.07%) of patients died in Emergency department.[13] We observed some distinct findings from some other studies in that a higher percentage of patients with severe ADRs were male (44%) compared with patients with mild ADRs (38% male).[13] The degree of severity was minor in 72.9% of the reports, moderate in 22.4%, severe in 4.4%, and fatal in 0.3% (4 cases).[16]

Four (0.42%) lethal effects were observed in the study patients, among this 3 (0.32%) from female and 1 (0.11%) from male patients, which is contrast to an study showed 28(2.3%) patients died as a direct result of the index ADRs and gastrointestinal bleeding was responsible for 15 (54%) deaths, while aspirin in isolation or in combination with other drugs was implicated in 17 (61%) deaths.[9]

Causality assessment revealed, twenty (2.11%) ADRs were definitely related to drugs, 759 (79.89%) ADRs were probably related to drugs, 165 (17.37%) ADRs were possibility related to drugs and 6 (0.63%) ADRs were unlikely related to drugs. Similar findings were noted from other studies also, most of the reported ADRs belonged to the category of probable (70%) followed by possible in 30% of the cases.[10] All ADRs were found to be probably related to the antibiotic administration.[17] Causality assessment revealed that no reactions were certain or definite, 9 were probable and 52 were possible reactions.[20]

Probability assessed revealed that 22 ADRs were certain, 758 ADRs were probable or likely, 160 ADRs were possible,

5 ADRs were unlikely, 5 ADRs were un-assessable or unclassifiable and none of the ADRs was conditional or unclassified. This is contrast to a study in that causality assessment showed 46% possible, 23% probable and 29% were un-assessable because the drug was unknown.[22] Three hundred and eighty four (40.42%) ADRs were definitely preventable, 294 (30.95%) ADRs were probably preventable and 272 (28.63) ADRs were identified as not-preventable. These findings were similar to a study, of the 316 reported ADRs, majorities (56%) of the reaction were predictable and 33 % of the reactions were preventable.[10] The findings were different from other studies in that a majority of ADRs were not preventable (n=57; 79%).[22] None of the ADRs were definitely probable, 84 ADRs were probable preventable and 12 ADRs were not preventable.[8]

In 89.89 (n=854) percent patients, the reactions were managed by withdrawing the offending drug and dose was altered in 10.11 (n=96) percent of patients. Similar findings were observed in another study; In 90% of the cases, the suspected drug was withdrawn whilst no change was made with the suspected drug in 9% of the cases, and dose was altered in 1% of cases.[10] 56% of ADRs were managed by withdrawing the drug and altering of the dose, 43.75% of ADRs were treated with other drugs.[8] In our study, symptomatic treatment was given in 236 (24.84%) patients and specific treatment was given to 28 (2.95%) patients.

All our study patients (n=948; 99.79%) were recovered from the reactions, but only 2 (0.21%) patients experienced a fatal reaction. One patient died due to Dapsone induced agranulocytosis and other with carbamazepine induced Stevens Johnson syndrome (SJS). Similar fatality was observed in one study, 1(0.27%) patient died due to ADRs caused by Dapsone induced agranulocytosis and 15 (40.54%) cases got hospitalized due to ADRs.[12] 2 patients died of allopurinol related SJS which is the second most common drug associated with fatal ADRs.[15] 5(0.67%) deaths were reported out of 12 severe acute cutaneous drug reactions.[19]

In the current study, dechallenge was done in around 927 (97.58%) patients and rechallenge was performed in only 23 (2.42%) patients. From the 927 (97.58%) dechallenged patients, 925 (97.37%) patients were completely recovered with a recovery percentage of 99.78 and from 23 (2.42%) rechallenge patients, 20 (2.11%) patients were completely recovered. But in another study, an accidental rechallenge was occurred in 3 cases leading to recurrence and 3 patients died of SJS. Dechallenge was performed in 63 (41.6%) ADRs and the response were satisfactory.[22]

CONCLUSION

Adverse drug reactions are a significant cause of morbidity and mortality and contribute to the incidence of adverse events, resulting in increased healthcare costs. It is important to motivate health care professionals to understand their role and responsibility in the detection, management and reporting of suspected ADRs and all essential activities for optimizing patient safety. The reporting of ADRs needs continuous stimulation. It is important to achieve the development of a positive attitude towards pharmacovigilance among health care professionals, including pharmacist, so that ADRs reporting becomes an accepted and understood routine.

A limitation of the study was that the rate of ADR related hospitalization was probably an underestimate due to underreporting or misclassification, because all ADRs possibly were not identified. The actual number of ADRs in our patients might also have been higher than the number of ADRs detected and reported during hospitalization because of relatively short length of stay in our hospital (mean 7±1.5days).

REFERENCES

1. Hitesh Patel, Derek Bell, Mariam Molokhia, et al. Prevalence of adverse drug reactions with commonly prescribed drugs in different hospitals of Kathmandu valley. BMC Clin Pharmacol 2007; 7:9:10.
2. Monica Zolezzi, Nirasha Parsotam. Adverse drug reaction reporting in New Zealand: implications for pharmacists. Ther Clin Risk Manag 2005; 1(3):181-8.
3. Rao PG, Archana B and Jose J. Implementation and results of an adverse drug reaction reporting programme at an Indian teaching hospital. Indian J Pharmacol 2006; 38:293-4.
4. Mehta DJ. Methods of reporting adverse drug reactions. Indian J Pharmacol 1972;4(2):67-74.
5. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981; 30(2):239-45.
6. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. Am J Hosp Pharm 1992; 49(9):2229-32.
7. Lau PM, Stewart K, Dooley MJ. Comment: hospital admissions resulting from preventable adverse drug reactions. Ann Pharmacother 2003; 37(2):303-4.
8. Venkatesan R, Ravisankar S, Lakshminarasu M, Rajendran SD. Indian J Hosp Pharm 2012;49:46-50.
9. Munir Pirmohamed, Sally James, Shaun Meakin, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ 2004; 329:15-9.
10. Rajesh R, Ramesh M, Parthasarathi G. A study on adverse drug reactions related hospital admission and their management. Indian J Hosp Pharm 2008; 45:143-8.
11. Dilip C, Lise Mary Mani, Saraswathi R, et al. Adverse drug reactions monitoring in tertiary level referral hospital, Perinthalmanna, Kerala. Indian J Hosp Pharm 2011; 48:107-11.

12. Jha N, Bajracharya O, Namgyal T. Prevalence of adverse drug reactions with commonly prescribed drugs in different hospitals of Kathmandu valley. Kathmandu Univ Med J 2007; 20(5):504-10.
13. Chen Wu, Chaim MB, Walter PW. Incidence and economic burden of adverse drug reactions among elderly patients in Ontario emergency departments- A retrospective study. Drug Saf 2012; 1-13.
14. Martin Wawruch, Martina Zikavska, Ladislava Wsolova, et al. Adverse drug reactions related to hospital admission in Slovak elderly patients. Arch Gerontol and Geriatr 2009: 48:186–90.
15. Agnes LF Chan, Haw Yu Lee, Chi-Hou Ho, et al. Cost Evaluation of Adverse Drug Reactions in Hospitalized Patients in Taiwan: A Prospective, Descriptive, Observational Study. Curr ther res 2008; 69(2).
16. Morales-Olivas FJ, Martinez-Mir I, Ferrer JM, et al. Adverse drug reactions in children reported by means of the yellow card in Spain. J Clin Epidemiol 2000; 53:1076–80.
17. Renata Shichmanter, Edward B. Miller, Zvi Landau. Adverse drug reactions due to prolonged antibiotic therapy for malignant external otitis. Euro J Intern Med 2004; 15:441-5.
18. Berga C Cullere, Gorgas MQ Torner, Altimiras J Ruiz, et al. Detecting adverse drug events during the hospital stay. Farm Hosp 2009; 33(6):312-23.
19. Chatterjee S, Ghosh AP, Barbhuiya J, Dey SK. Adverse cutaneous drug reactions: A one year survey at a dermatology outpatient clinic of a tertiary care hospital. Indian J Pharmacol 2006; 38(6):429-31.
20. Al-Malaq HM, Al-Arfaj HF, Al-Arfaj AS. Adverse drug reactions caused by methotrexate in Saudi population. Saudi Pharm J (2012) article in press.
21. Watters AL, Epstein JB, Agulnik M. Oral complications of targeted cancer therapies: A narrative literature review. Oral Oncol 2011; 47:441-8.
22. Shah SP, Desai MK, Dikshit RK. Analysis of Cutaneous Adverse Drug Reactions at a Tertiary Care Hospital – a Prospective Study. Trop J Pharm Res 2011; 10(4):517-522.