



Causality Assessment and Outcome of Adverse Drug Reaction Related Hospitalization in a Tertiary Care Teaching Hospital

Authors

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Abstract

Background: Adverse Drug Reactions (ADRs) are one of the leading causes of morbidity and mortality worldwide. They are important cause of hospitalization and rank fifth among all causes of death in developed countries. The present study was aimed to study the causality assessment and outcome of ADR related hospitalizations in the Medicine department of our tertiary care teaching hospital.

Methods: A prospective, observational study was conducted over a period of 10 months and included all adult patients with suspected ADR admitted to the Department of Medicine. Each patient of ADR was assessed for causality using the WHO Probability Scale.

Results: ADR related hospitalizations accounted for 0.24% of the total admissions to the Medicine department. The commonest ADR was hypoglycemia, followed by cutaneous drug reactions. Insulin and sulfonylureas were the most common suspected medications followed by antimicrobials. The most common predisposing factor was polytherapy. Causality assessment revealed that 36% of cases were certainly associated, 45% probably associated and 19% possibly associated with the respective suspected drugs. Death occurred in 2.2% of the ADR patients.

Keywords: pharmacovigilance, polytherapy, hypoglycaemia.

Introduction

Modern medicine has revolutionized the way diseases are being treated and has saved lives of millions. But these medicines come with a price, the risk of adverse drug reactions. ADRs are one of the leading causes of morbidity and mortality worldwide¹. In developed countries, around 3% to 6% of hospital admissions are due to ADRs, they rank fifth among all causes of death² and the incidence of fatal ADRs is 0.23% to 0.4%¹. There is very limited data from India, a study shows that 0.7% of hospital admissions were due to ADRs and fatal ADR was 1.8%³.

Adverse Drug Reaction (ADR) is a response to a drug which is noxious and unintended at doses normally used in humans for the prophylaxis, diagnosis or treatment of diseases or for the modification of physiological function⁴. ADRs may be predictable or unpredictable. The former may be due to the intrinsic dangers associated with the drugs themselves while in the latter individual patients may exhibit particular and unpredictable sensitivities to certain medicines. Also there is a risk of adverse drug interactions when more than one drug is prescribed.

Causality assessment is the method by which the extent of relationship between a drug and a suspected reaction is established. A wide variety of causality assessment scales are available currently, out of which Naranjo's scale⁵ and WHO scale of assessment⁶ are most commonly used. This helps us to be careful about the future use of the drug in the same or other individuals. There is a scarcity of data regarding drug induced hospitalizations in India. Hence the present study was aimed to evaluate the ADR related hospitalizations, their causal association and outcome in our tertiary care teaching hospital.

Materials and Methods

This was a prospective, observational study which was conducted over a period of 10 months i.e. from January 2016 to October 2016 in the Department of Medicine in collaboration with the ADR Monitoring Centre, Department of Pharmacology, S.C.B. Medical College, Cuttack, after approval by Institutional Ethics Committee.

Inclusion Criteria: All adult patients (aged >14 years) with suspected adverse drug reactions admitted to the department of Medicine, and willing to participate in the study.

Exclusion Criteria: All patients with accidental or intentional poisoning and those with drug abuse.

An informed consent was taken from the patients. A detailed history was taken regarding all the drugs consumed, whether prescribed or self-medication and duration of treatment with the suspected drug. The details of the clinical features, routine haematological and biochemical investigations like complete blood count, blood glucose level, liver function tests, kidney function tests, coagulation profile were done. Whether the drug was withdrawn, dose reduced or treatment continued, were also recorded. Causality assessment was done in the department of Pharmacology in collaboration with the concerned treating physician, by using the WHO-UMC scale⁶. All the patients were followed up during the course of hospitalization and the outcome, discharge or death was recorded.

Results

A total of 91 (0.24%) patients of ADR were admitted in the Department of Medicine out of the total 37,902 patients admitted for various causes during the study period of 10 months.

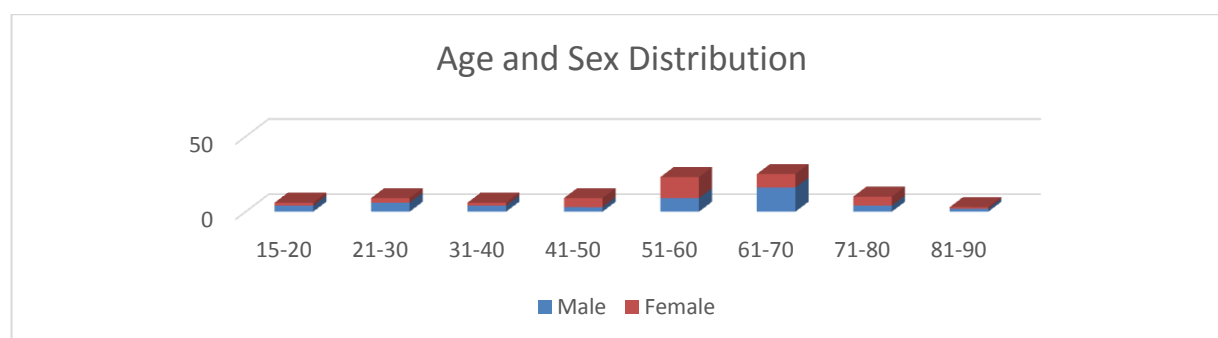


Fig 1: Age and Sex wise distribution of Patients with ADR

Most of the patients were above 50 years (66%), mean age was 54.71 years. Males comprised of 55(60.44%) and females 36(39.56%) patients. Maximum number of male cases were in the (61-

70) years age group whereas females were in (51-60) years age group. The difference of age distribution between male and female patients was statistically not significant ($p=0.444$).

Table 1: Clinical spectrum of ADRs and suspected drugs according to WHO-ART (Adverse Reaction Terminology) 2012

Clinical Spectrum	No. of cases	Suspected Medications
Hypoglycaemia	45	Regular insulin, pre-mixed insulin Glimepiride, Gliclazide, Glipizide
Drug rash	7	Ceftriaxone, Paracetamol, Vancomycin, Etoricoxib Sulfamethoxazole + Trimethoprim
Hepatopathy	6	Isoniazide, Rifampicin, Pyrazinamide
CVA(ICH)	6	Aspirin, Clopidogrel, Sunitinib
Hyponatemia	6	Hydrochlorthiazide, Olanzapine, Thioridazine
SJS-TEN	5	Phenytoin, Levofloxacin, Azithromycin, Sulfadoxine + Pyrimethamine
Upper GI bleed	4	Aceclofenac, Diclofenac
FDE	3	Levofloxacin, Piroxicam, Phenytoin
Acute gastritis	2	Aceclofenac, Paracetamol
Anaphylaxis	2	Piroxicam, Cefaclor
Dapsone reaction	1	Dapsone
Anemia	1	Methotrexate
Haemoglobinuria	1	Primaquine
Myopathy	1	Prednisolone
Hyperkalemia	1	Digoxin
TOTAL	91	

Hypoglycaemia was the leading cause of ADR related hospitalization in 45(49%) cases. It was followed by cutaneous drug reaction (17%). The

most common suspected drugs causing ADR were Insulin and sulfonylureas.

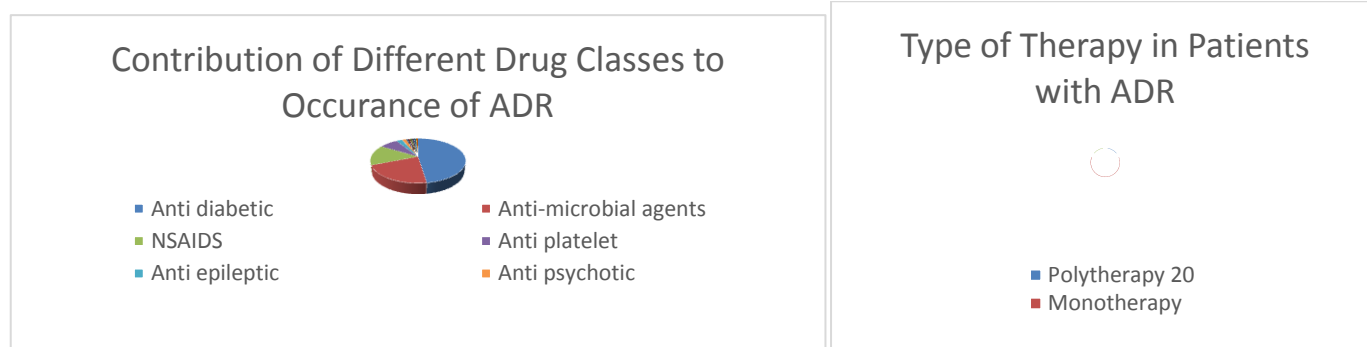


Fig 2 : Class of Suspected Drugs causing ADR and Type of Therapy in Patients with ADR

Anti-diabetic drugs were the most common class of drugs causing ADR followed by antimicrobial agents. Polytherapy (two or more drugs) was

found in 60.4% cases, monotherapy (one drug) and FDC (fixed dose combinations) in 19.8% cases in each category.

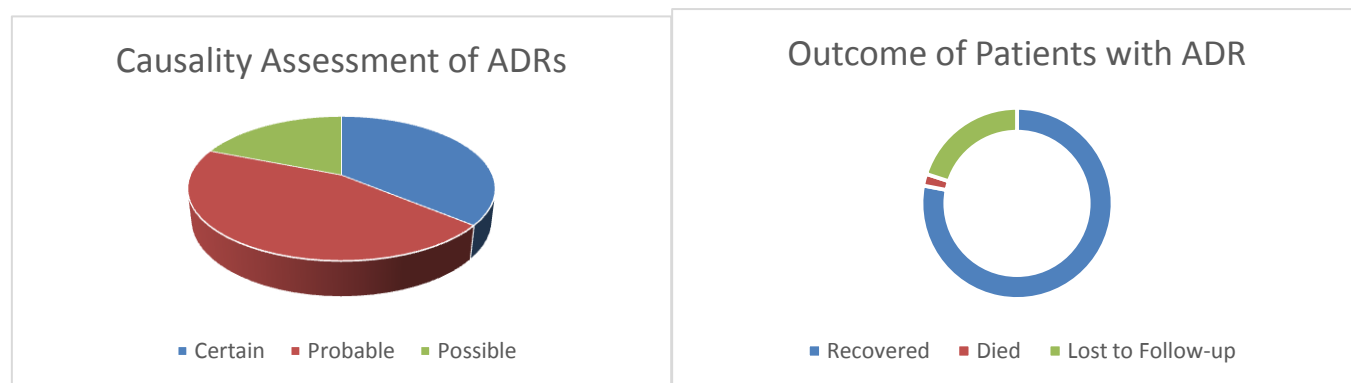


Fig 3: Causality assessment of ADRs (using WHO-UMC Assessment Scale) and Outcome of Patients with ADRs.

The causality association between the suspected drug and the adverse reaction revealed that 36% of cases were seen to be certainly caused by the suspected drugs, 45% of cases were probably and 19% of cases were possibly caused by the suspected medications.

Out of 91 ADR cases admitted, 71(78%) patients recovered, 18 (19.8%) lost to follow up and 2 (2.2%) were found to be fatal. Among the two deaths one was Steven-Johnson syndrome and the other was anaphylactic reaction. The overall fatality was 0.005% of all the cases admitted in the Department of Medicine.

Discussion

In our study, the number of hospital admissions in the Department of Medicine due to ADR was 91(0.24%). This is comparable with the study done by Jamunarani et al (0.12%)⁸, but lower than many studies^{1,3,7} which ranged from 0.7 to 24.1%, the reason being that some ADR patients are admitted to other departments (cutaneous ADRs to Dermatology ward and drug induced hepatitis to Hepatology ward). Further under-reporting may be a factor due to inadequate awareness about ADR reporting system among health care personnel.

The leading cause of ADR causing hospitalization was hypoglycemia, followed by cutaneous drug reactions (Table-1). Anti-diabetic drugs including Insulin and sulfonylureas, were the most common drugs causing ADR related hospitalization (Figure-2). This is in contrast to many studies who have reported dermatological reactions^{8,9,10} or gastrointestinal symptoms^{2,7} being the most common ADRs. This might be because our study included ADR patients admitted only to Medicine department, where all hypoglycemic patients are admitted on emergency basis.

Polytherapy was found in more than half of our hospitalized ADR patients (Figure-2), which is similar to the findings by Carbonin et al¹¹ who had shown that multiple medications is one of the predisposing factors for occurrence of drug reactions. Drug reactions due to polytherapy could be explained by drug interactions¹².

While evaluating ADR, causality assessment is the means by which the extent of relationship between drug and suspected reaction is established. The most difficult part of causality assessment is the involvement of multiple drugs in causing drug reactions. In our study we did the causality assessment by using WHO-UMC scale.

The scales assume different criteria for causality assessment. Some common points of consideration are temporal relationship between drug intake and onset of reaction, de-challenge, re-challenge, documented evidence about the reaction etc. So, the results of causality assessment completely depends upon quality and state of information obtained for each case. In our institute re-challenge was not done for ethical purpose. In many cases we got positive history of same reaction due to same drug or drug of similar class that could be called as re-exposure or accidental re-challenge.

While using the WHO-UMC scale (Figure-3), ADRs classified as "Certain" was 33 cases (36%). In most of the cases while analyzing effect of drug withdrawal on reaction, we found either disappearance or decrease severity of the reaction (dechallenge positive) and so large majority i.e 41 cases (45%) were classified as "Probable". Since in many of the cases multiple drugs were responsible for adverse event, we classified 17 cases (19%) under "Possible". Thus the majority of the ADRs were evaluated as being probable. This was similar to the results of past studies^{8,9,10}. 78% of cases recovered fully and 2.2% of the ADR patients died (Figure-3). This matches with the observation in past studies^{3,7}. In our study the overall fatality was 0.005% of all the patients admitted to the department of Medicine. The 2 patients who expired included Steven Johnson's syndrome and anaphylaxis.

However our study has certain limitations. We considered hospitalizations due to ADRs and did not include adverse events occurring during hospital stay of patients. Moreover ours is a tertiary care hospital where, on average, we get to

see more serious patients usually, including severe ADR cases.

Conclusion

ADRs are important causes of hospital admissions, resulting in significant morbidity and mortality. The prescribing practitioner thus requires considerable skill in the selection and use of the best and safest medicines for a given individual out of the choices available. It is also vital to develop proper mechanisms for evaluating and monitoring the safety of medicines in clinical use in order to prevent or reduce harm to patients and thus improve public health.

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