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ORIGINAL ARTICLE

Drug-Related Hospitalizations at a Tertiary Level Hospital in Bangalore: A Prospective Study

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ABSTRACT

The Objective of the present study was to determine the causality, severity, preventability, classification of adverse drug events, and drug therapeutic failures resulting in hospitalization, at a tertiary level hospital in Bangalore. Prospective data was collected from a total of 155 consecutive adult patients hospitalized during a period of six months due to drug related events at the Kempegowda Institute of Medical Sciences, Bangalore. The prevalence of Drug-related hospitalizations was (6.4%)[95% CI 5.6%-7.7%] in the study. Multiple drug therapy in patients was associated with drug related hospitalizations. 50 % of the admissions were due to Adverse Drug Reactions (ADR), 38% due to Dose Related Therapeutic Failure (DTF), and only 12% were due to Self or Intentional Poisoning (SIP). On sub-group analysis, 64% of ADR were noted to be due to normal side effects; and 68% of DTF were due to non-compliance. Using Naranjo's probability scale for causality assessment, 58% of Drug Related Hospital Admission (DRHA) was classified as definite; whereas 36% was probable. Out of these, 84% of DRHA were predictable, whereas 16% were non-predictable. 72% of DRHA was managed by altering the dose. The prevalence of Drug-related hospitalizations is high in this hospital, which merits further research and intervention.

Key Words: Drug, Hospital, Admission, Adults

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Introduction

Adverse drug events are defined as unfavourable medical events related to drug therapy [1]. Studies in the United States have estimated that adverse drug events account for up to 28% of emergency department visits, and 25% of ambulatory care encounters. Upto 70% of these visits are deemed preventable [1,2]. In addition to the morbidity and mortality associated with adverse drug events, the resulting costs contribute to the overall pressures on our health care system [3]. A probability model estimated that from 1995-2000, costs due to drug-related morbidity and mortality had more than doubled, from $76.6 billion to more than $177.4 billion [4, 5].

Numerous studies have investigated the problem of drug-related morbidity in ambulatory care, emergency department, and hospitalized patients [6]. Earlier research has been retrospective, resulting in inherent methodological limitations, with a possible underestimation of the problem. Also, the definition of an adverse drug event varies significantly among studies, limiting both comparative evaluation and external validity. In most studies, an adverse drug event has been limited to adverse drug reactions. The World Health Organization (WHO) defines adverse drug reaction as any noxious, unintended, or undesired effect of a drug occurring at dosages administered to humans for prophylaxis, diagnosis, or treatment [7]. This definition excludes many other classifications of adverse drug events that may result in hospitalization, such as untreated indication, improper drug selection, sub-therapeutic or supra-therapeutic dosage, noncompliance, drug interaction, and drug use without an indication [8].

The purpose of this study was to prospectively evaluate the frequency, severity, preventability, and classification of adverse drug events resulting in hospitalization in an internal medicine service of a large tertiary care hospital in South India.

Materials and Methods

Study Design and Setting

The present study was a prospective, observational study, conducted at the internal medicine unit of Kempegouda Institute Medical Sciences (KIMS), Bangalore, a tertiary level referral center and University teaching hospital in South India. Patients admitted to this service are hospitalized for diverse medical conditions such as cardiovascular disease, diabetes mellitus, pneumonia, gastrointestinal haemorrhage, liver, renal failure and haematological abnormalities, Ethics approval was obtained from the Research Committee of KIMS.

Patient Selection

Consecutive adult patients hospitalized to the internal medicine units for the period January 10 to June 15, 2007, were enrolled for the study. Inclusion criteria were patients of either sex, aged between18-80 years, and admitted with drug related problems. Exclusion criteria were pregnant and lactating women, patients unwilling to comply with the protocol requirements, organs-phosphorus poisoning, and reactions attributed to blood or blood product transfusions.

Data Collection

A daily admission census list generated by a computerized patient care information system was used to identify all the patients hospitalized to the hospital during the study period. The enrolling clinical pharmacist obtained a bedside history from each patient to determine the chief complaint, history of the present illness, medical and drug history, compliance with drug therapy, and allergy status. For patients unable to provide their medical or drug history due to acute illness, language barrier, or other issues, information was obtained by chart review.

The drug events considered were classified as either Adverse Drug Reaction (ADR) or Dose Related Therapeutic Failures (DRTF, dose too low, recent dose reduction, non-compliance or inadequate monitoring), or Overdose/Self Intended Poisoning (SIP). ADR were further classified as idiosyncratic; due to a normal side effect of the drug; drug related toxicity; or due to a drug interaction.

We used Naranjo's Causality Assessment scale to characterize the relationship between drug intake and adverse drug reactions (ADR)[9]. The criteria used for rating of causality in dose related therapeutic failure (DTF) were as follows:

1. The symptoms of the disease are known to reappear at insufficient doses
2. The symptoms were not likely to have been caused by a progression of the disease
3. A reasonable temporal relationship between the start of inadequate dosage and the appearance of symptoms
4. The symptoms resolved upon adjustment to all adequate dose
5. No other condition present could explain the symptoms
6. Drug levels were clearly below the therapeutic range, or there was clear evidence of intake or an insufficient dose.

Causal relationship was termed '*Definite*' if all the criteria were satisfied. Causal relationship was termed '*Probable*' if Criteria 1, 2, 3, 4 and 5 were satisfied. Causal relationship was termed '*Possible*' if Criteria 1, 2, 3 and 4 were satisfied.
Following evaluation of the relationship between drug intake and the ADR or DTF, the significance of the suspected symptoms for the hospital admissions was evaluated. This was largely based on notes of the referring physician. In all cases, where there was a 'definite' or 'probable' causal relationship between drug intake and the drug event, a further evaluation was made as to whether the event could have been avoided by appropriate measures taken by the health service personnel or the patient.

The drug event was considered '*Preventable*' if it was due to a drug treatment procedure inconsistent with the present day knowledge of good medical practice or was clearly unrealistic, taking the known circumstances into account.
The drug event was considered '*Probably preventable*' if the prescription was not erroneous, but the drug event could have been avoided by any reasonable means, or it was an unpredictable event in the course of a treatment fully in accordance with good medical practice.

The drug event was considered '*Non-preventable*' if the drug event could not have been avoided by any reasonable means, or it was an unpredictable event in the course of a treatment fully in accordance with good medical practice.

Overdose or Self intended Poisoning was judged by the admitting physician or medical team managing the patient's care.

Results

A total of 2340 patients were admitted to the department of medicine during the study period. A total of 155 (6.4%) [95% CI 5.6% - 7.7%] subjects fulfilled the criteria under the Drug Related Hospital Admission (DRHA).

1. *Demographic Profile of DRHA patients*: There were no sex differences in the studied patients [75(48%) females vs. 80 (52%) males]. A majority of the patients were above the age of 40 years; 24% were in the age group of 61-70 years, followed by 18% between 41-50 years, and 16% each in the age group of 51-60 years and 71-80 years.
2. *Occupation of DRHA Patients*: A majority of the patients (68%) admitted were from rural areas, and 32% patients were from urban areas. Of the 105 rural subjects, 41.1% were farmers, and 38.2% were housewives. Among the 50 urban patients, 62.5% were housewives.
3. *Multiple Drug Therapy*: A majority of the patients (56%) were on more than five drugs. There were 24% and 16% patients on more than four and three drugs, respectively.
4. *Duration of Stay in Hospitalization*: It was observed that 50% patients stayed in the hospital for 0-10 days. A significant proportion was hospitalized for more than 10 days (40% for 10-20 days, 6% for 20-30 days, and 4% for more than 30 days).
5. *Number of Patients with Multiple Diagnoses*: 42% patients had 2 diagnoses, whereas 20% had more than 2 diagnoses.
6. *Classification of Drug Related Hospital Admission*: 50 % hospitalizations were due to ADR, 38% due to DTF, and 12% were due to overdose/SIP. It was also noted that 21% of DTF was due to low dose, 11% due to recent dose reduction, and 68% due to non-compliance. With regard to adverse drug reaction 12 % was due to allergy, 16 % due to idiopathic reactions, 64 % was due to normal side effects, and only 8 % was due to drug interaction.
7. *DRHA Assessment*: Causality Assessment showed that 58% patients were *Definite*, 36% (56 cases) were *Probable,* and 6% (9cases) were *Possible*. With regard to ADR, 48% (37cases) were *Definite*, 48% (37cases) were *Probable,* and 4% (3 cases) were *Possible*. With respect to DTF, 58% (34cases) were *Definite*, 31 % (18cases) were *Probable,* and 11% (7cases) were *Possible*. In the overdose/SIP category, 83 %(15cases) were *Definite* and 17% (3 cases) were *Probable,* and there were none in the *Possible* group.
8. *Predictability and preventability assessment*: 84% (130 cases) of the DRHA were predictable, and 16 % (25cases) of the DRHA were non-predictable. In addition, 64% (99cases) of the DRHA were preventable, and 36% (56 cases) of the DRHA were non-preventable.
9. *Predisposing factor for DRHA*: Multiple drug therapy was responsible for 52% was the main predisposing factor for DRHA, the inter-current disease was responsible for 14%, and the idiopathic causes were responsible for 8% of drug related admissions
10. *Drug and disease responsible for DRHA*: Most common categories of drugs showing DRHA were anti-diabetic (16%), Cardiovascular drugs (18%), Steroid (14%), NSAID (12%), Antibiotic (12%), Anticonvulsant (12%), Anti-tubercular (6%), Respiratory drugs (6%), H1-Antagonist (2%), Antiretroviral (2%). Most of the common diseases involved in the DRHA were Hypertension (16%), Diabetes Mellitus (16%), Asthma (16%), Self-intended poisoning (12%) and Epilepsy (8%).
11. *Management and Outcome of DRHA*: DRHA was managed by altering the dose in 72% cases, and by the drug withdrawn in 28% cases. A definite improvement was seen in 56% of the cases.

Discussion

We prospectively evaluated the prevalence of Drug-related hospital admissions to be 6.4%, at the medicine department of a tertiary level university teaching hospital in South India. This report also gives insights into various causes of hospitalizations due to drug-related adverse events.

The reported prevalence of DRHA is 11.4% in UK, 5.7% in Denmark, 9.4% in Germany, 5.7% in Australia, and 5.9% in India [10-14]. We also observed a prevalence of 6.4% in our study. However, our data is limited to the medical

admissions, and it needs to be further studied what impact it will have on the prevalence, to involve hospitalizations in other departments such as surgery and pediatrics.
Similar to findings in our study, multiple drug therapy was also seen in all the drug related hospital admissions in other studies [15]. Nelson and Talbert have observed that approximately half of the drug-related hospital admissions are avoidable if patients taking multiple drugs are targeted [15].

Drug Related Therapeutic Failure (DTF)
Our study has found that noncompliance was the main factor responsible for the drug therapeutic failure in DRHA. This has been the observation in many other studies [14]. Noncompliance cases were mainly related to diabetes, hypertension, asthma and tuberculosis, which were also noted in the present study [16]. Non-compliance may be due to factors like non-adherence, poor administration technique, missed dose, substandard drugs, or the patient's inability to pay for the prescribed drug [17]. Noncompliance can be overcome by the pharmacists by actively involving in patient education, counseling, training, follow-up etc. [18]. Under-dosing was one of the common problems for DTF. The under-dosing problem is usually overcome by individualizing dose and dosing regimen, based on the patient's medical condition. Knowledge of clinical pharmacokinetics is a useful tool in understanding maximal response of the drug after commencing drug treatment. Cases of recent dose reduction were seen in the present study because of the patient's complaints of normal side effects of drugs. A common difficulty in managing patients is highlighted by two examples in our study. In a Diabetic patient in hypoglycaemic shock, the physician reduced the dose of insulin and oral hypoglycaemic agents, but the patient later presented in coma. Similarly, reduction of the doses of phenytoin and phenobarbitone in an epileptic patient for loss of appetite and nausea resulted in later hospitalization, with status epilepticus. Though the patients in both the cases were advised for regular follow-up, they were non-compliant, and presented later only with severe complications. Similar observations have been made in other studies [19]. Patient counseling, education and follow-up are thus the key to overcome such problems.

Classification of Adverse Reactions
Adverse drug reactions are generally sub-classified as due to allergy/ hypersensitivity, idiopathic/ idiosyncratic, normal side effects of the drug, and drug interaction. The normal side effect of the drug in the study was most commonly responsible for ADR related hospitalization. Similar results were found in other studies [20]. The common complaints in patients related to ADR were loss of conscious, giddiness, weakness, loss of appetite, gastritis, diarrhoea, muscle cramps and breathlessness. The patient's knowledge about the normal side effects was noted to be very limited. Education and counseling on managing the normal side effects could reduce DRHA due to normal side effects of drugs.

Predisposing factors
Predisposing factors contributing to DRHA in this study were multiple drug therapy, inter-current disease, age, and idiopathic causes. Patients with multiple drug therapy were more prone to develop an adverse drug reaction, either due to alteration of drug effect through an interaction mechanism, or by synergistic effect. The amount of risk associated with multiple drug therapy, increased in direct proportion to the number of drugs administered. Patients with multiple diseases are at an increased risk of developing an ADR due to multiple drug use for their multiple diseases. Elderly patients were more vulnerable to develop ADR, and more susceptible to ADR due to the physiological changes (pharmacokinetic and pharmacodynamic) accompanying aging. In some cases, the idiopathic causes, in which actual pharmacological reasons were not seen, were also noted in the study.

Management of Adverse drug related events
Management of ADRs is a crucial aspect of patient care. We used an algorithmic approach for management in patients. Dose was generally altered in the cases where the risk benefit decision could be taken into account. When the patients were on several medications, the non-essential drugs were withdrawn first; when the reaction was dose related; the dose was altered according to the condition.

The causality assessment was done by the Naranjo's probability scale for ADR. A significant proportion of severe cases with drug related events in our study, probably reflects lack of drug monitoring, as well as a lack of patient understanding of their medications. This

highlights the need for better communication between primary and secondary care and improved counseling of patients. 84% cases were categorized as predictable because they had explainable reasons (pharmacological, patient interview and other findings), whereas 16% were categorized as nonpredictable because they did not have any specific pharmacological explanation.

Sixty four % cases were categorized as preventable. It was found in this study, that with drug monitoring, patient education, and regular follow-up, and with proper counseling, these cases could have been prevented. 20% of the cases were found to be "probably preventable" because the prescriptions were not erroneous, but the drug event could have been avoided by an effort exceeding the obligatory demands. The 16% cases were non preventable, the drug event could not have been avoided by any reasonable means, or it was an unpredictable event in the course of a treatment fully in accordance with good medical practice

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