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ORIGINAL ARTICLE

Adverse Drug Event (ADE) related Medical Emergency Department visits and hospital admissions: a prospective study from a North Indian Referral Hospital

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ABSTRACT

Objective: To analyse the contribution of adverse drug events to the overall number of visits, to the emergency medical outpatient department (EMOPD) of a tertiary care centre. The aim of the present study was also to characterise the different causes of drug related visits or admissions and the consequences of it on the cost of health care.
Patients and methods: All visits to the medical emergency were recorded in a prospective, non-interventional design study, over a period of 6 months. In order to maximize uniformity and minimize interpersonal variability and bias, the correlation of suspected drug(s) causing the problem that led to the EMOPD visit and hospital admission, was assessed by using the Naranjo probability scale . The cases of suspected ADEs were followed-up to find out whether they were discharged from the EMOPD itself, or whether they subsequently required hospitalisation.
Results: A total of 1200 patients were included in the study .Fifty patients (4.2%, 95% CI: 1.21 – 6.53) were considered to be related to adverse drug events. Half of all the adverse effects could be attributed to three drugs: NSAIDS associated GI bleeding (22%), antitubercular drug associated hepatitis (20%),and beta-lactam associated hypersensitivity reactions (8%). In the present study, we found that 10% of ADEs were life threatening, and 30% were serious to warrant hospitalisation .The hospital admissions that were related to adverse drug events accounted for US$6712 or US $134 per admission.
Conclusion: ADEs account for a sizable proportion of all visits to a medical emergency unit, and some are serious enough to require hospitalisation .A large number of ADE related visits and admissions are preventable, which highlights the importance of public education on the proper use of drugs, and also, the need for regulation of the practice of unregistered medical practitioners in developing countries.
Keywords: adverse drug events, medical emergency visits, hospital admission, cost.

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Introduction

Adverse drug reactions (ADRs), including interaction, are a common cause of admission to a hospital, and are an important cause of increased morbidity and mortality.[1], [2] Adverse events during drug therapy are believed to contribute significantly to rising health costs.[3], [4]

Previous studies of drug-related visits to hospitals and emergency departments demonstrated that 1-4% of all visits were due to inappropriate use of medications. [5], [6] However, all these studies had the methodological limitation of being performed retrospectively. In retrospective studies, non-recorded facts and missing information can lead to underestimation of the prevalence of possible drug-related emergency

department visits. So, the true prevalence of ADRs leading to medical emergency department visits may actually be higher than indicated in earlier retrospective studies. We have earlier reported the proportion of drug-related visits to the medical emergency to be 5.9%. [7] Since then, a number of new drugs have been introduced. Their contribution towards emergency visits or hospital admissions remains unknown.

The studies on drug-related visits to the medical emergency department and hospital can contribute to a more comprehensive evaluation of drug-related problems that arise from prescriptions of general practitioners. The information generated from such prospective studies can be utilized in such a manner, to try and establish as to what proportion these events are avoidable, so that an intervention can be carried out in future.

So, the aim of the present study was to analyse the contribution of adverse drug events to the overall number of visits to the emergency medical outpatient department (EMOPD) and hospital admissions. We also intended to characterise the different causes of drug related visits and the consequences on health care costs.

Patients and Methods

The present study was a prospective and a non-interventional study. All visits to the EMOPD and Internal Medicine in-patient department of the Nehru Hospital attached to the Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India, were recorded over a period of 6 months (April, 2003 to September, 2003). The PGIMER is a 1500-bed tertiary care hospital, and its emergency department has a multi-disciplinary structure (Internal Medicine, Cardiology, Pulmonary Medicine, Intensive Care, etc.). The residents on round-the-clock duty in the EMOPD and Internal Medicine indoor department were informed about the study objectives. They were asked to elicit information from all patients regarding whether the patient's visit was due to an ADR, drug interaction, or patient non-compliance. This was further subjected to verification by a consultant from the EMOPD. Medical records of all the patients visiting the EMOPD were then reviewed by two clinical pharmacologists. Also, all patients (relatives, if patients were unconscious) were interviewed to elicit more information and reassess the causes for the EMOPD visit and hospital admission. Correlation of suspected drug(s) causing the problem that led to the EMOPD visit and hospital admission was assessed by using the Naranjo probability scale. [8] For each patient, the following information was recorded: demographic characteristics, diagnosis, drug history, type of ADE and clinical condition.

The cases of suspected ADEs were followed-up to find out whether they were discharged from the EMOPD itself, or whether they subsequently required hospitalisation.

Definitions

The definitions used in this study, as described in similar studies, were [7] (1) Adverse Drug Event (ADE): Injury or adverse events resulting from medical intervention related to drug. (2) Adverse Drug Reactions (ADRs): ADRs were defined as any "noxious and unintended reaction, and occurs at doses used in humans for prophylaxis, diagnosis, therapy or modification of physiologic functions". (3) Drug-Drug Interactions: A drug interaction was considered to have occurred when the effects of one drug were modified by the presence of another drug. (4) Patient non-compliance: Determining whether a patient's history of non-compliance was attempted in a non-judgemental way. The question was asked as follows "Many patients that are taking different medications over long periods of time will occasionally not take one or more of their medications. How often do you? Do you ever take more or less of the prescribed amount for any reasons?" (5) Accidental or intentional drug overdose: This information was obtained from the patients themselves or relatives, and was further confirmed from the resident concerned. Plasma concentrations were measured for the poisoning cases, wherever possible.

Definitions used in assessing causality were[9] (1) Definite or probable: The reaction commonly known to occur, with clear cut temporal association or laboratory confirmation, signs and symptoms were improved by dose adjustment, stopping or reinstating the drug; the signs and symptoms could not reasonably be explained by the known characteristics of the patient's clinical condition or by the effects of other drugs. (2) Possible: Reaction known to occur with less clear-cut temporal relationship; other causes also possible; the signs and symptoms were improved by dose adjustment, stopping or reinstitution of the drug therapy. (3) Contributing factor: There is

a definite or probable link between drug treatment and the diagnosis at admission. However, there are other complications that are unrelated to drug treatment, which are also a cause of admission. The total hospital cost of all drug related admissions (including ADRs, patient non-compliance, drug-interaction and over-dose), was calculated by calculating the cost of admission, drug-cost, cost due to investigations(laboratory and clinical), and physician and nursing charges.

Statistical Analysis

Rates of ADE-related emergency visits/admission were calculated as the ratio between the number of ADEs causing visits/admission, and the total number of visits/admissions in 6 months. Students `t' test was used to compare the mean number of drugs prescribed between patients whose visit was due to an ADE, and patients whose visit was not due to an ADE. The chi-square test was used to compare the percentage of ADE that occurred between different age groups of patients. A `p' value of less than 0.05 was considered to be statistically significant. The online statistical programme (Graph Pad Instat 3) was used for analysis.

Results

A total of 1200 patients were included in the study. The median (IQR) age range was 18 to 80 years, and the male to female ratio was 0.93.

Among 1200 patients who visited the Emergency OPD and were admitted in Internal Medicine Ward during six months duration, 50 patients (4.2% ,95% CI: 1.21 – 6.53) were considered to be related to adverse drug events, and 24 (2%) were admitted due to poisoning. The mean age of these patients was 47.3± 18.9 years, and the male to female ratio was 0.85. The average number of drugs prescribed to the patients who visited the EMOPD was 6.01 ± 1.9. At the time of emergency visits, patients whose visit was due to ADEs, were consuming more drugs (7.7 ± 3.1 vs 3.5 ± 2.1; $p<0.01$). The highest percentage of ADEs was seen in the more than 80 years age group (42%), and in the less than 20 years age group (26%), both being statistically significant when compared with other age groups ($p<0.05$) [Table/Fig 1].

Table/Fig 1: Age and sex distribution of emergency department visits and related adverse drug effects.

Age class (years)	Female	Male	Total
≤ 20 years	8	5	13 (26%)
21-40 years	3	2	5 (10%)
41-60 years	2	2	4 (8%)
61-80 years	4	3	7 (14%)
≥ 80 years	10	11	21 (42%)
Total	27	23	50

The 50 ADEs were associated with 21 different drugs. The most frequent sub-group of ADE related visits were ADRs (90%) and patient non-compliance (6%), followed by overdose (2%) and drug interaction (2%), and the duration of hospital stay with ADE was longest with ADR (Table/Fig 2). The most frequent ADRs were NSAIDs-induced gastritis and upper GI bleeding (22%), followed by antitubercular drug-induced hepatitis (20%) and betalactam antibiotic-induced hypersensitivity (8%) reactions.

Table/Fig 2: Types of Adverse Drug Events, mean duration of hospital stay and total cost of all ADEs.

ADEs	No. of patients	% of patient among total admission	Duration of hospital stay (days, Mean±SD)	Total cost (US$)
ADR	45	90	4.41 ± 2.50	
Patient non-compliance	03	06	3.3 ± 0.47	
Drug-interaction	01	02	3.0 ± 0.0	
Over-dose	01	02	4.0 ± 0.0	
				6712.34

In the present study, we found the incidence of fatal ADEs to be 0.2%. Among them, 10% were life threatening, and 30% were serious [Table/Fig 3].

The hospital admissions that were related to adverse drug events accounted for US$ 6712.34 or US$ 134.25 per admission [Table/Fig 2].

According to the Naranjo probability scale, all the ADEs reported have been classified as definite or probable (40%), possible (34%), or a contributing factor (26%). Among 50 ADE-related visits, 15 cases (30%) were thought to have been preventable or avoidable.

Table/Fig 3: Life-threatening ADRs

1. Carbamazepine induced Stevens-Johnson Syndrome
2. Allopurinol induced Stevens-Johnson Syndrome
3. Streptokinse induced intracranial bleeding (died)
4. Linezolid induced bradycardia
5. Insulin induced hypoglycemia
6. Netilmicin induced anaphylaxis

Another important cause of hospital visits apart from ADEs in our hospital was poisoning with various non-therapeutic chemicals. During 6 months of duration (April 2003 to September 2003), 24 cases (2% of all admissions) that were admitted to the EMOPD, were due to poisoning and organophosphorus compounds.

Discussion

In large hospital based studies, the incidence of ADEs was 3.4 – 3.7%. [10], [11] The leading cause of medical injury was use of drugs, accounting for 19.4% of these injuries, and therapeutic mishap occurred in 7.5%.[12] A meta-analysis of 39 prospective studies, covering 32 years, revealed a 6.7% incidence of serious and fatal ADRs, and a 0.32% death rate among patients admitted to the hospital because of an ADR, and those having an ADR while in hospital. The study showed that a large number of serious ADRs occur, even when the drugs are properly prescribed and administered. [13]

In the present study, we estimated the proportion of drug-related visits to be 4.2%, which is consistent with other studies.

In the present study, ADRs were seen with the highest frequency in the age group above 80 years and below 20 years. We had earlier reported that more than 14% of elderly admissions were due to drugs.[14] In other studies, the incidence of drug-related adverse events in the elderly population was 28.2%,[9] whereas in our study, it was higher 42%. Elderly age group patients are at high risk of developing drug related adverse effects because of increased sensitivity to the unintended side effects or adverse drug reactions of medications that could result from incorrect dosing, and their use of more medications. In the present study, we estimated the incidence of ADEs in the age group $\leq$ 20 years to be 26%, which was higher as compared to other age groups ($p<0.05$). This reflects two problems. Firstly, that of unregulated sale of drugs without prescription in the Indian market, a problem faced by many developing countries, and secondly, many cases of teenage depression may be going unrecognised.

The other aspect is that of non-compliance, especially the patient's non-compliance. Compliance issues have been a major area of concern in many studies. [15], [16] In the present study, 4% of patients were admitted to the EMOPD due to patient non-compliance. The causes of patient non-compliance were due to a majority of them switching over to alternative systems of medicine. In a country like India, superstitions, illiteracy, poverty, and certain deficiencies in the conventional medicine make patients seek alternative therapies.

In the present study, NSAIDs, antitubercular drugs and antimicrobials were the most commonly implicated drugs, which probably reflects their widespread use.

For the patient, economic consequences of drug related problems would include cost of medical care, loss of wages, impact on household services of the injured, and effects on quality of life (damages for pain and suffering).[17] The estimated annual cost of drug related problems in outpatient clinics in the US, is $ 76,600 million. The largest component of this cost was due to drug-related hospitalisation.[17]. In the present study, we estimated that the total projected annual cost of drug related visits and admissions in the EMOPD and the Internal Medicine in-patient department, was about US$ 6712.34 in our hospital. Since this was single centre study and limited to two departments only, the total costs across all the departments and all the hospitals in India is likely to be high.

Ours is a public sector institution and the costs of physician visits and nursing charges are negligible, while the costs of investigations and stay are highly subsidized. Thus, our costs are much lower than the costs, not only in developed countries[18], but also in comparison to the private sector institutions of our country.

Most studies reviewed above, suggest that a significant percentage of AEDs and DRPs are preventable[19]. In our study, 30% of ADEs were preventable. Many health care delivery systems, especially in hospitals, could be redesigned to significantly reduce the likelihood of error[20]. Like the other ADR-related emergency studies,

the aim of this present study was to highlight the importance of public education on the proper use of drugs, necessity of compliance, and also regulation of the practice of unregistered medical practitioners in the developing countries. Like other hospitals, the physician should take advantage of computerised prescribing[21]. Because of the increasing number of drugs, regimen complexity, continuously changing drug interactions and adverse effects, physician memory can no longer serve as a reliable bridge between research advances and clinical practice. We must remember that "there are no biologically safe drugs; there are only safe physicians" [19].

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