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Monitoring and Analysis of Adverse Drug Reactions in A Private Tertiary Care Hospital

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Abstract
The detection of ADRs has become increasingly significant because of introduction of a large number of potent drugs in the last two or three decades, especially antimicrobials. ADRs could be monitored through active monitoring or through voluntary reporting system in a hospital set up. This observational prospective study spread over 12 month's duration, was conducted on admitted patients after obtaining approval of ethics committee of the hospital. 3150 subjects receiving antimicrobial therapy were included in the study.
The overall incidence of ADRs to antimicrobials in our study was 6.12%. ADRs related to gastrointestinal tract 117(60.62%) were most frequent. The lowest were blood dyscrasias 02(01.03). The highest incidence local site ADR's was seen with piperacillin + tazobactum (1.5%) and (1.2%) respectively. Practically all antimicrobial agents cause local irritation at the site of administration.
Highest incidence of GI effects was observed with ceftriaxone (10.9%). Diarrhoea occurred maximum with amoxycillin+clavulanic acid (4.1%). Amongst CNS manifestations the highest incidence of headache was with ciprofloxacin (0.9%). Cephalosporins (5.1%) had the highest incidence of development of dermatomucosal effects. Blood dyscrasias were seen in patients treated with metronidazole and cefoperazone+sulbactum. In the analysis of antimicrobial-related ADRs, it was found that most episodes were type A (87.05%). In this study majority of the ADRs episodes 106(54.9%) were judged as probable, 44(22.8%) as possible, and 43(22.3%) as definite. The implementation of adverse event monitoring and notification programs in hospital settings is an important action for the prevention of these events. These programs promote event surveillance and encourage their documentation and notification.

Introduction

ADRs are common occurrences in a hospital setting, attributed to the severity and complexity of the disease process, use of multiple drugs, drug interactions and possible negligence.[1] ADRs could be observed upto 10-20% of patients and may be responsible for prolongation of the hospital stay.[2] Lazarou et al reported an overall incidence of serious and fatal ADRs of 6.7% and 0.32%, respectively, in hospitalized patients.[3]

The detection of ADRs has become increasingly significant because of introduction of a large number of potent drugs in the last two or three

decades, especially antimicrobials. ADRs could be monitored through active monitoring or through voluntary reporting system in a hospital set up.

Towards this end, we decided to monitor Adverse Drug Reactions to Antimicrobials in our hospital for a period of one year.

Materials and Methods

This observational prospective study spread over 12 month's duration, was conducted on admitted patients after obtaining approval of ethics committee of the hospital. 3150 subjects receiving antimicrobial therapy were included in the study.

In case of suspected ADRs, all relevant information about the patient and all the drugs administered as well as the details of the ADRs were recorded in a standard Proforma prepared for the purpose.

The following variables were documented: Patient-related: gender, age, relevant medical history, diagnosis. Drug-related: antimicrobials and other drugs prescribed. Those related to antimicrobials use: indication, purpose of use, dose and route of administration, dosage form, and treatment duration. Adverse drug reaction: Description of the event: Type, Intensity, Seriousness, Expectedness, Outcome and Causality Assessment.

The exclusion criteria was patients below the age of 14 years, unconscious / comatose, terminally ill, stayed less than 48 hours in the hospital, patients from the intensive care unit, with medico legal cases, who received antimicrobials for the treatment of fungal or viral infections.

For patients with ADRs, further information was collected, including the onset of ADRs (duration of start of medication to occurrence of ADRs); probability, type, and severity of ADRs; clinical manifestations of ADRs; number of concomitant medications used and relevant laboratory data. If patients had several clinical manifestations at the same time, each manifestation was counted as a separate episode.

The ADRs was attributed to a given drug as per the accepted criteria and further confirmation in most of the cases was obtained when the ADR was checked after the drug was withdrawn. Since several antimicrobial agents were being administered at the same time, the agent most likely to cause was identified by the attending physician. If this could not be decided, all agents were regarded as causative agents.

The incidence of ADRs was expressed as the number of antimicrobial-related ADR episodes per 100 antimicrobial courses.

The ADRs were classified as Type A and Type B according to the definitions by Rawlins and Thompson. The probability of causative agents was assessed by the ADR probability scale designed by Naranjo et al and classified as definite, probable, possible, and suspected.

The severity of ADRs was graded as mild (no need to treat or to stop or change medication), moderate (treatment antidote, admission or prolonged hospitalization from 1 to 6 days required), and severe (ADR treatment for at least 7 days; life-threatening; need for intensive care unit; disability; or death due to ADR, congenital anomaly, intervention required to prevent permanent impairment / damage).

Antimicrobial agents were classified into 15 different classes, including penicillins, first and second generation cephalosporins, third and fourth generation cephalosporins, monobactams, carbapenems, macrolides, lincosamides, tetracyclines, aminoglycosides, sulphonamides and trimethoprim, quinolones, glycopeptides and metronidazole.

The clinical manifestations of ADRs were categorized as follows: Allergic reactions, Blood dyscrasias, Cardiovascular effects ,Dermatomucosal effects, Endocrine-metabolic effects, Neurotoxicity, Gastrointestinal (GI) effects, Hepatotoxicity, Nephrotoxicity, local site adverse effects.

Statistical analysis was performed using the Statistical Package for the Social Sciences for Windows (Version 12.0; SPSS, Chicago, IL, USA) software package.

Results

Demography

Table No 1:*Incidence of ADRs*

Number	male	female
3150 (total)	2048(65.0%)	1102 (35.0%)
193(ADRs)	74.6% (144	25.4% (49).

Most ADRs 46/699(6.58%) developed in patients aged 15-30 years old with 29/438 (6.62%) in male patients and 17/261(6.51%) female patients.

Table no 2: Incidence of ADRs drug–wise Profile of ADRs

ADRs	*Incidence N(%)*	*Common manifestation*	*Incidence N(%)*	*Highest incidence with*
gastrointestinal tract (GI)	117(60.6)	nausea	39(20.2).	ceftriaxone (10.9%).
local site ADRs	27(13.98)	pain at the injection site thrombophlebitis	18(9.3) 9 (4.7)	piperacillin+tazobactum (1.5%)
central nervous system	24(12.43)	headache	16(8.3)	ciprofloxacin (0.9%).
dermatomucosal (DE) effects,	16(08.29)	Skin rashes	12(6.2)	cefuroxime (0.7%).
febrile reactions (FR)	07(03.62)	febrile reactions	7(3.6)	cefuroxime (0.7%)
Blood dyscrasias	02(01.03)	neutropenia	02(01.03).	metronidazole (0.5%).

Type, causality assessment and severity of ADRs

1. **Type of ADRs**

The ADRs were classified using Rawlins & Thompson criteria.

Table no 3: Type of ADRs

ADRs	Type A	Type B
	168(87.05%)	25(12.95%)

Type A ADRs were from gastrointestinal tract, CNS, local adverse effects. Type B ADRs were dermatomucosal effects, blood dyscrasias and febrile reactions.

2. **Causality assessment and severity.**

The causality assessment was done by the ADRs probability scale designed by Naranjo et al.

Table no 4: causality assessment and severity assessment

causality Assessment	incidence	Severity Assessment	incidence
definite	43(22.3%)	Mild	16183.4%)
probable	106(54.9%)	moderate,	32 (16.6%)
possible	44(22.8%)	Severe	0(0%)
Suspected	0 (0%)		

Discussion

In Diarchy's report, antibiotics accounted for 11% of iatrogenic diseases.[4] Classen states that, although adverse events seem to occur in a small proportion of antibiotic courses, the frequency of antibiotic use makes them account for 23% of all adverse events recorded.[5]

The overall incidence of ADRs to antimicrobials in our study was 6.12%. This study was done involving 3150 patients admitted to the Medicine, Surgery and Orthopedic wards of our hospital. This figure is quite low in comparison to the study conducted by Leape et al [1] in which they observed an incidence of 16.2%.

A study done in 1991 by Audi et al observed that the incidence of ADRs to antimicrobials was 4%.[6] Because of differences in study design, data collection, and definition of ADRs, the diversity of drugs used, and the heterogeneity of the investigated populations, the reported incidence of ADRs varies greatly in the literature.

The present study showed an incidence of 6.12% for antimicrobial-related ADRs in hospitalized patients treated with antimicrobials.

The low incidence of ADRs in our study could be attributed to the fact that this study was done in a teaching hospital where the drug use is expected to be regulated, rational and supervised. Further, the one who monitored the ADRs was assigned to this task full time, under supervision, and therefore it is unlikely that the low incidence in our study could be because of missed reactions. Various other factors may account for this apparently low rate of ADRs. This may include genetic factors, ethnic factors, dietary and environmental factors etc. There is a need to explore the reasons for this relatively low incidence rate of ADRs in the Indian population.

In our study, a significantly large number of patients (90%) developed ADRs in the first 5 days. This emphasizes the need of observing the patients closely in the initial period of treatment.

ADRs related to gastrointestinal tract 117(60.62%) were most frequent, followed by local site ADRs 27(13.98%), CNS effects 24(12.43%), dermatomucosal effects 16(08.29%), and febrile reactions 07 (03.62%). The lowest were blood dyscrasias 02(01.03). Diarrhea was again the most common adverse effect seen in another study by Angeles Tan Alora et al.[7]

Highest incidence of GI effects was observed with ceftriaxone (10.9%). Diarrhoea occurred maximum with amoxycillin+clavulanic acid (4.1%) but there were no cases of superinfection. The incidence in this study is much lower than that reported in some other studies. For example Mandell et al reported diarrhea as representing 25% of adverse drug reactions and oral amoxicillin to be its most common cause 11.4%.[8]

The highest incidence local site ADR's was seen with piperacillin+tazobactum (1.5%) and (1.2%) respectively. Practically all antimicrobial agents cause local irritation at the site of administration.[6]

Amongst CNS manifestations the highest incidence of headache was with ciprofloxacin (0.9%). The highest incidence of dizziness 6(3.1%), was seen with gatifloxacin (0.9%). CNS side effects, predominately mild headache and dizziness, have been seen in 0.9% to 11% of patients receiving fluroquinolones in a similar study conducted by Schwartz et al 1988. [9]

Cephalosporins (5.1%) had the highest incidence of development of dermatomucosal effects. Most episodes occurred within 5 days after prescription. The incidence in this study was much higher than that reported by van der Linden et al, who found that trimethoprim-sulfamethoxazole (2.1%), fluoroquinolones (1.6%), and penicillins (1.1%) were the most common agents causing dermatomucosal ADRs.[10]

Cephalosporins (5.1%) had the highest incidence of development of dermatomucosal effects Neutropenia 2(1.0%) was the most commonly seen presentation of blood dyscrasias from our observations, and most episodes occurred within 1-5 days after initiation of medication. Blood dyscrasias were seen in patients treated with metronidazole and cefoperazone+sulbactum. This incidence is much lower as compared to the incidence of neutropenia in patients receiving

vancomycin (13%), and beta-lactam agents (3-8%) as per the studies by Hoffman-Terry et al.[11]

In the analysis of antimicrobial-related ADRs, it was found that most episodes were type A (87.05%). Surprisingly, in a study done by Hsin-Yun Sun et al in 2008 the incidence of type B ADRs was 93.1%.[12] This observation differs from the traditional concept that type A reactions are more common than type B reactions.

In this study majority of the ADRs episodes 106(54.9%) were judged as probable, 44(22.8%) as possible, and 43(22.3%) as definite. This assessment of causality was based on Naranjo algorithm. There is no formula for an absolute and safe outcome since this analysis always involves personal evaluation and allows for different interpretations.

There are some limitations exist in the present study. First, the severity of the patient's infectious diseases, detailed underlying conditions, and previous drug history were not recorded.

Second, the study period is short and the number of cases is limited, which might have biased our observations. Third we did not evaluate the outcome of the ADRs in terms of cost. Fourth, few comparable studies in India are reported in the literature, making it difficult to make valid comparisons between our study and others.

The implementation of adverse event monitoring and notification programs in hospital settings is an important action for the prevention of these events. These programs promote event surveillance and encourage their documentation and notification. Thus, they support mechanisms for safe use of drugs in patients and promote education of health providers enabling them to identify potential events. Mazzeo et al [27] monitored antimicrobial induced adverse events in an university hospital in Italy and noted this was a good strategy for detecting associations between drug exposure and the occurrence of adverse events in both children and adults.

Antimicrobial agents being one of the most widely used groups of drugs in hospitalized patients, all efforts must be made to detect record, analyze and prevent ADRs to this important class of Therapeutic agents.

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