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Research Article

MONITORING AND ANALYSIS OF ADVERSE DRUG REACTIONS IN A PRIVATE TERTIARY CARE TEACHING HOSPITAL

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ABSTRACT

Objectives: To monitor and analyse the suspected adverse drug reactions (ADRs) reported at Vydehi Hospital, Bengaluru.

Methods: A prospective observational study was conducted between July 2011 and August 2012. Suspected ADR - Central Drugs Standard Control Organization forms submitted to pharmacovigilance unit were analysed for: (1) Type of reaction, (2) severity, (3) seriousness, (4) causal relationship with the drug using the Naranjo and World Health Organisation (WHO) - UMC causality scale, (5) predictability of ADR and (6) group of suspected drugs associated with ADR.

Results: 45 forms out 54 were complete as per the Pharmacovigilance Programme of India, which were analysed. 44 (97.7%) of the reactions were Type B and 1 (2.2%) Type A. 24 (53.3%) of the reactions were mild, 20 (44.4%) were moderate, and 1 (2.2%) severe. 4 (8.8%) reactions were considered serious. As per the Naranjo causality scale, 81.8% were possibly related and 18.2% probably related. Analysis as per WHO-UMC causality scale showed that 16.6% of the reactions were probably or likely related and 83.3% possibly related. The predictability of an ADR was assessed for 30 of the 45 reports where single drug or fixed drug combination were prescribed. 27 (90%) were considered predictable amongst them. The major group of drugs that caused the reactions were antimicrobials. The most common ADRs in our study were cutaneous reactions. 37.7% of ADRs were noted in patients on combination of drugs.

Conclusions: Study revealed that the reporting rate was low. Only cutaneous reactions were reported. More awareness needs to be created to address these issues.

Keywords: Adverse drug reactions, Pharmacovigilance, WHO-UMC, Naranjo's casuality scale.

INTRODUCTION

Adverse drug reaction (ADR) is defined by the World Health Organisation (WHO) as "any noxious, unintended or undesired effect of a drug that occurs at doses used in humans for prophylaxis diagnosis, therapy or modification of physiological functions" [1]. ADRs are the fourth leading cause of death ahead of diabetes, pulmonary disease, AIDS, road traffic accidents [2]. Serious ADRs account for 6.7% of all hospital admissions and account for 5% of all hospital admissions and occur in 10-20% of hospitalized patients [3,4]. They place a substantial burden on health care resources.

Pharmacovigilance aims to identify the rare and serious drug reactions of marketed products through rigorous monitoring and reporting [5]. This helps the regulatory authorities to permit safe medicines in the market benefitting the patients.

In 2010, Central Drugs Standard Control Organization (CDSCO) under the aegis of Govt., of India, Ministry of Health and Family welfare and Phamacovigilance Programme of India (PvPI) has established adverse drug monitoring centres in various tertiary care hospitals all over India with the objective to improve the reporting rate of ADRs in India [6].

Inspite of the above measures, under reporting is still a matter of concern. Therefore there is a need a need to enhance physicians' awareness about detection, management, prevention and reporting of ADRs [7]. More importance should be given to voluntary reporting as it contributes significantly to successful pharmacovigilance [8].

With this background the present study was conducted with the aim of improving the clinicians' awareness about monitoring and reporting ADRs which would ultimately benefit the health of the patients. The study was also intended to identify areas which should be addressed to improve the reporting rate.

The primary objectives of the present study were to:

- Characterize the nature, severity, seriousness and predictability of the ADRs
- Estimate the incidence of ADRs
- Identify the drug most commonly involved in ADRs.

METHODS

A prospective non-interventional observational study was conducted over a period of 12 months from July 2011 to August 2012. Permission was obtained from Head of Institution as well as the institutional ethics committee to conduct the study. The clinicians and support staff was oriented towards the importance of pharmacovigilance and spontaneous reporting system by conducting lectures, academic society meets, newsletters. They were also briefed on the method of filling the CDSCO forms.

The CDSCO forms were distributed to all the clinical departments personally by the phamacovigelance co-ordinators. The forms contained the patient details, treatment given, reaction details, concomitant drug details, past history, dechallenge and rechallenge. Regular visits were done twice weekly to collect forms.

Once the forms were collected by the pharmacovigilance co-ordinators, they were carefully evaluated for quality based on the following essential elements: 1 (patient initials), 5 (date of reaction started),

7 (describe reaction or problem), 8 (suspected medications), 11 (concomitant medical product including self medication and herbal remedies), 15 (outcomes), 16 (name and professional address) and 18 (date of this report) as per the PvPI [9].

Evaluation of the reports
The reports which had complete information of the essential elements were selected for analysis. The reactions were analyzed based on the following categories.

1. Type of reaction - (based on Rawlins and Thompson criteria) [10]
   - Type A: Augmented pharmacologic effects - dose dependent and predictable
   - Type B: Bizarre effects/idiosyncratic - dose independent and unpredictable
   - Type C: Chronic effects
   - Type D: Delayed effects
   - Type E: End of treatment effects
   - Type F: Failure of therapy
   - Type G: Genetic reaction.
2. Severity
   The severity of a reaction was determined based on the classification systems of WHO and system of Hartwig *et al*. [11].
   The severity of a reaction was classified as mild, moderate and severe reaction.
   In mild reactions (ADRs) the reaction was self remitting. Over a period of time with or without an antidote and did not extend the stay of the patient in the hospital.
   Moderate ADRs were those reactions which required therapy and hospital admission for 1 day. The reactions resolved within this period due to the change in the drug or administration of specific treatment to prevent further reactions.
   Severe ADRs were those which were considered life threatening - leading to disability and required prolonged hospital stay usually in the intensive care unit
3. Seriousness of a reaction based on the following: (WHO criteria) [1]
   - Death
   - Life threatening
   - Hospitalization (critical/prolonged)
   - Disability (significant, persistent/permanent congenital anomaly)
   - Required intervention to prevent further impairment or damage.
4. The causality of the drug to reaction established by Naranjo scale [12] and WHO scale [5]
5. The predictability of ADR based on criteria modified from the Council of International Organization for Medical Sciences [13] considering the incidence of the reactions as reported in the literature and past history of reactions to the suspect drug
6. Groups of suspected drugs associated with ADR. The suspect drugs were grouped on their pharmacological class to know most common group causing the reactions.

The results were analyzed using descriptive statistics and a feedback was sent to the clinical departments on the common drugs that caused the reactions. Alert cards were distributed to all the clinical departments to be given to patients who present with ADR due to suspect drugs which would help during follow-up and further management.

RESULTS

54 ADR forms were received by the pharmacovigilance unit from various clinical departments. Forty five out of the 54 forms were selected for analysis since they satisfied the criteria laid down by the PvPI, the rest were rejected as they were incomplete in terms of the essential elements as shown in Table 1.

Evaluation of quality of the reports
Therefore 45 reactions were analysed for the type, severity, seriousness, causality and predictability of the ADR.

20 (44.4%) of the suspect ADR forms had multiple drugs prescribed and it was found that more than one drug was found to be suspected in causation of the reaction. Therefore causality was done for each of the suspect drug.

Demographic characteristics of patients with suspect ADR
Out of the 45 patients 31 (69%) were between 20 and 60 years and 14 (31%) were <20 years of age. Almost equal gender distribution was found with slight male preponderance. 24 (53%) males and 21 (47%) females.

Type and severity of suspect ADRs
44 (98%) were of Type B and only 1 (2%) was Type A as per Rawlins and Thompsons criteria. 24 (53%) were of mild, 20 (45%) were moderate and 1 (2%) was severe in nature.

Seriousness of reactions
There were, 4 (9%) serious reactions, categorized as serious as they required hospitalization as shown in Fig. 1. Table 2 shows the reactions observed. There was no death reported due to the ADRs.

Causality of drugs implicated in suspect ADRs
The causality was assessed for 66 drugs from 45 reactions using Naranjo scale as show in Fig. 2.

Predictability of the reactions
The predictability of an ADR was assessed for 30 of the 45 reports where single drug or fixed dose combination were prescribed.Among the 30 reports, 27 (90%) were predictable (reference in product literature is available). Three out of the 27 reactions had previous history of ADR to the same suspect drug. 3 (10%) were not predictable reactions as literature showed <1% incidence of ADR to that particular drug.

Major classes of drugs implicated in suspect ADRs
Antibiotics were implicated as most common groups of drugs associated with ADRs followed by non-steroidal anti-inflammatory drugs (NSAIDS) shown in Table 3. Among the antibiotics, ciprofloxacin had contributed to majority of reactions. Diclofenac and paracetamolwere the majorly involved NSAIDs. Most of the reactions that occurred were cutaneous in nature.

Table 1: Missing data in the report

S.No.	Missing data elements	Number of reports
1	Date of starting and stopping drug	4
2	Drug name	2
3	Date of reaction	3

Table 2: Serious reactions observed

S.No	Reaction	Suspect drug/drugs
1	Stevens–Johnson syndrome	Carbamazepine, sodium valproate, erythromycin
2	Bullous fixed drug reaction	Ciprofloxacin
3	Multiple erythematous wheals	Nimesulide Chlopheneramine Caffeine
4	Fixed drug eruption	Levofloxacin

Table 3: Class of drugs

Class of drugs	ADRs (n)	ADRs (%)
Antimicrobials	16	32.67
Antifungal	3	6.12
Antiepileptics	6	12.25
Analgesics	12	24.49
Others	12	24.49

ADR: Adverse drug reaction

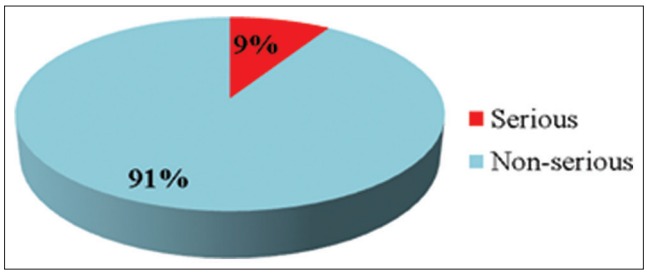

Fig. 1: Adverse drug reactions analysis based on seriousness

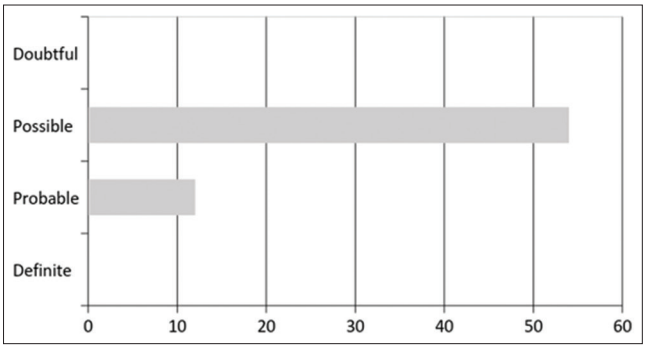

Fig. 2: Causality assessment

DISCUSSION

The present study showed a reporting rate of 0.43% of voluntary reporting of ADRs. The review of literature in this area has shown that the reporting rates in many hospitals range from 0% to 21% [14]. There are various probable reasons identified for underreporting such as lack of aptitude and knowledge of physicians, time constraint, non-accessibility of ADR (CDSCO) reporting forms, lack of incentives etc., [15]. In our interaction with clinicians, similar reasons for underreporting were found.

Data quality is essential to establish causality which is the most essential aspect in the analysis of suspect ADR reports. This helps in establishing the probable association of the reaction with the drug. If the reaction is definitively due to the drug further precautions can be taken while prescribing the same medication. In our study we observed that 9 out of 55 reports were incomplete indicating poor quality of reporting. The probable reasons could be once again lack of awareness or aptitude.

A review by Routledge *et al*. reports that more than 80% of ADRS causing admission or occuring in the hospital are Type A in nature and thus predictable from the known pharmacology of the drug and therefore potentially avoidable. However our study showed that the reactions were predominantly of Type B. The variation is probably due to the fact that detailed observations are done while treating an inpatient while only the obvious cutaneous reactions are observed in voluntary reporting on outpatient basis. Similar observations as ours in a study by Lazarou *et al*. [4].

Most of the reactions were mild in nature and probably required minimum medical intervention for management. This is similar to another study by Arulmani *et al*. [16]. However, there were serious suspect ADRs the causality of which could not be assessed conclusively because of multiple drug administration. There was one case of Steven–Johnson syndrome due to possible association to carbamazepine or sodium valproate or erythromycin ciprofloxacin and levofloxacin produed bullous fixed drug eruption.

Most of the reactions were predictable, predictability being assessed by literature search and history of similar reaction. Such reactions could have been prevented by careful history taking and/or carrying out the patch test [17] to identify of causality of reaction. Giving alert cards have shown to reduce further incidence of drug reactions [18]. Hence we also followed the same and distributed the cards.

Causality assessment showed that most of them were in the possible category. This could probably due to the fact that multiple drugs were prescribed at the same time and there was insufficient data.

CONCLUSION

The study showed that the reactions were mild in nature, mainly of Type 1 and hypersensitivity cutaneous reactions, possibly related to the suspect drugs. The systemic reactions were underreported. The overall reporting rate was low. There is a need to improve awareness among the clinicians to emphasise their role in voluntary reporting of ADRs, on generating quality reports, critically monitor the ADRs so as to prevent them further.

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