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A Study of Implementation of Adverse Drug Reaction Monitoring System in India

[1]Manoj Kumar & [2]Dr. Satyavir Singh

[1]Research Scholar, OPJS University Churu, Rajasthan (India)
[2]Assistant Professor, OPJS University Churu, Rajasthan (India)

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ABSTRACT

Adverse drug reactions (ADR) are a significant cause of morbidity and mortality, often identified only post-marketingly. Improvement in current ADR reporting, including utility of underused or innovative methods, is crucial to improve patient safety and public health. Hospital-based monitoring is one of the methods used to collect data about drug prescriptions and adverse events. The aims of this study were to identify the most frequent ADRs recognized by the attending physicians, study their nature, and to target these ADRs in order to take future preventive measures. A prospective study was conducted over a 7-month period in an internal medicine department using stimulated spontaneous reporting for identifying ADRs. Out of the 254 admissions, 32 ADRs in 37 patients (14.56%) were validated from the total of 36 suspected ADRs in 41 patients. Female predominance was noted over males in case of ADRs. Fifty percent of total ADRs occurred due to multiple drug therapy. Dermatological ADRs were found to be the most frequent (68.75%), followed by respiratory, central nervous system and gastrointestinal ADRs. The drugs most frequently involved were antibiotics, anti-tubercular agents, antigout agents, and NSAIDs. The most commonly reported reactions were itching and rashes. Out of the 32 reported ADRs, 50% of the reactions were probable, 46.87% of the reactions were possible and 3.12% of the reactions were definite. The severity assessment done by using the Hartwig and Seigel scale indicated that the majority of ADRs were 'Mild' followed by 'Moderate' and 'Severe' reactions, respectively. Out of all, 75% of ADRs were recovered. The most potent management of ADRs was found to be drug withdrawal. Our study indicated that hospital based monitoring was a good method to detect links between drug exposure and adverse drug reactions. Adequate training regarding pharmacology and optimization of drug therapy might be helpful to reduce ADR morbidity and mortality.

1. Introduction

Drug event monitoring is a method of active pharmacovigilance surveillance. Schemes for spontaneous reporting of suspected adverse drug reactions (ADRs) have an important role in identifying such effects which were not found in pre-marketing trials. In many instances, regulatory and public health decisions have to be made on the basis of data from spontaneous reports. Although such schemes are useful to safeguard public health, they have several weaknesses, including underreporting. Active surveillance can be achieved by reviewing medical records or interviewing patients and/or physicians to ensure complete and accurate data on adverse events. Hospital based monitoring is one of the systems used to collect data on drug prescriptions and adverse events. In this approach, trained health personnel monitor patients, admitted to selected hospitals by reviewing their clinical charts and conducting structured interviews of both patients and physicians. Information on patient demographics, indication for treatment, duration of therapy, dosage, clinical events and reasons for discontinuation can be included in the questionnaire. Such projects have proved useful for the study of acute and relatively common ADRs. ADRs and events have a considerable impact not only on the health of the population but also on health care costs; they account for 5% of all hospital admissions, occur in 10–20% of inpatients, cause death in 0.1% of medical and 0.01% of surgical inpatients and increase the costs of patient care .

The presence of ADRs may be underestimated in part because treating physicians fail to recognize ADRs, as they tend to mimic any naturally occurring disease process, by acting through the same physiological and pathological pathways. A study demonstrated that up to 57% of the community acquired adverse drug reactions are not recognized by the attending physician upon hospital admission, leading to inappropriate management of the adverse event, exposure of the patient to additional ADRs of the drugs and prolonged hospitalization.

2. Adverse Drug Reaction Reporting Systems

With the use of any medication comes the possibility of unwanted consequences. According to the Centre for Health Policy Research, in 1998, more than 50% of approved drugs in the US were associated with some type of adverse effect not detected prior to approval.1 Various studies in the US have identified adverse drug reactions (ADRs) as between the fourth and sixth leading cause of death (higher than motor vehicle accidents, breast cancer or AIDS), with an estimated fatality rate of 0.32% among hospitalised patients.2–4 A single adverse drug event (ADE) has been costed at approximately US$2500, and hospitals in the US pay approximately US$4 billion per year for drug-induced injuries.5 Another American

study found that in the nursing home, for every dollar spent on drugs, US$1.33 was spent on the treatment of drug-related problems.6 In England and Wales, deaths related to ADRs have increased during the last decade.3 It was also estimated that in 2000, ADRs were accountable for up to 7% of hospital beds occupied in the UK.2 Approximately 2% of general practitioner (GP) consultations were due to ADRs, and many drugs were returned from patients to pharmacies due to ADRs.7 In another UK study, 37% of pharmacists had identified an ADR in the previous year.8 More recently, a study reported that 33% of hospital accident and emergency visits were due to ADRs or side-effects, from data extrapolated from a survey of 2636 patients over a two-year period.9 In 1999–2000, 2–3% (about 140 000 admissions) of all hospital admissions (5.9 million) annually in Australia were related to problems with prescription medicines, and approximately 100 000 admissions may have been associated with adverse drug events.10,11 The financial implications have not been calculated.

Voluntary reporting of ADRs by health professionals is considered the cornerstone to the management of ADRs in any healthcare system. Reporting is usually undertaken electronically (online), verbally (hotline), by paper (mail) or facsimile. The use of electronic reporting is increasing, as the paper-driven process is labour intensive to manage.12 It is recognised that community pharmacists are in a key position to detect and report ADRs, as they are in regular contact with patients.13,14 However, limited research has suggested that community pharmacists in most countries have not been reporting to their full potential. A lack of time in pharmacy practice, workload and time taken to report have been identified as the main obstacles to reporting by pharmacists.7,15 Moreover, international studies have confirmed that increased participation by community pharmacists can play a significant role to counter underreporting of ADRs.14 The question is how to increase the participation of community pharmacists. Timely detection of possible new ADRs is one of the major goals of any ADR reporting system, and consequently, various countries have adopted electronic or online ADR reporting systems. However, the effectiveness of these systems is not yet established. A recent survey of pharmacists (number of participants unknown) in the US revealed that 68% of pharmacists preferred online reporting to hard copy, and 77% reported this system as easier to use. This survey also reported a 93% increase in the number of ADR reports after one month of this system's implementation.16 No data from other countries are currently available. It is evident that ADRs are a major problem and have significant economic impact on healthcare systems. Various studies have been undertaken worldwide to identify the prevalence of ADRs. However, the methods and results of these studies are neither consistent nor based on community data, limiting the applicability of their findings. The objective of this study was to review ADR reporting schemes in selected developed countries, with emphasis on identifying community pharmacists' roles in ADR reporting.

3. Adverse Drug Reaction Reporting Programme In Indian Hospital

Adverse drug reactions (ADRs) are negative consequences of drug therapy. At least one ADR has been reported to occur in 10 to 20% of hospitalised patients. In the recent past, pharmacists and pharmacologists have been encouraged to participate in and contribute to the ADR monitoring and reporting programmes in different parts of the world.

ADR monitoring and reporting activity is in its infancy in India. ADR reporting programmes on an institutional basis can support the setting up of a sound pharmacovigilance system in the country. Furthermore, productive hospital-based ADR programmes can provide valuable information about potential problems in drug usage in an institution.

Dr. T.M.A. Pai hospital, Udupi is a 200-bed teaching hospital and is a constituent of Kasturba Hospital (KH), Manipal (a tertiary care hospital). The department of pharmacy practice has been carrying out an ADR reporting programme at KH from July 2001. Dr. T.M.A. Pai hospital did not have such a system. Therefore, the present study was undertaken with the objective of initiating a similar system at the hospital to study the incidence and the pattern of ADRs occurring in this hospital.

This was a spontaneous reporting study conducted for a period of seven months (October 2003- April 2004) and coordinated by clinical pharmacists. Various methods were adopted to create awareness about ADR reporting system. These included ADR reporting awareness posters and personal interaction with health care professionals.

Health care professionals were encouraged to report all suspected ADRs through various modes, which included reporting through ADR reporting forms available at all the nursing stations and out-patient departments, telephonic reporting, and direct reporting to the clinical pharmacist who attended ward rounds in various departments on rotation basis. After the intimation of suspected ADR, additional details were collected for further assessment of the ADR by the clinical pharmacist.

In the present study, only the reports of ADRs in the inpatients were evaluated. The incidence and pattern of ADRs were evaluated. Further, the individual ADR reports were assessed to find out whether the ADR was the reason for the present admission of the patient to the hospital. All reported ADRs were evaluated for the following parameters using appropriate scale.

1) Causality (Naranjo's algorithm)
2) Severity (Hartwig *et al* scale)

A total of 1821 patients were admitted in the hospital, and 65 ADRs were reported from 51 patients during the seven-month study period. At least one ADR was reported in 2.8% of hospitalised patients. Among the reported ADRs, in six cases the ADR was the sole reason or one of the reasons which contributed to the hospitalisation of the patient. Out of the 65 ADRs reported, 42 (64.6%) were identified and reported by physicians and nurses, while the remaining 23 (35.4%) were identified and reported by the clinical pharmacist. Majority of the reports were from the medicine department (84.6%), followed by pediatrics (10.8%), OBG (3%) and orthopedics (1.5%).

In terms of the patient demographics in the reported ADRs, 32 were females and 19 were males. Number of patients in pediatric (0-18 years), adult (19-60 years), and geriatric (>60 years) groups were 6, 27, and 18, respectively.

Drug class implicated in the ADR reports and the system affected by the reactions are represented in , respectively. Upon causality assessment it was found that most of the ADRs belonged to the category possible (52.3%), followed by probable (46.2%) and unlikely (1.5%). Of the reported ADRs, 64.6% were moderate in severity, 29.2% were mild, and 6% were severe. Most of the ADRs (52.3%) were managed by symptomatic treatment, while 4.6% cases required specific treatment.

The incidence of ADRs observed in this study was found to be low compared with the incidence mentioned by Murphy *et al* based on the data from other studies. According to Murphy *et al* as many as 35% of hospitalised patients experienced an ADR during their hospital stay. One major reason for this could be underreporting, similar to that observed in another Indian study. Out of the 92 health care professionals who were working in the hospital during our seven-month study period, only 14 (15.2%) reported at least one ADR. The concept of such a reporting system was new to the health care professionals, which might have contributed to underreporting. Underreporting, a major drawback of spontaneous ADR reporting, is prevalent even in developed countries with a long history of functional ADR reporting system. A method that could be employed to tackle this problem in a hospital set-up is to increase awareness about an existing system and the advantages of ADR reporting. Furthermore, provision of 'thank you' note to the reporters along with additional details that could be educational in nature, on the reported ADR, could help in motivating them for future reporting. Periodic dissemination of data on the reported ADRs to the health care professionals would provide information to them on the pattern of ADRs occurring in the local population. These are some of the methods that could probably improve compliance with spontaneous ADR reporting among the health care professionals.

Antibiotics were the most commonly implicated drug class, a finding consistent with other studies. Among the various systems affected by ADRs, gastrointestinal system was the one most commonly associated with ADRs, and this finding is consistent with the reports of an Indian study.

This study was useful as a preliminary study in initiating a culture of ADR reporting among health care professionals in the hospital under study. Reporting programmes are necessary to educate and to increase awareness about reporting of ADRs among the healthcare professionals in the developing countries. Furthermore, these programmes help to obtain information on the incidence and the pattern of ADRs in the local population.

4. Adverse Drug Reaction Monitoring System

This study was a concurrent, spontaneous reporting, involving both active and passive methods. Active methods include physicians, pharmacists and nurses actively looking for suspected ADRs and passive methods include stimulating prescribers to report suspected ADRs. The study was conducted in a 35-bed internal medicine ward of the Holy Family Hospital, Bandra (W), Mumbai, India, over a period of 7 consecutive months, starting from July 2008 to January 2009. The study protocol was reviewed and approved by the University Ethics Committee.

All the physicians in the ward were informed about the study, outlining the ADRs' negative impact and were asked to report all observed adverse events. In order to ensure that the rate of notifications remains constant during the whole study period, the physicians were regularly reminded about the study taking place.

An Adverse Drug Reaction Reporting Form was designed and made available at all nursing stations of the ward of the hospital for easy access to all healthcare professionals. The Adverse Drug Reaction Reporting Form was prepared with reference to the ADR reporting form of the Central Drug Standard Control Organization (CDSCO) which includes information about the patient, like name, age, sex, medication history, diagnosis history, name of the suspected drug along with batch number, lot number manufacturing date and expiry date. The route of drug administration, frequency and dose is also mentioned in the form. Basic information of adverse reaction caused by the suspected drug was also included. We defined adverse drug reactions according to the World Health Organization definition, as being all "noxious and unintended drug response, which occur at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiological function. By this definition, ADRs primarily include allergic reactions and adverse effects. Therefore, we excluded all the intentional overdoses, poisonings and therapeutic failures.

In addition, the patient's medication history was also taken and any co-morbidity identified to assess the causality relationship between the suspected drug and reaction. Patients who developed an ADR were interviewed daily from the day the ADR was reported with regard to consumption of any other medication. The relationship between ADR and the suspected drug was assessed. The severity of the ADRs was also assessed in different categories as mild, moderate and severe for each ADR. All the reported ADRs were assessed for their preventability criteria. Personalized letters and circulars signed by the director of the hospital were circulated to all residents and practitioners, visiting practitioners and nursing stations. These letters contained information on the number of suspected ADRs that had been reported till date, need for continuing reporting of ADRs and a request to maintain a high degree of suspicion for the ADRs. The data observed were analyzed in order to study the characteristics of the ADRs and to determine the nature and pattern of ADRs related to hospital admission and difference in the severity of ADRs and management and outcome of management of the reported ADRs. Causality assessment is the method by which the extent of relationship between a drug and a suspected reaction is established. The assessment of causality relationship is often subjective, based upon an individual clinician's assessment. One clinician's judgement may appear unlikely to another clinician. If an ADR is suspected, the assessment starts with collection of all the relevant data pertaining to patient demographics, medications, including non-prescription (OTC) drugs, comprehensive ADR details including a description of the reaction, time of onset and duration of the reaction, complications and/or sequelae treatment of the reaction and outcome of the treatment and further relevant investigation reports. The collected data were used to correlate and categorize the relationship between the suspected drug and the adverse drug reaction. Causality assessment was

done using the Naranjo's scale. The data were also analyzed as per severity (Mild, Moderate and Severe) of the suspected adverse drug reaction and categories as death, life threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention to prevent permanent impairment or damage, not serious, and others.

5. Conclusion

The stimulated spontaneous reporting used in the present study turned out to be a pragmatic method which allowed the detection and characterization of ADRs. However, monitoring of adverse drug reactions is an ongoing, ceaseless and continuing process. Since newer and newer drugs hit the market, the need for pharmacovigilance grows more than ever before. Monitoring of the adverse effects of newer drugs, particularly of serious nature, is mandatory. Imparting knowledge and awareness of ADRs reporting among health care professionals would introduce the reporting culture among medical practitioners and increase the reporting rates of ADRs. Careful consideration involved in planning and monitoring of drug therapy will lead to prevention of ADRs. On balance, this study suggests that hospital-based monitoring is a good method to detect known and unknown links between drug exposure and ADRs.

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