Drugs Ther Perspect (2015) 31:402–406
DOI 10.1007/s40267-015-0231-z

ORIGINAL RESEARCH ARTICLE

Profile of adverse drug reactions in patients admitted to general surgical wards of a rural tertiary-care hospital in India

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Published online: 23 July 2015
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Abstract

Aim To find the incidence rate of adverse drug reactions (ADRs) and investigate its various aspects in patients admitted to surgery wards of a rural tertiary-care hospital in India.

Methodology A prospective observational study, involving 800 patients over a period of 1.5 years, was carried out to find the incidence rate of ADRs, and various aspects of such events (e.g. causality, severity, preventability, causative drugs, organs/systems involved, and management strategy with outcome). A structured and pre-tested form was used to compile the data.

Results An ADR was reported in 3.9 % of patients. Neither the age nor gender of the patients influenced incidence rate. Type A (augmented) reactions accounted for 83.9 % of ADRs. Causality assessment, using the WHO-UMC method, revealed that 58.1 and 41.9 % of ADRs fell into the 'probable' and 'possible' categories, respectively, whereas the corresponding proportions were 71.0 and 29.0 % using the Naranjo ADR probability scale. As the number of drugs per patient increased, the incidence of ADRs also increased. The majority (77.4 %) of ADRs were associated with antimicrobial drugs, followed by analgesics, with 71 % of ADRs involving the gastrointestinal system. No ADRs were fatal. Suspected drugs were discontinued in 64.5 % of patients and 96.8 % patients had fully recovered at the time of discharge.

Conclusion Identification and monitoring of ADRs among various patient groups, including those admitted to general surgical wards of a hospital, along with meticulous reporting thereof, can help provide better and more rational patient care. Few studies that monitored ADRs in surgical patients are available. The incidence rate of ADRs amongst surgical patients in this Indian hospital appears to be much lower than commonly reported (3.9 vs. 10–25 %).

Introduction

An adverse drug reaction (ADR) describes harm associated with the use of given medications at a normal doses [1]. The World Health Organization (WHO) defines an ADR as "a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for the modification of physiological function excluding failure to accomplish the intended purpose" [2]. Any medication may cause known or unknown ADRs, and, therefore, the occurrence of ADRs remains a common clinical problem. ADRs may result in diminished quality of life, hospitalizations, increased health care costs and even death [3].

Continuous monitoring and evaluation of the safety and effectiveness of all medicines is essential through pharmacovigilance. Clinicians who prescribe and follow-up treatment outcomes are able to detect ADRs based on their own clinical observations and information obtained from their patients. The lack of a well-structured and effective ADR monitoring and reporting programme is a major problem in India. In order to identify and prevent ADRs,

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methods that can accurately predict the subpopulation of patients who are most at risk must be developed. Such methods must be efficient, practical and less expensive than current methods [4].

Surgeons, who prescribe a number of drugs (most commonly antimicrobial agents), are among the healthcare professionals that must be vigilant about the spontaneous reporting of ADRs. Irrational antimicrobial usage is a common problem, leading to the emergence of multidrug resistant organisms, a high incidence of ADRs and increased costs. The problem becomes more complicated when new antimicrobials and other drugs are launched in the market [5].

Though there has been a noticeable improvement in overall pharmacovigilance activity in India during the past 5 years, a search of the literature could not find any studies exclusively pertaining to ADRs in general surgical patients in India. In the international literature, only one study that monitored ADRs exclusively in surgical patients was found (this study was in the subspecialty of paediatric surgery) [6], with two additional studies describing ADRs in surgical patients as part of a comprehensive study of ADRs in all patients admitted to hospital [7, 8]. Therefore, the present study was conducted to monitor the incidence rate and other aspects of ADRs exclusively in the patients admitted to the general surgical wards of a rural tertiary-care hospital in India.

Methodology

This prospective observational, cross-sectional study was conducted at Dhiraj Hospital (a rural teaching tertiary-care hospital attached to the Smt. B. K. Shah Medical Institute and Research Centre) in Gujarat, India from December 1, 2009 to June 30, 2011. Ethical approval was obtained from the Institutional Ethics Committee before the commencement of the study. Each patient was given a printed participant information sheet in a language they could understand, and their written, informed consent was obtained prior to their enrolment as a study participant. Confidentiality with respect to information obtained about the participating patients and surgeons was maintained at all levels. An appropriate form for recording and monitoring ADRs was developed and validated by a pilot study conducted in 20 patients admitted to the general surgical wards of the hospital.

Patients of either sex aged >10 years who were admitted to the general surgical wards during the study period were eligible for study enrolment. Children aged >10 years were included as they can perceive, comprehend and report any change in their health condition, including ADRs; younger children were not included because they may not have this ability and also because they are generally treated in the paediatric, rather than general, surgical wards.

Patients referred by or transferred from other departments, patients discharged or transferred to other departments within 24 h, patients not willing to participate in the study, patients unable to communicate (e.g. patients on ventilators or suffering from serious diseases), and patients admitted with a diagnosed ADR were excluded from the study.

Participant information (e.g. relevant patient history, examination details, investigations and pharmacotherapy) was collected and recorded in the case record form each day (from the day of admission till discharge from the hospital). Any ADR, reported by the patient or observed by the investigator or treating surgeon, was recorded in the pretested standardized form, as well as in the 'Suspected ADR Reporting Form' issued by Indian government. In cases of differences of opinion with respect to potential ADRs, the opinion of the treating surgeon was considered as final. Only ADRs were monitored and no observations were made with regard to diagnosis or patient management.

Data were analysed to find the incidence rate of ADRs in the overall population and in various patient subgroups (defined by age, sex and number of concurrent medications), as well as other various aspects of the ADRs (e.g. causality, severity, preventability, causative drugs, organs/systems involved, and management strategy with outcome). The ADRs were assessed for causality [using the WHO-Uppsala Monitoring Centre (WHO-UMC) criteria [9] and Naranjo ADR probability scale [10]], severity (using the modified Hartwig and Siegel scale [11]), and preventability (using the modified Schumock and Thornton criteria [12]).

Data were subjected to statistical analysis using appropriate methods, such as χ^2 or t test; p values ≤ 0.05 were considered significant.

Results

The study included a total of 800 patients admitted to general surgical wards, of whom 521 (65 %) were male and 279 (35 %) were female. By age group, 74 (9 %), 456 (57 %), 204 (26 %) and 66 (8 %) patients were aged >10–20, >20 to 50, >50 to 65 and >65 years of age, respectively.

In the total population, 31 patients (3.9 %) developed an ADR, of whom 21 (67.7 %) were male and 10 (32.3 %) were female. There was no significant between group difference (BGD) when the rate of occurrence of ADRs was compared in subgroups of patients determined by sex (4.0 vs. 3.6 % of male and female patients, respectively; $\chi^2 = 2.75$; $p = 0.75$), or age (2.7, 3.1, 5.9 and 4.5 % of patients aged >10–20, >20 to 50, >50 to 65 and >65 years of age, respectively; $\chi^2 = 3.35$; $p = 0.34$).

However, there was a significant ($\chi^2 = 50.68$; $p < 0.001$) association between the rate of ADRs and the number of

concurrent drugs a patient was receiving. An ADR developed in 0 (0 %) of the 21 patients receiving ≤2 drugs, 3 (0.7 %) of 436 patients receiving 3–5 drugs. 17 (6.0 %) of 284 patients receiving 6–10 drugs, and 11 (18.6 %) of 59 patients receiving >10 drugs.

Causality assessment of the 31 suspected ADRs using the WHO-UMC criteria [9] indicated that 18 (58.1 %) ADRs fell into the 'probable' category and 13 (41.9 %) into the 'possible' category. When the Naranjo scale [10] was used to assess causality, 22 (71.0 %) ADRs fell into the 'probable' category and 9 (29.0 %) into the 'possible' category. No ADRs fell into the other categories (i.e. 'definite', 'unlikely', 'conditional/unclassified' or 'unassessible/unclassifiable') of either causality assessment method. A significant association was found between the results of these two methods ($\chi^2 = 31.00$, $p < 0.001$).

As assessed by the modified Hartwig and Siegel scale [11], the severity of the 31 reported ADRs was determined to be either mild (20 ADRs; 64.5 %) or moderate (11 ADRs; 35.5 %). Using the modified Schumock and Thornton criteria [12], 6 (19.4 %) ADRs were found to be definitely preventable, with the remaining 25 (80.6 %) not being preventable. Of the 31 ADRs, 26 (83.9 %) were type A (augmented) and only 5 (16.1 %) were type B (bizarre).

Antimicrobial agents (most commonly amoxicillin) were most frequently associated with the 31 reported ADRs, followed by analgesics (most commonly diclofenac), with a few other drugs being implicated in a limited number of cases (Table 1). Over two-thirds (71.0 %) of reported ADRs involved the gastrointestinal tract (12 cases of diarrhoea, 8 of vomiting and 2 of epigastric discomfort); in addition there were 2 cases of allergic reaction, 3 cases each of allergic dermatitis and haematuria, and 1 case of vertigo and dizziness.

All 31 ADRs occurred within the first 2 days of drug administration. The suspected drug was continued with addition of another drug to overcome ADR in 11 (35.5 %) patients, the suspected drug was discontinued without addition of another drug in 4 (12.9 %) patients, and the suspected drug was replaced by another drug in 16 (51.6 %) patients. All ADRs subsided within 4 days of initiating appropriate measures, and all patients fully recovered from the ADR (30 patients by the time of discharge from the hospital; 1 patient remained in hospital for other reasons). No study deaths were related to an ADR.

Table 1 Drugs implicated in suspected adverse drug reactions (ADRs) [$n = 31$]

Drug class/drug	No. of ADRs (%)[a]
Antimicrobial agents	24 (77.4)
Amoxicillin	8 (25.8)
Ciprofloxacin	4 (12.9)
Metronidazole	3 (9.7)
Cefixime	3 (9.7)
Ceftriaxone	2 (6.5)
Cefoperazone + sulbactam	2 (6.5)
Ofloxacin + ornidazole	1 (3.2)
Piperacillin + tazobactam	1 (3.2)
Analgesics	13 (42.0)
Diclofenac	5 (16.1)
Mephenamic acid	4 (12.9)
Tramadol	2 (6.5)
Paracetamol	2 (6.5)
Other agents	5(16.1)
Anaesthetic agent	2 (6.5)
Packed red cells	2 (6.5)
Enoxaparin	1 (3.2)

[a] Some ADRs were likely caused by more than one drug

Discussion

ADRs remain a common clinical problem since they can mimic many diseases and cause significant morbidity and mortality. ADR monitoring is an essential aspect of therapeutics, and spontaneous reporting plays an important role in pharmacovigilance activity. The primary aim of pharmacovigilance is to collect, collate and analyze data to formulate conclusions in order to recommend regulatory interventions and communicate risks to healthcare professionals and the public [13].

In the present study, the demographic analysis showed predominance of males over females, with other studies in India showing a similar pattern [14, 15]. These observations may indicate that, in rural India, males have more illnesses and/or there is a gender bias towards providing healthcare for males over females. However, there was no significant BGD in the incidence of ADRs between male and female patients or between different age groups. In the present study, 31 ADRs were reported, which is equivalent to an incidence rate of 3.9 %. This is comparable with the results of some other Indian studies [14, 16], but lower than the rate of 9.8 % reported in one Indian study [17]. In general, the rate of ADRs in the Indian subcontinent appears to be far lower than the incidence reported in a study conducted in a hospital in the USA (10–20 %) [18]. The reasons for the same could be lack of awareness about pharmacovigilance, reticence in reporting ADRs, and the belief of the physicians that an ADR reflects of bad therapeutics on their part. Several other factors—genetic, ethnic, dietary and environmental—could also be the reason for this relatively low rate of ADRs.

All the ADRs in the present study were known reactions to the drugs concerned and none was a newly observed

ADR. Moreover, the most commonly observed ADRs were augmented (Type A) reactions (83.9 %), with is consistent with the reported rate of Type A reactions ($\approx$80 %) in other studies [19].

Causality was assessed using the WHO-UMC criteria and the Naranjo scale, two well accepted, widely used and simple methods. There was a very highly significant association ($p < 0.001$) between the results of the two methods, which is similar to the findings of another study [20]. It appears, therefore, that either method can be used, with reasonable certainty, to grade the ADR; however, it is more time consuming to use the Naranjo scale. The WHO-UMC assessment revealed that 58.1 % of ADRs fell into the 'probable' category and remaining 41.9 % into the 'possible' category, which are consistent with the findings of Gor and Desai [14]. In a comparison of WHO-UMC causality findings between our study and the Gor and Desai study [14], there was no significant between-study difference. This appears logical since both these studies have been carried out in Central Gujarat region and hence study populations would expectedly be similar in genetic, ethnic, dietary, social and environmental aspects. However, when the findings of our study using the WHO-UMC method were compared with those of a similar study by Sriram et al. [15], the difference was statistically significant ($p < 0.05$). The Naranjo causality assessment indicated that 71.0 % of ADRs fell into the 'probable' category and the remaining 29.0 % into the 'possible' category, which was significantly ($p < 0.05$) different to the Naranjo causality findings in studies by both Sriram et al. [15] and Arulmani et al. [17]. These between-study differences may reflect the influence of differences in genetic, ethnic, dietary, social and environmental factors between Gujarat in Western India (where our study was conducted) and Tamilnadu in South India (where the other two studies were conducted) [15, 17].

Assessment of the severity of the suspected ADRs revealed that nearly 65 % were mild, with the rest being moderate. It is well established that as the number of drugs that a patient receives increases, the number of ADRs also increases [21]. In our study, as the number of administered drugs increased, there was a highly significant increase ($p < 0.001$) in the rate of occurrence of ADRs. The number of drugs administered to a patient should be kept as low as possible in order to minimize the risk of ADRs. The rational use of medicines can help achieve this goal.

In the present study, 71 % of ADRs were related to gastrointestinal system, most commonly diarrhoea and vomiting, which is similar to the findings of other studies [14, 15]; the most culpable drug groups for causing ADRs were antimicrobials (77.4 %) and analgesics (41.9 %). Antimicrobial drugs likewise caused 72 % of ADRs in the Gor and Desai study [14], but only 23 % of ADRs in the Sriram et al. study (of note, they accounted for the highest number of ADRs by drug class) [15]. Patients, particularly surgical patients, receiving antimicrobial drugs should be closely monitored for the occurrence of ADRs. The inappropriate use of antimicrobials should be avoided to reduce the development of multidrug resistance, as well as to reduce the risk of ADRs [5].

Patients should be observed closely for ADRs during the initial period of treatment. ADRs generally start within first week of drug administration and stop within a week or so after discontinuing the offending drug, with or without replacement of the same, and treatment for the ADR [22]. In our study, all ADRs occurred within the first 2 days of drug administration and had subsided within 4 days of initiating appropriate measures for combating the same.

The first principle that is usually followed in the management of patients of ADRs is to discontinue the suspected drug, and replace with treatment with another drug if required. In our study, the suspected drug was discontinued in 64.5 % patients. In remaining 35.5 % of patients, the suspected drug was continued and an additional drug was given to treat the ADR. In the Gor and Desai study [14], the suspected drug was discontinued in 88.9 % of patients and continued in only 11.1 % of patients. In the present study, no ADR was rated as a serious reaction, no patients died as a sequela of an ADR, all patients discharged from hospital recovered fully from the ADR prior to discharge, the treatment to combat the ADR was not required to be continued at the time of discharge, and no patient had a prolonged hospital stay on account of an ADR. Likewise, Gor and Desai found that 94.4 % of patients with an ADR fully recovered while they were in the hospital [14].

Possible limitations of the present study include the small (albeit adequate) sample size, the inclusion of patients admitted to only general surgical wards, the lack of inclusion of records regarding the administration of anaesthetic agents during study, and, in several patients, a lack of an accurate history of the drugs received, and their nature, prior to hospital admission.

Conclusion

Pharmacovigilance is still in infancy in India. Therefore, there is a need to inform physicians about the importance of monitoring for ADRs, recording their occurrence scrupulously and without reticence, and reporting them promptly to the relevant authority. This practice will prove very valuable in promoting the safe and rational use of drug therapy. However, due to the lack of interest, clinical acumen, aptitude and/or time, many untoward adverse incidents pass unnoticed. Moreover, many physicians are

unaware that all ADRs—common or uncommon, mild or serious—can be reported to the ADR Monitoring Centres. As a result, ADRs are often not detected or documented. Improved awareness of the problem and increased ADR reporting by healthcare professionals may be achieved through the establishment of hospital-based or local ADR reporting and monitoring programmes A medical pharmacologist, who is primarily a physician, can contribute effectively toward meeting this goal. Of note, there is a paucity of studies investigating ADRs in surgical patients. We have tried to address this issue in this study; however, there is a need to carry out similar studies in larger number of patients.

Compliance with ethical standards

Funding No sources of funding were used to conduct the study or prepare this report.

Conflict of interest Nirav N. Patel and Sagun V. Desai declare that they have no conflicts of interest relevant to the content of this manuscript.

Ethical approval Ethical approval was obtained from the Institutional Ethics Committee before the commencement of the study. Written informed consent obtained from all the patients.

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