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Spontaneous reporting of adverse drug reactions at a department of Internal Medicine

Research Article

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Abstract: The aim of the present study was to characterize the pattern of adverse drug reactions (ADRs) reported in a university teaching hospital in south-east Serbia. The study was conducted based on ADRs reported during a six-month period to the ADR reporting unit of the university clinical center. Evaluation of data was done for various parameters, such as patient demographics, drug and reaction characteristics, and outcome of reactions. Assessment was also done for causality, severity and predisposing factors. During the 6-month study period, 44 ADRs were reported, with an overall incidence of 0.33%. No significant difference was seen in the overall incidence of ADRs observed in males and females. Incidence of ADRs among elderly (43.2%) and older (25%) adults was significantly higher than in other age groups. Type A reactions (66.7%) accounted for majority of the reports. The most commonly affected organ system was the renal system, (22.7%) with hyperkalemia as the only reported reaction. ACE inhibitors (48.6%) were the drug class most commonly involved, where fosinopril (25.7%) was the individual drug most frequently reported. Additional treatment was pursued for management of ADRs in majority (52.3%) of the reports. In 52.3 % of the reports, the patient had recovered from the reaction by the time of evaluation. Upon causality assessment, the majority of the reports were rated as probable (43.2%). Mild and moderate reactions accounted for 43.2% and 54.6%, respectively. In 36.3% of the reports, the reaction was considered to be preventable. The most common predisposing factors were polypharmacy and multiple disease state. The pattern of ADRs reported in our hospital is comparable to the results of studies conducted in hospital set up elsewhere. Our evaluations revealed opportunities for intervention to ensure safer drug use.

Keywords: *Adverse drug reactions • Spontaneous reporting • Hospitals*

1. Introduction

Adverse drug reactions (ADRs) are common problems that affect patients in the hospital and community setting [1]. According to the World Health Organization (WHO) definition, an ADR is "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function". Some authors report adverse drug events in accordance with the WHO definition as "any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment" [2].

ADRs are a frequent cause of hospitalization, and occur often in hospitalized patients [3-7]. Around 6% of hospital admissions are estimated to be due to ADRs and about 6-15% of hospitalized patients experience a serious ADR [8-10]. However, the frequency of ADRs leading to hospitalization or occurring after admission to hospital differs markedly from study to study [10]. This can be attributed in part to differences in study design regarding methodology, terminology and populations studied.

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Reporting of ADRs has become an important component of monitoring and evaluation activities performed in hospitals [11]. Such ADR reporting programs promote surveillance for ADRs, the reporting of ADRs and stimulate education of health professionals regarding potential ADRs, [12] thereby leading in the long run to improvement in patient care.

A spontaneous reporting program, a common method of drug surveillance, is capable of recognizing ADRs in the daily medical practice, even though its disadvantages are underreporting and absence of information on the number of people actually exposed to the drug [13,14]. Periodic evaluation of ADRs reported in a hospital helps to characterize the pattern of ADRs and thereby helps to design steps leading to improved safety of drug use in the working setup. Better health care practice could be ensured by applying this knowledge to individual patients [15].

Even though monitoring and reporting of ADRs is still in its infancy in this developing country, an ADR reporting unit has existed in our hospital since 2004. The present study was undertaken to characterize the pattern of ADRs reported at the Department of Internal Medicine of our university teaching hospital (Nis, South-east Serbia) with regard to patient demographics, drug and reaction characteristics, outcome, causality, severity, preventability and predisposing factors of the ADRs.

2. Material and Methods

This study was conducted in the nephrology ward, Department of Internal Medicine, University Clinical Center, Nis, Serbia based on reported ADRs. The mode of reporting is discussed elsewhere in the text. ADRs reported between February and July 2006 (6 months) were evaluated for the purpose of this study. Additional details on the ADRs for evaluation purposes were collected from the respective case records wherever required.

2.1. Functioning of ADR reporting system

During the study period, health care professionals reported all suspected ADRs by means of a printed ADR notification form to the hospital's ADR reporting unit. We noted all ADRs that occurred on the ward. After initial notification of the suspected ADR, additional details were collected regarding previous allergies, concomitant medications, co morbidities, management and outcome of the ADR, and other details necessary for evaluation. Similar data was collected by review of patient case records and by patient interview. The treating physician was approached whenever required to get additional details and clarification. All necessary information was recorded in a notification form designed for this purpose.

2.2. Evaluation of data

Data on reported ADRs was evaluated to understand the pattern of the ADRs with respect to patient demographics, nature of reactions, characteristics of the drugs involved, and outcome of the reactions. Causality, severity, preventability and the presence of factors predisposing to the reactions in question were analyzed. Further, any possible relationship between the patient characteristics and characteristics of the reaction were assessed.

2.3. Patient characteristics

Patient age and sex were considered for evaluation. Patients were subdivided into 5 age groups: young adults (16–30 years), adults (31–45 years), older adults (46–60 years), elderly adults (61–75 years) and very elderly adults (over 75 years). ADRs were reported in a population of patients with chronic kidney disease with a glomerular filtration rate (GFR) of 40 mL/min or lower. Accompanying pathological states included hypertension, diabetes mellitus, secondary anaemia and chronic obstructive pulmonary disease.

2.4. Reaction characteristics

Individual reactions were classified depending on the type of reactions as type A (where A stands for "augmented" response, i.e., a pharmacologically mediated response) and type B (where B stands for "bizarre", i.e., usually an immune-mediated response) based on the classification by Rawlins and Thompson [16]. A type A reaction is one when a patient has an ADR that is predictable from the drug's pharmacological effect; generally, the drug may be recommenced relatively safely at a reduced dose. Type B reactions are not predictable from the drug's pharmacological effects; they are rare and more often associated with life-threatening symptoms. Rechallenge is not recommended. The most florid example of this is anaphylaxis [16]. Reactions were also classified depending on the organ system affected.

2.5. Drug characteristics

Drugs involved in the ADRs were classified into various drug groups according to the anatomical therapeutic chemical (ATC) classification based on WHO-ATC Index 2005 [17].

Table 1. Patient characteristics.

Age group	Number of ADR reports (%)	Number of patients with ADRs/total number of patients, incidence (%)	Gender	Number of ADR reports (%)	Number of patients with ADRs/total number of patients, incidence (%)
16-30	5(11.36)	2(0.22)	Male	24(54.5)	14(0.31)
31-45	2(4.6)	2(0.21)	Female	20(45.5)	13(0.35)
46-60	11(25)	7(0.35)			
61-75	19(43.2)*	12(0.42)*			
>75	6(13.6)*	4(0.28)*			
total	44(100)	27/8221(0.33)			

*$P<0.05$

2.6. Management and outcome

Management strategies employed for the ADRs were categorized as drug withdrawal, dose reduction, additional treatment for ADR, and no change in regimen with no additional treatment. Further, categorization of the ADRs was done for response after dechallenge and the final outcome of the event.

3. Analysis of ADRs

3.1. Causality

To assess the likelihood that a drug had caused the reaction, causality assessment was done using Naranjo's ADR probability scale, [18] whereby the ADRs were classified as certain/definite, probable, possible and unlikely to be drug induced depending upon the level of association.

3.2. Preventability

ADRs were categorized as definitely preventable, probably preventable and not preventable using the criteria of Schumock and Thornton modified by Lau et al. [19].

3.3. Severity

Depending upon severity, ADRs were classified into mild, moderate and severe reactions using the criterion developed by Hartwig et al. for severity assessment [11].

3.4. Predisposing factors

Factors that could have predisposed to the occurrence of ADRs in the individual reports were evaluated. They were classified as age, gender, genetics, multiple and intercurrent disease state, and polypharmacy [20,21]. Age above 60 (geriatrics) was considered as a predisposing factor under the criterion 'age'. Polypharmacy was considered as minor (2–3 drugs), moderate (4–5 drugs) or major (>5 drugs) based on the characterization of Veehof et al. [22]. Sex was considered as a factor only if there was previous information indicating that the gender of the patient is known to predispose for the reaction in question. Genetics was considered if any genetic assessment was done on the patient, where obtained results were expected to predispose to the ADR in question. A multiple disease state was considered if more than 2 diseases had been diagnosed in the patient at the time the reaction developed; and intercurrent disease, if any intercurrent disease was present in the patient that is known to alter the response to the drug in question and predispose the patient to the ADR under consideration.

3.5. Statistical analysis

Analysis related patient characteristics (age groups and gender) to characteristics of the reaction (type of reaction, system affected, severity and preventability of reaction).

All data was statistically analyzed using the SPSS software package 10. Comparisons between groups were made by using χ^2 test. Differences were considered statistically significant for $P< 0.05$.

4. Results

A total of 44 ADRs from 27 patients were reported to the ADR reporting unit during the 6 month period. The number of patients who were admitted and those who visited the hospital as outpatients during the study period were 2015 and 5206, respectively, for a total of 8221 patients, among whom the 44 ADRs were reported. Based on these numbers, the overall incidence of ADRs was 0.33%. The majority of the reports were from hospitalized patients (65.5%) and the remaining from outpatients (34.1%), resulting in an incidence of 0.94 and 0.15 in inpatients and outpatients, respectively.

Upon evaluation of patient characteristics, more reports involved males (54.5%) and elderly adults

Table 2. Nature (type) of the reported ADRs.

Type	Number (%) of ADRs
Type A	41(66.7)
Type B	3(33.3)

(43.2%). However, no significant difference was seen in the incidence of ADRs observed in males (0.31) and females (0.35). Incidence of ADRs among elderly and older adults was significantly higher than that in other age groups (P=0.043) (Table 1).

Of the reactions reported, the majority (93.2%) were type A reactions (Table 2). The organ system most commonly affected was the renal system (22.7%) where the only reported reaction was hyperkalemia (Table 3). Angiotensin-converting enzyme (ACE) inhibitors were the drug class most commonly involved, where fosinopril (25.7%) was the individual drug most frequently reported as the suspected drug in the reactions. Drug class and individual drugs, apart from ACE inhibitors, that were prescribed to the patients during the study period are presented in Table 4. The six most frequently prescribed drugs during the study period were furosemide, calcium carbonate, fosinopril, enalapril, metoprolol and amlodipine (Table 4). Fosinopril and enalapril were related to ADRs affecting the renal system (hyperkalemia). Enalapril was also associated with chronic cough. Furosemide was mostly linked to hypotension and hypokalemia, which were reported infrequently. Metoprolol and amlodipine were linked to ADRs affecting the cardiovascular and gastrointestinal systems. No ADRs were reported on taking calcium carbonate.

In majority (52.3%) of the reports, an additional treatment for the reaction was instituted: the drug dose was altered in 27.3% of the reports, while the suspected drug was withdrawn for the management of an ADR in 18.2% of the reports. In 52.3% of the reports, the patient had recovered from the reaction by the time of evaluation of the ADR report. An improvement in the adverse reaction was observed in majority (52.3%) of the patients in whom dose reduction or additional treatment was instituted (Table 5).

Upon causality assessment, the majority of the reports were rated as probable (43.2%) followed by possible (29.6%). Mild and moderate reactions accounted for 43.2% and 54.6% of the reports, respectively, and only 2.3% of the reactions were judged to be severe. In 36.3% of the reports, the reaction was considered to be preventable (definitely or probably preventable) (Table 5). Predisposing factors most commonly identified to be associated with the reported reactions included polypharmacy (59.1%) and a multiple disease state (40.9%) (Table 6). Among the reports with

Table 3. Classification of ADRs evidenced by spontaneous reporting by system-organ class.

System-organ class	Number (%) of ADRs
Respiratory disorders	9 (20.5)
Gastrointestinal disorders	8 (18.2)
Central nervous system disorders	9 (20.5)
Cardiovascular disorders	8 (18.2)
Renal disorders	10 (22.7)
Total	44 (100)

polypharmacy as a predisposing factor, mild, moderate and major polypharmacy was present in 25.9%, 44.4%, and 29.6% of the reports, respectively.

Evaluating the relationship between patient characteristics and reaction characteristics, type A reactions were more common in males (80%) than in females (57%), and type B reactions were found to be more common in females (66.7%) compared to males (33.3%), but the difference was not statistically significant. No significant relationship was observed with regard to the organ system affected by the reaction and the patient characteristics. Mild reactions were more common in males (57.9%) compared to females (42.1%), moderate reactions were more common in females (62.5%) compared to males (37.5%), while a severe reaction was noted only in one woman. The differences observed were not statistically significant. Severity of the reaction showed a uniform distribution in various age groups. Further, analysis of the results did not reveal a significant influence of patient characteristics on preventability of the reactions.

5. Discussion

Despite extensive study, there is no doubt that ADRs still represent a significant clinical problem. An ongoing ADR program in a hospital can help assess the safety of drug therapies, measure ADR incidence rates over time, and educate health care professionals about drug effects and increase their level of awareness regarding ADRs [12]. Periodic evaluation of ADR data for incidence and pattern is essential where dissemination of this information to the health care professionals helps in promoting drug safety in institutions.

In this paper, we report the results of a pilot study that will inform the design of a larger study to fully investigate the burden of ADRs in the hospital setup. The overall incidence of reported ADRs was 0.33, which included reports from both inpatients and outpatients. In our study, incidence of ADRs in hospitalized patients was 0.94%, which was low compared to the results of the

Table 4. Drug class and frequency of individual drugs utilized during the study period.

Drug class (according to second level of ATC classification)	Drug	Frequency (%)
Antiulcer agents (A02)	Ranitidine	0.4
	Omeprazol	0.4
Drugs used in diabetes (A10)	Insulin	2.47
Dietary minerals (A12)	Calcium	10.29
	Magnesium	0.4
Vitamins (A11)	Vitamins B group	4.12
Antianemic preparations (B03)	Iron salts	4.12
	folic acid	2.88
Antithrombotic agents (B01)	Acetilsalycilic acid	1.23
Cardiac glycosides (C01A)	Digoxin	1.65
Antiarrhythmic agents (C01B)	Amiodarone	0.8
Vasodilators used in cardiac disease (C01D)	Glyceril trinitrate	0.4
	Pentaerythritol tetranitrate	1.23
	Isosorbide-5 mononitrate	2.88
	Molsidomine	2.47
Diuretics (C03)	Furosemide	14.4
	Bumetanide	2.06
	Spironolactone	1.23
Diuretics combinations (C03E)	Hydrochlorothiazide,amiloride	0.4
	Methyclothiazide, amiloride	0.8
Vasodilators (C04A)	Pentoxifylline	2.06
	Dihydroergotoxin	0.8
Calcium channel blockers (C08)	Amlodipine	6.17
	Nifedipine	1.23
Beta blockers (C07)	Metoprolol	7.41
	Bisoprolol	1.23
	Karvedilol	2.47
ACE inhibitors (C09)	Enalapril	8.23
	Fosinopril	10.28
	Ramipril	0.4
Antihyperlipidemics (C10)	Atrovastatin	0.4
Corticosteroids for systemic use (H02)	Prednisone	1.23
Psycholeptics (anxiolytics) (N05)	alprazolam	0.8
Drugs for obstructive airway diseases (R03)	Salbutamol	0.8
	Amiophylline	1.6
	243	100

metaanalysis conducted by Lazarou et al. [10] where 15.1% of hospitalized patients developed an ADR. The major reason for this low number is that our data is based on spontaneous reporting, while the incidence reported by Lazarou et al. [10] was mainly based on prospective surveillance studies. However, in a study by Bennett and Lipman, [23] the incidence of ADRs by spontaneous reporting was 0.08% compared to 7.2% when ADRs were identified by prospective surveillance in the same setup. Our study revealed a similar incidence in outpatients (0.15%). Epidemiological data on outpatients are scarce for effective comparisons. In a metaanalysis of 17 prospective studies, [24] an ADR incidence of 1.4% was reported in outpatient children. The lower incidence in ADR reports in outpatients could reflect the fact that ADRs in these patients are more likely to be mild (patients with more severe reactions are more likely to be admitted to hospital). Secondly, as a result of work overload, ADRs in outpatients are more likely to be missed.

More ADRs were reported in males than in females; however, this difference was not statistically significant, which is similar to the results obtained by spontaneous reporting by Montastruc et al [25]. Also, incidence of

Table 5. Management and outcome of the ADRs.

	Number (%) of ADRs
Management	
Drug withdrawn	8 (18.2)
Dose altered	12 (27.3)
Additional treatment given	23 (52.3)
No change in drug regimen and no additional treatment	5 (11.4)
Outcome	
After additional treatment/ dechallenge/dose alteration	34 (77.3)
Improved	23 (52.3)
Not improved	4 (9.1)
Unknown	7 (15.9)
Final outcome	
Fatal	0
Recovered	23(52.3)
Continuing	10(22.7)
Unknown	11(25)

Table 6. Analysis of ADRs for selected parameters (causality, severity, preventability and predisposing factors).

Parameters	Number (%) of ADRs
Causality	
Definite	9(20.5)
Probable	19(43.2)
Possible	13(29.6)
Unlikely-doubtful	3(6.8)
Severity	
Mild	19(43.2)
Moderate	24(54.6)
Severe	1(2.3)
Preventability	
Definitely preventable	6(13.6)
Probably preventable	10(22.7)
Not preventable	28(63.6)
Predisposing factors*	
Age	16(36.4)
Gender	6(13.6)
Multiple and intercurrent disease	18(40.9)
Polypharmacy	26(59.1)
Nil	8(18.2)

** Total is different from the total number of ADR reports as in many of the reports more than one predisposing factor was observed.*

ADRs among older (0.35) and elderly adults (0.42) was higher than in other age groups.

Given that most of the ADRs were type A reactions (66.7%) - which is consistent with literature [14,16] - and are predictable from the known pharmacology of the compound, [16] we should be able to develop strategies to prevent these ADRs.

The drug class most commonly involved in the reactions were ACE inhibitors (48.6%), a finding not consistent with other studies in which antibacterials or analgesics were most commonly associated with the reports [26-29]. The renal system (22.7%) was the organ system most commonly affected by the ADRs in our study, with hyperkalemia as the only individual reaction related to this system, similar to the reports of other studies. ACE inhibitors and angiotensin-receptor blockers are used commonly in clinical practice to treat hypertension and decrease cardiovascular events in high-risk patients. A side effect of such therapy is the development of hyperkalemia. Hyperkalemia has been attributed to the use of ACE inhibitors in 10% to 38% of hospitalized patients with this complication [30-33]. Hyperkalemia develops in approximately 10% of outpatients within a year after these drugs are prescribed [34]. Patients at greatest risk for hyperkalemia include those with diabetes and those with impaired renal function; in these patients, a defect in the excretion of renal potassium may already exist, a situation consistent with our patient group.

Drug withdrawal or dose reduction is usually the first step in the management of an ADR. In our study, the suspected drug was withdrawn or dose was reduced after the ADR was suspected in 45.5% of the reports. Additional treatment was instituted in the majority of cases (52.3%). The fact that most of the reactions were regarded as being moderate could account for these values. In the majority of the reactions (52.3%), patients recovered completely, similar to the reports of some studies [28].

Most of the reactions belonged to the category “probable” based on causality assessment similar to the results of another study, [28] but different from the results obtained by Murphy and Frigo, [27] in which more of possible reactions were noticed. Considering the severity of the ADRs, majority were moderate similar to the results of some studies [3,5,28] but different from the results of certain other studies [36,37] in which reported ADRs were more often mild. Only a small percentage of the reactions were severe in nature.

Through preventability analysis, our study revealed a preventability rate of 36.3%, which is comparable to the results of other studies [38].

Studies have shown that age, gender, co morbidity, number of drugs, and length of hospital stay are significant risk factors for development of ADRs [36,39-44]. Our study revealed polypharmacy and multiple disease state as the most prevalent predisposing factors in patients

who developed ADRs. Since many of the reports were from a department where patients usually have multiple co morbidities - in our study coexisting renal impairment was the major among them - polypharmacy contributed to the high percentage of reports with these factors as predisposing ones in our study.

Gender was specifically a predisposing factor only in a few (13.6%) of the reports. Female gender contributing to the ACE inhibitor induced by dry cough was included in this number. Age (36.4%) was a contributing factor in many of the reports, with geriatric group (68.2%) being the major one.

Considering the influence of patient characteristics on the nature of the ADRs, no significant influence of patient characteristics on the system affected by the ADRs and severity of the reactions was observed in our study.

Our study had some limitations. Underreporting is a well-known limitation of spontaneous reporting and should be taken into consideration when interpreting the data. Since the study data was obtained from only one hospital, the results may not be applicable to the entire population. However, our study data does give insight into the pattern of ADRs which do occur in tertiary care hospitals with a comparable pattern of patient demographics and drug usage.

In conclusion, the pattern of ADRs reported in our hospital is comparable with the results of studies conducted elsewhere in the hospital setup. Results of many of the evaluated parameters were similar to other studies [26-29,35], while some aspects were different from other studies [27,28,36,38-44]. The results of this study confirm that ADRs represent an important problem, especially in the geriatric population. Spontaneous reporting seems useful for examining the occurrence of ADRs. Although criticisms can be made concerning the methodology applied, we consider this study to be useful for its educational contribution to our hospital staff. Since other methodologies are not possible in terms of personnel investment, we will focus on stimulating spontaneous reporting in different hospital wards to increase awareness about ADRs and to find pathways to reduce their occurrence.

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