

*Original Article***A prospective pharmacovigilance study in the infectious diseases unit of a tertiary care hospital**Berna Karaismailoglu¹, Nese Saltoglu¹, Ilker Inanc Balkan¹, Bilgul Mete¹, Fehmi Tabak¹, Recep Ozturk²¹ *Infectious Diseases and Clinical Microbiology Department, Istanbul University - Cerrahpasa, Cerrahpasa Medical Faculty, Istanbul, Turkey*² *Infectious Diseases and Clinical Microbiology Department, Istanbul Medipol University Medical Faculty, Istanbul, Turkey***Abstract**

Introduction: The frequency, causality, severity, preventability and risk factors of ADRs (adverse drug reactions) in infectious disease units are not well defined in the literature. Thus, the aim of this study was to determine the characteristics of the ADRs encountered in an infectious disease unit of a tertiary teaching hospital.

Methodology: The patients who were admitted to the infectious disease unit of a tertiary teaching hospital longer than 24 hours between January and December of 2016 were followed prospectively. Patients were observed and questioned for any sign of ADRs. The proportion of ADRs and patient characteristics were investigated. Causality was evaluated by the Naranjo algorithm, severity was determined using the Hartwig classification, and preventability was assessed using the Schumock and Thornton scale.

Results: 210 patients were admitted to the unit during the study period, of whom 44 patients (20.9%) experienced 51 ADRs. 5.9% of ADRs were found to be serious according to the Hartwig severity classification. In addition, 88.1% of ADRs were not preventable. The most frequently detected ADR was skin and subcutaneous tissue reactions (33.3%), and systemic antimicrobials were the most common type of drugs that caused an ADR. Prolonged hospitalization ($p < 0.001$) and usage of an increased number of drugs ($p < 0.001$) were found to be significant risk factors for ADR development.

Conclusions: Prolonged hospital stay and polypharmacy are significant risk factors that increase the incidence of ADRs in infectious disease units. The likelihood of unavoidable ADRs should arouse the attention of clinicians when prescribing antimicrobials.

Key words: pharmacovigilance; infectious diseases; adverse drug reactions; preventability; severity; risk factors.

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Introduction

Adverse drug reactions (ADRs) are defined by the World Health Organization (WHO) as ‘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 modifications of physiological function’. This term includes adverse effects that are dose-dependent and predictable, as well as drug allergies. High proportions of hospital admissions due to an ADR are reported by several studies (ranging between 3% and 35%), revealing the epidemiological importance of ADRs [1]. Many risk factors influence drug metabolism, and it might not always be possible to predict the effects of a drug during routine treatment. Hospitalized patients carry a high risk due to comorbidities and the intake of an increased number of drugs. The characteristics of ADRs can vary according to the drugs, diseases and

clinical circumstances. There are many predisposing factors in the development of ADRs. These include age, gender, race, genetics, comorbidities, polypharmacy, and inadequacy of the medical history of patients with previous drug allergies.

ADRs in hospitalized patients are one of the major causes of morbidity and mortality and constitute a large amount of health expenditures [2,3]. Although they are usually mild and resolve with the discontinuation of the drug or the reduction of the dose, some ADRs may be more severe and may persist for longer periods. For example, in recent epidemiological studies, ADRs were estimated to be the 4th to 6th most common cause of death [4]. The incidence of fatal ADRs was found to be between 0.23% and 0.4% [4].

Increased morbidity and health expenditures caused by serious ADRs constitute a major public health problem [3,5]. Although there are many studies

reporting ADR characteristics from various disciplines, the literature lacks information about the ADR characteristics of an infectious disease unit, which is a department highly vulnerable to ADRs due to the usage of numerous antimicrobial drugs.

Our aim was to detect and define the characteristics and risk factors of ADRs in an infectious disease unit of a tertiary teaching hospital in Turkey and to evaluate their causality, severity and preventability.

Methodology

General Information

The investigation was carried out in compliance with relevant laws and guidelines, in accordance with the ethical standards of the Declaration of Helsinki. The study was approved by the local ethical committee (approval number: 89125526-806.01.03-3154560). All patients gave informed consent to be included in the study. For each patient with an adverse reaction, an 'Adverse Reaction Reporting Form' created by the Turkish Ministry of Health Pharmacovigilance Center was filled out, and necessary notifications were made to related institutions.

Study Design and Patients

All patients hospitalized for >24 hours in the infectious disease unit of Istanbul University Cerrahpasa Medical School in Turkey between January 2016 and December 2016 were consecutively included in the study. The ward contained 20 patient beds in 8 separate rooms. Patients were followed during the entire hospitalization period and were questioned for the presence of any new complaints that might be a signal of an ADR. All data were collected prospectively, and the patients were observed for ADRs by one trained infectious disease specialist using a specific data collection form developed for this study. The ADRs present at admission were not included.

Data Collection

The demographic characteristics of the patients, previous medications, drugs started during the hospital stay, and laboratory test results were recorded. The accompanying diseases, the length of hospital stay, detected ADRs, and drugs responsible for the adverse reactions were documented. Obesity, alcohol usage, smoking status, history of diabetes, and immunosuppressive medication usage were also recorded. The adverse effects were categorized according to the systems they affected. The responsible drugs were classified according to the Anatomical Therapeutic Chemical (ATC) classification system,

which allows active substances to be divided into different groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties.

The Naranjo algorithm was used to categorize causality. For each drug suspected of causing an ADR, ten questions in the Naranjo algorithm were answered, and according to the scores, the drugs were classified as definite, probable, possible or doubtful [6]. The severity of the adverse events was assessed using the Hartwig severity scale [7]. According to the Hartwig scale, they were classified as mild, moderate and severe [7]. The preventability of ADRs was classified as definitely preventable, possibly preventable and not preventable, using the scale of Schumock and Thornton [8].

Data Analysis

Patients with and without ADRs were compared to determine any possible risk factor leading to an ADR. The risk factors analyzed were age, gender, length of hospital stay, number of comorbidities and number of prescribed drugs. Descriptive statistics were employed using measures of the mean, standard deviation (SD), median and interquartile range (IQR). Categorical variables were analyzed using the Chi-square test. The continuous data were subjected to the D'Agostino-Pearson test for normality. Student's t-test was used for two-group comparisons of quantitative data with a normal distribution, and the Mann-Whitney U test was used for two-group comparisons of data without a normal distribution. All variables with $P < 0.25$ on the univariate analysis were entered into the multivariate analysis. Multivariate logistic regression analysis was employed to determine an independent association between the risk factors and ADRs. The results are given with the adjusted odds ratio (OR) and 95% confidence intervals (CI). P values of < 0.05 were considered statistically significant. Statistical analysis was performed with the SPSS 22.0 (Statistical Package for the Social Sciences) program.

Results

Patient Characteristics

A total of 210 patients were included in the study, and 51 ADRs were detected in 44 patients (20.9%). The mean age of the 210 patients was 54.94 ± 18.16 years, and 50.9% were female. Among the 210 patients, 186 (88.6%) were discharged from the hospital after recovery, 13 patients (6.2%) were transferred to the intensive care unit, 9 patients (4.3%) were transferred to other hospital units, and 2 patients (0.95%) died.

Table 1. ATC classification of the drugs responsible for ADRs.

ATC	Active ingredient	Number	Percent (%)
J	Systemic antimicrobials	41	83.6
	Antibiotic	32	65.3
	Antituberculosis agents	14	28.57
	β-lactam inhibitors	10	20.41
	Carbapenem	2	4.8
	Chloramphenicol and tetracycline	2	4.08
	Quinolones	1	2.04
	Oxazolidinone	1	2.04
	Polymyxin	1	2.04
	Cephalosporins	1	2.04
	Antifungal	2	4.08
	Antiviral	7	14.21
H	Systemic hormonal preparations (Except sex hormones and insulins)	4	8.1
B	Drugs related to blood and blood forming organs	1	2.1
C	Cardiovascular system drugs	1	2.1
L	Antineoplastic and immunomodulatory drugs	1	2.1
V	Other	1	2.1

ADR: adverse drug reaction, ATC: Anatomical Therapeutic Chemical.

ADR Characteristics

The most common diagnoses in patients with ADRs included acquired immunodeficiency syndrome (9.6%), diabetes (7.8%) and hypertension (7.8%). The mean duration of usage of the drug responsible for ADR was 19.1±31.3 days. In 89.8% of detected ADRs, one drug was considered responsible, and in 10.2% of the ADRs, two drugs were held responsible. Systemic antimicrobials were the most common types of drugs causing ADRs (n=41, 83,6%), with antituberculosis agents being the most common group among them (Table 1). The most common ADRs were skin and subcutaneous tissue reactions, hepatotoxicity and elevated serum creatinine. Skin and subcutaneous tissue was detected as the most commonly affected body site, with 33.3% (n=17) of all ADRs, followed by the gastrointestinal and hepatobiliary system (n=14, 27.4%) (Table 2).

Causality, Severity, and Preventability

According to the Naranjo causality classification, 4 (7.8%) ADRs were definite, 21 (41.2%) ADRs were probable, and 26 (50.1%) ADRs were possible. According to the Hartwig severity classification, 3 (5.9%) of the ADRs were severe, 32 (63%) were moderate, and 16 (31%) were mild. Three ADRs were life-threatening. These reactions were anaphylactoid shock (due to ampicillin-sulbactam), severe hypoglycemia (due to fluconazole) and hemorrhagic shock (due to warfarin sodium). Fifteen ADRs caused prolongation of hospitalization. Among the 51 ADRs detected, 7.8% were definitely preventable, 3.9% were

possibly preventable, and 88.1% were not preventable according to the Schumock and Thornton scale.

Risk Factor Analysis

The variables with P < 0.25 in the univariate analysis, namely, age, gender, length of hospital stay, number of diagnoses, and number of drugs used before and after admission, were entered into the multivariate analysis as independent variables.

The differences in age and gender distributions between the groups were not significant (Table 3, 4). The mean duration of hospital stay was longer in patients with ADRs (32.0±24.1 versus 16.5±16.2 days, P < 0.001) and was related to increased ADR development (Table 3). More than 14 days of hospitalization led to higher risk of ADR development

Table 2. Detected ADRs and their frequency.

Adverse reaction	Number (n = 51)
Skin and subcutaneous tissue reaction	17
Hepatotoxicity	9
Elevated blood creatinine	5
Leukopenia, thrombocytopenia, pancytopenia	4
Uric acid elevation	3
Diarrhea	3
Hypoglycemia, hyperglycemia	2
Prolonged prothrombin time	2
(One of these patients developed hemorrhagic shock)	2
Anaphylaxis	1
Joint pain	1
Drug fever	1
Nausea-vomiting	1
Hypercalcemia	1
Stomach-ache	1

ADR: adverse drug reaction.

Table 3. Statistical comparison of mean values of hospital stay, number of comorbidities and number of drugs between the patients with and without ADR.

Variables	Patients without ADR Mean ± SD (Median, IQR)	Patients with ADR Mean ± SD (Median, IQR)	p value
Age	55.3 ± 18.6 (57, 30)	53.4 ± 16.5 (53.5, 26.3)	0.504
Length of hospital stay	16.5 ± 16.2 (12, 15)	32.0 ± 24.1 (27.5, 34.5)	< 0.001*
Number of comorbidities	2.58 ± 1.37 (2, 1)	2.61 ± 1.22 (2, 1.8)	0.674
Number of drugs being used on admission	3.06 ± 3.08 (2, 5)	3.45 ± 3.27 (2.5, 5)	0.448
Number of drugs initiated after admission	6.17 ± 5.0 (5, 7.3)	9.09 ± 5.16 (9, 8)	< 0.001*

ADR: adverse drug reaction. SD: standard deviation, IQR: interquartile range. *p < 0.001.

with an adjusted OR of 5.26 (CI:2.27-12.51, P < 0.001) (Table 4). The average number of diseases diagnosed in patients with and without ADRs (2.61±1.22 versus 2.58±1.37, P=0.869) was similar.

The average number of drugs used before and after admission was 3.06±3.08 and 6.16±5.01, respectively, in patients without ADRs, while the averages were 3.45±3.27 and 9.09±5.16, respectively, in patients with ADRs. The number of drugs used before admission was not significantly different between the groups (P=0.475). However, the number of drugs used after admission was significantly higher in patients with ADRs (P < 0.001) (Table 3). Usage of more than 7 drugs after admission increased the risk of ADR development with an adjusted OR of 3.44 (CI:1.66-7.69, P < 0.001) (Table 4).

Discussion

The frequency of ADRs in our study was 20.9%. Prolonged duration of hospital stay and increased

number of drugs started after admission were found to be risk factors for ADR development. Three ADRs (5.9%) were life-threatening.

Epidemiological surveys from the US report ADR rates of 10-20% in hospitalized patients [9]. A recent epidemiological study found that 35% of hospitalized patients developed ADR during hospitalization [10]. Our ADR rate, which was 20.9%, is similar to the rate in these studies. In our study, gender, age, number of comorbidities and number of drugs before admission did not significantly affect the development of ADR. The effect of gender on the development of ADR has been investigated in the literature, and women were found to have ADRs more commonly [11]. The authors attributed this finding to pharmacological, immunological and hormonal differences and the possibility that women tend to take more drugs [11]. Several other studies have also reported that women have higher rates of ADR [12–14]. In our study, we found no difference between male and female patients

Table 4. Results of logistic regression analysis for variables.

Variables	Patients without ADR (n = 166)	Patients with ADR (n = 44)	Adjusted OR	95% CI	p value
Gender					
Female	86	21	1.17	0.60-2.29	0.6305
Male	80	23			
Age					
< 65	102	31	0.66	0.32-1.37	0.2721
≥ 65	64	13			
Length of hospital stay					
≤ 14 days	107	9	5.26	2.27-12.51	< 0.001*
> 14 days	66	28			
Number of diagnoses					
≤ 2	95	26	0.92	0.47-1.81	0.8242
> 2	71	18			
Number of drugs used before admission					
≤ 3	105	24	1.45	0.73-2.85	0.292
> 3	61	20			
Number of drugs started after admission					
≤ 7	117	14	3.44	1.66-7.69	< 0.001*
> 7	56	23			

ADR: adverse drug reaction, OR: odds ratio, CI: confidence interval, *p < 0.001; > 14-day hospitalization and usage of > 7 drugs after admission led to significantly higher risk of ADR development.

in the development of ADRs, which was similar to the results of a study by Patel *et al.* [15].

Age-related changes in drug pharmacokinetics cause older age to be a significant risk factor for the development of ADRs. Prescription of multiple drugs (due to multiple comorbidities) and the high risk of complications expected in elderly patients increases the likelihood of developing an ADRs. Mandavi *et al.*, in their two-year prospective study involving 4005 elderly (60 years and older) patients who were referred to outpatient clinics, found that ADR development risk is greater in patients > 80 years of age than in the 60-69 year age group. The researchers also showed that there was a greater tendency to develop ADRs in patients with comorbidities, multiple drug use and long-term treatment [16]. In a study conducted at an internal medicine clinic that analyzed 143 ADRs in terms of predisposing factors, Raut *et al.* reported that multidrug use was the most common, comorbidities was the second most common, and age was the third most common risk factor for ADR development [17]. The possible reason why older age and number of comorbidities were not found to be risk factors in our study might be the relatively smaller sample size for patients over 65 years. A low number of patients older than 65 years also led to a low number of patients with comorbidities, preventing an accurate analysis of the effect of comorbidities on ADRs. This situation can also explain why the comorbidities did not affect the incidence of ADR significantly.

In a study evaluating the activities of a pharmacovigilance center in Portugal, 3165 cases of ADRs were examined, and the most common group of drugs causing ADRs were antibiotics followed by vaccines, the central nervous system and nonsteroidal anti-inflammatory drugs. Among the antibiotics, β -lactamase inhibitors and penicillins were the most frequently associated agents [18]. In a study reporting 1418 ADR cases from six regional pharmacovigilance centers in Korea, antibiotics (31.6%), contrast agents (14%) and nonsteroidal anti-inflammatory drugs (11.6%) were reported as the most frequently responsible agents [19]. In our study, with an 83.6% ratio, systemic antimicrobials were found to be the most common cause of ADRs, whereas systemic hormone-regulating drugs were found to be the second most common cause, occurring in 8.1% of the patients. Since our study was conducted in an infectious disease unit, systemic antimicrobials were inevitably the most commonly used agents. Consequently, the ADR development rate due to systemic antimicrobials, which

are among the most common causes of ADRs in the literature, increased even more.

In a study conducted by Aagard *et al.* [20], skin and subcutaneous tissue reactions, nervous system diseases and gastrointestinal diseases were found to be the most frequently detected ADRs. In our study, skin and subcutaneous tissue reactions, hepatotoxicity and elevated blood creatinine were the most frequently detected ADRs, accounting for 62% of all detected reactions, similar to the literature. This result allows us to conclude that physicians working in an infectious disease ward should be cautious about possible ADRs affecting the skin, hepatic and renal systems of the patients.

In a study conducted in an internal medicine ward by Camargo *et al.*, the Naranjo algorithm was used in the assessment of causality, and 36.1% of the ADRs were found to be in the definite and probable class [21]. This ratio was found to be 26.1% when Lagnaoui *et al.* used a similar methodology in a different study [22]. In our study, 49.1% of all ADRs were found to be in definite and probable groups according to the Naranjo algorithm. No ADRs were in the doubtful category. Therefore, it is possible to claim that the drug spectrum used in infectious diseases mostly causes ADRs with determinable causality.

Marques *et al.* examined 3165 cases of ADRs; the rate of life-threatening ADRs was 10.9%, and the rate of mortality was 1.1% [18]. Most of the ADRs identified in our study had mild and transient effects. Although less frequently observed, severe reactions were also detected. The life-threatening reaction rate was 5.9%, which is the same as the severe ADR rate according to the Hartwig classification. Although the severe reaction rate was found to be relatively low, it is important to keep in mind that it is also possible to experience a life-threatening ADR in an infectious diseases clinic. Therefore, physicians should be alerted about a possible severe ADR while following the patients in infectious disease wards.

Patel *et al.* investigated ADRs related to ceftriaxone and reported that 30% of the adverse reactions developed were severe reactions such as cardiac arrest, anaphylaxis, anaphylactoid reaction and that 15.2% were found to be preventable [23]. In some other previous studies, 65-91% of ADRs were found to be preventable [21,22]. In our study, 7.8% of the identified ADRs were definitely preventable, 3.9% were possibly preventable and 88.1% were not preventable. The probable reasons for the high variability of rates between the studies are the inclusion of different patient groups and the selection of different criteria for

assessing preventability. The high proportion of unpreventable ADRs in our study can be attributed to the high frequency of unpreventable ADRs due to antimicrobials. The likelihood of an unavoidable ADR should arouse the attention of clinicians when prescribing antimicrobials.

ADRs may lead to prolongation of hospitalization. Meanwhile, long-term hospitalization may increase the risk of ADR development due to the possibility of longer and increased drug exposure. Exposures to more drugs. Therefore, the causal relationship between ADRs and long hospital stays cannot be assessed clearly. Vora *et al.* and Moore *et al.* are among those who have shown that the rate of ADRs can increase proportionally to the length of hospital stay [24,25]. In our study, the duration of hospitalization for patients with ADRs was significantly higher than that for patients without ADRs. The physicians working in infectious disease wards should be more cautious about a possible ADR when following patients with a prolonged hospitalization.

Giardina *et al.* observed internal medicine unit patients for one year and found multidrug usage to be a risk factor for ADR development [26]. Similarly to their study, polypharmacy was found to be an important risk factor for ADR development in our study. The hospitalized patients in infectious disease wards should be more closely observed and questioned about a possible ADR when the number of drugs used increases.

This study has some limitations. The results cannot be generalized to the general population and to other clinic units since this study only includes patients from an infectious disease ward in a tertiary hospital. The number of patients was relatively low compared to that in similar studies mostly reported from internal medicine units since internal medicine units generally have larger wards, a greater number of beds and probably a more rapid patient turnover. Despite these limitations, this study also has several strengths. To the best of our knowledge, this is the first prospective pharmacovigilance study in the literature to be conducted in an infectious disease unit. The prospective design of the study allowed us to perform accurate data collection and appropriate causality and preventability determinations. The patient follow-up and the data collection were conducted by the same physician, which makes the results more reliable.

Conclusion

The results of this study define the characteristics of ADRs in an infectious disease unit of a tertiary hospital.

The detailed information about the characteristics of ADRs occurring in an infectious disease unit might be useful for predicting possible ADRs and taking precautions to prevent them, especially in units with similar patient characteristics. The likelihood of unavoidable ADRs should arouse the attention of clinicians when prescribing antimicrobials.

It is important to raise awareness among all health-care providers, develop strategies to prevent ADRs and increase the reporting rates since ADRs are still one of the leading reasons for hospital admission and numerous new drugs are being marketed every year. More comprehensive multicenter pharmacovigilance studies in infectious disease units are needed to support these findings.

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