Brief Communication

Potential of Drug Interactions as a Cause of Adverse Drug Reactions in Patients with Kidney Diseases

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ABSTRACT

Objective: Adverse drug reactions (ADRs) are one of the major causes of mortality. One of the major causes of ADR is drug–drug interactions. The purpose of this study was to evaluate the prevalence and characteristics of ADRs caused by the drug interactions in the nephrology departments. **Methods:** This cross-sectional prospective study was carried out in the nephrology department on 117 patients who received at least two medicines. Drug interactions were determined, and the patients were evaluated for the presence of a drug complication. **Findings:** A total of fifty ADRs were observed in 39 patients, whereas 26% of total ADRs (13 drug complications) were due to drug interactions. About 69% and 31% of complications were classified in terms of severity, in the category of "severe" and "moderate" complications, respectively. Warfarin had the highest contribution to major interactions (33.33%). **Conclusion:** ADRs, which specially occurred due to drug interactions, are particularly important for patients taking multiple medications (e.g., patient with renal insufficiency). Therefore, special attention should be paid to preventing and reducing ADRs in these patients' population.

Keywords: *Adverse drug reaction, drug interaction, kidney disease*

Introduction

Adverse drug reactions (ADRs) are one of the major causes of mortality and health problems in many patients. The importance of ADR and its burden on the health-care system is significant.[1]

The results of many studies show that 2.9%–5.6% of hospital admissions are due to ADRs and up to 35% of patients experience ADR during hospitalization.[2,3] It is important to note that one of the major causes of ADR is drug–drug interactions (DDI).[4] In a recent study, it was found that 25.9% of the ADRs were due to drug interactions.[1] The incidence estimation of ADR due to DDI is very difficult due to the different types of studies, population, frequency measurements, and classification systems.[5] Patients with polypharmacy are particularly at risk of these events. Kidney disease is one of the most commonly complicated diseases. As a function of the kidney decreases, many complications arise that require multiple medications. The same issue, as well as changes in the kinetics of drugs due to renal dysfunction, makes it possible for ADRs and multiple interactions. Therefore, recognition of ADR and DDI in this population can improve the quality of life and reduce the costs, hospitalization, and mortality.[6]

The purpose of this study was to evaluate the prevalence and characteristics of ADRs caused by the drug interactions in the nephrology departments in order to improve the pharmacotherapy process of patients with two important aspects of predictable and preventable risk factors be taken into account.

Methods

An observational, cross-sectional study was performed for 6 months on 117 patients hospitalized in Al-Zahra Hospital and Noor Medical Center in Isfahan, Iran. All admitted patients receiving at least two drugs during the hospitalization period were included in this study.

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Patients who were intentionally or accidentally poisoned or suspected of substance abuse were excluded from the study. Patients with incomplete information or those transferred to the other wards during the study and missed follow-up appointments were also excluded from the study.

Information on prescribed medications and laboratory and paraclinical tests of patients was collected from medical records. Drug interactions were determined, and the patient was evaluated for the presence of a drug complication.

The Naranjo algorithm was applied to establish causal links between drug administration and adverse reactions.[7] Subsequently, ADR was evaluated regarding severity according to the standard definitions mentioned in scientific resources.[8] After the incident of ADR and the intervention of the medical team, the final outcome of complication was evaluated as follows: fatal complication, complete recovery, relative improvement (but not complete recovery), or uncertain (the outcome of the patient has not been documented). Then, classification of any drug interactions as Class A, B, C, D, and X and the number and type of interaction (pharmacokinetic or pharmacodynamics) were investigated using the Lexi-Interact™ online program.[9]

Finally, by reviewing the available data on the type and characteristics of the interactions, any ADR that occurred due to drug interactions were identified and reported. In addition to drugs' side effects, the involved system or organ was separately presented based on the tenth revision of the International Statistical Classification of Diseases and Related Health Problems classification.[10]

Results

In 117 included patients (67 males, 57.2%), adverse events were recorded for twenty men (29.8%) and 19 women (38%), whereas 78 patients (66.66%) did not show any complications. There were more than one complication for 8 (6.8%) patients, so that fifty ADRs were observed in all cases. The age range of patients was 19–94 years, of which 86 patients were in the adult (19–65 years) and 31 were in the elderly (over 65 years) population. The most complications were recorded in the age range of 50–59 years (32.5%). In about 64% of the patients with a drug complication, the history of high blood pressure, diabetes, end-stage renal disease, or kidney transplantation were among the most commonly reported underlying illnesses.

About 91.5% of the patients encountered drug interactions. In this study, 1155 drugs were prescribed (on average, 11 medicines [standard deviation: 4.4] for each patient). A total of 1318 drug interactions were identified, of which 671 cases (51.1%) and 647 cases (48.9%) were pharmacodynamic and pharmacokinetic interactions, respectively.

According to the results, 26% of the total ADRs (13 drug complications) were due to drug interactions; of these, eight cases were in hospitalized patients and five cases in patients came to the hospital with a complication.

Out of the 13 cases that were eventually approved, 9 (69%) complications were classified in the category of "severe" and 4 (31%) were in the category of "moderate" complications.

Of the total drug interactions that resulted to ADR, nine were of Type C, one of Type D, and three of Type X interactions. The most frequent interactions were in the C category, and the highest contribution to the interaction was with warfarin, so that the overall complications due to this drug were 33.33%.

The most commonly observed adverse drug side effects were hematological complications, and most of the cases showed an increase in prothrombin time, partial thromboplastin time, and international normalized ratio, as well as thrombocytopenia.

All the details of these interactions and their attributed complications are presented in Table 1.

Discussion

ADRs incidence in hospitalized patients is one of the main problems in the health-care system. According to the results of various studies, it is estimated that about 2%–6.6% of admissions to hospital are due to ADRs, and 2%–20% of patients suffer ADRs during hospital admission.[1,11]

In a study, 300 patients were diagnosed with ADRs in patients with renal failure. A total of 159 drug complications were reported in 122 patients (40.6%).[12]

In the present study, in 23% of patients, the complications occur during the hospitalization and 14.5% of the patients were admitted because of ADRs, which is higher than previous reports (in the nonrenal patient population), and may indicate that renal insufficiency is probably a risk factor for ADRs.

Previous studies show that one of the risk factors in the occurrence of drug side effects is polypharmacy.[8] Patients with chronic kidney disease have many underlying illnesses that necessitate the administration of complex drug regimens; it can cause DDIs that can increase the incidence of ADR.[9]

Table 1: Characteristics of 13 drug interactions lead to adverse drug reaction

Drug (pair)	Complication	ICD-10	Naranjo score*	Time of occurrence	Severity of drug interaction	Category of drug interaction**	Patient's outcome
Prednisolone, rituximab	Esophageal candidiasis	I: B99	5	During admission	Severe	C	Partial recovery
Mycophenolate mofetil, prednisolone	Oral candidiasis	I: B99	7	Before admission	Severe	C	Complete recovery
Mycophenolate mofetil, prednisolone	Oral candidiasis	I: B99	4	Before admission	Severe	C	Complete recovery
Warfarin, cilostazol, fluconazole	↑ INR	III: D65-D69	8	During admission	Moderate	D	Partial recovery
Warfarin, posaconazole	↑ INR, PT	III: D65-D69	8	During admission	Moderate	C	Partial recovery
Warfarin, heparin	Bleeding	III: D65-D69	7	During admission	Severe	C	Partial recovery
Tacrolimus, spironolactone	Hyperkalemia	IV: E70-E90	5	During admission	Severe	X	Complete recovery
Spironolactone, cyclosporine	Hyperkalemia	IV: E70-E90	5	During admission	Moderate	X	Complete recovery
Cyclosporine, prednisolone	Dyspepsia	XI: K20-K31	2	During admission	Severe	C	Partial recovery
Amiodarone, atorvastatin	↑ ALT, AST	XI: K70-K77	8	During admission	Moderate	C	Partial recovery
Atorvastatin, gemfibrozil	↑ ALT, AST	XI: K70-K77	8	Before admission	Severe	X	Partial recovery
Ibuprofen, mefenamic acid	↑ Creatinine	XIV: N17-N19	8	Before admission	Moderate	C	Partial recovery
Cyclosporine, tenofovir	↑ Creatinine	XIV: N17-N19	4	Before admission	Severe	C	Complete recovery

*Naranjo score for establishing causal links between drug administration and adverse reactions, **Category of drug interaction: Risk C=Monitor therapy, Risk D=Consider therapy modification, Risk X=Avoid combination. ICD-10=ICD-10 (the 10th revision of the International Statistical Classification of Diseases and Related Health Problems, I=B99 (certain infectious and parasitic diseases), III=D65-D69 (diseases of the blood and blood-forming organs), IV=E70–E90 (endocrine and metabolic diseases), XI=K20–K31 (diseases of the esophagus, stomach, and duodenum), XI=K70–K77 (diseases of the liver), XIV=N17–N19 (diseases of the genitourinary system). INR=International normalized ratio, PT=Prothrombin time, ALT=Alanine aminotransferase, AST=Aspartate aminotransferase, ICD=International Classification of Diseases, ↑ = increase

In the study of the drug regimen of patients, from 117 patients, 91.5% of patients had drug interactions. Out of fifty documented ADRs, 13 complications (26%) occurred due to drug interactions. Of the total drug interactions that occurred and resulted in ADR, the drug that was in most interactions was warfarin, with a contribution of 37.5%. The most interaction of warfarin in this study was due to its metabolic inhibitors such as fluconazole.

Based on the results of this study, it seems that efforts to prevent ADRs and drug interactions in hospitals are not much considered. Therefore, it is necessary to consider holding advisory meetings with the presence of medical and pharmacotherapy specialists in hospitals as one of the main solutions to this problem.

One of the limitations of this study was delaying in getting the test result and eventually patient discharging, so it was not possible to achieve the outcome and thus to investigate the incidence or progress of the disorder according to the patient's laboratory tests. In some cases, due to early discharge of the patient with a personal satisfaction, the possibility of follow-up of the complications and drug interactions was not possible.

Based on the study, it is suggested that most attention to reduce the likelihood of side effects and drug interactions in future studies must be considered, and subsequently, cost-effectiveness studies can be done on the feasibility of reducing costs associated with occurrence of drug complications and interactions (if it be prevented).

Authors' Contribution

Shiva Seirafian and Shirinsadat Badri developed the idea of research, and designed the study. Fatemeh Yari performed all data gathering and patients' follow-up. Tahereh Gholipur Shahraki contributed in data analysis and prepared manuscript draft. All authors contributed in manuscript revision.

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Conflicts of interest

There are no conflicts of interest.

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