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Original Article

Evaluation of Drug-Drug Interactions in Chronic Kidney Disease Patients: A Single-Center Experience

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Abstract

Drug-drug interactions (DDIs) result from the simultaneous consumption of two or more drugs that alter the patient's response to the initial drug. The treatment regimen in patients with kidney disease is very diverse and may be associated with several diseases that increases the risk of DDIs. This study was carried out to investigate the DDIs incidence in patients with chronic kidney disease (CKD) in the nephrology ward. This descriptive-analytical study was performed in a 4-month period in 2017. The patients' information, such as age, sex, list of drugs during hospitalization, and kidney disease stage were recorded from patients' medical records. Drug-drug interactions were extracted using LexiComp Online. In this study 48.55% of patients were male, 51.45% were female, and 53.2% of patients were in stage 5 of kidney disease. There was a significant correlation between the incidence of drug-drug interactions with stage 5 of disease (P=0.02). The highest number of interactions was categorized as type C and interaction between atorvastatin and pantoprazole was the most frequent interaction. The maximum range of prescription drugs was between 6 and 10 items by 49.7% of patients. There was a significant correlation between the incidence of drug-drug interactions and the number of prescribed drugs (P=0.03). Drug-drug interactions are common in patients with chronic kidney disease. Based on the results, the number of prescribed drugs and the stage of the disease are effective in drug-drug interactions incidence. It is possible to reduce drug complications and to increase the life span of patients by recognizing drug-drug interactions.

Keywords: Chronic kidney disease, Drug-drug interaction, Nephrology.

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1. Introduction

Medication therapy is a common method for patient treatment. Correct and rational prescription of drugs is an important factor in providing community health [1]. Irrational drug prescribing is seen in many countries such as developing countries [2]. Drug-drug interactions (DDIs), as the most important medication errors, are common leading cause of patients' referral to treatment centers [3]. DDIs are problems resulted from medication prescribing and occur when two or more medications are prescribed simultaneously [4-6]. Drug-drug interactions can be seen in two categories: pharmacokinetics and pharmacodynamics. In pharmacodynamics interactions, the specific function of a drug is altered by another drug, in pharmacokinetics interactions, a drug changes the pharmacokinetics parameters (absorption, distribution, metabolism, or excretion) of another drug [7, 8]. It should be noticed that drug interactions are not limited to the simultaneous use of two or more drugs (drug-drug interactions), but also can be seen as drug-food, drug-environmental factors, drug-smoking, and drug-laboratory tests interactions [9]. Drug–drug interactions may be helpful or harmful. Harmful interactions between drugs are important, because 10-20% of the adverse drug reactions that lead to hospitalization are due to harmful type [10]. Incidence and severity of drug-drug interactions are influenced by the following factors: number of received medicines, length of treatment, age of the patients, number of prescribing physicians and stage of the disease [7, 8]. Drug interactions impose huge costs on the healthcare system every year. Based on a study in the United States, 7% of drug-related side effects have been developed by drug-drug interactions and 35% of adverse drug reactions (4% of all deaths) were caused by drug-drug interactions. Based on a report from the food and drug administration in Iran, 8% of hospital admissions are due to drug side effects [11]. Hospitalized patients receive more drugs than other people, so the risk of DDIs is higher in these patients [7, 8, 12-14].

Chronic kidney disease (CKD) is a common disease and a global concern [15]. Patients with CKD, especially end stage renal disease (ESRD) and dialysis patients, are sometimes treated with 10 to 12 medicines daily. Therefore, these patients are at high risk for developing drug-drug interactions [16]. This study was aimed to investigate the drug-drug interactions incidence in patients with chronic kidney disease in the nephrology ward.

2. Materials and Methods

This descriptive-analytical study was performed on admitted patients to the nephrology ward of Shahid Beheshti Hospital of Hamadan in a 4-month period in 2017. In

this study, 173 CKD patients were selected by census sampling. Demographic information of patients such as sex, height, weight, body mass index, age, smoking and alcohol consumption, medical and drug history, stage of CKD and number of received drugs were recorded during hospitalization. Died or discharged patients Before 24 hours of hospitalization and incomplete information cases were excluded from the study, while remaining patients were included in the study.

It should be noted that approving of study was done by Medical Ethics Committee of the hospital (IR.UMSHA.REC.1396.185) and informed consent form was signed by all participants after explanation of study protocol.

Patients with interaction category C, D and X were included in the study, while patients with interaction category A and B were excluded from the study. The list of all prescribed drugs for each patient was taken during hospitalization. Identification of drug-drug interactions was done using Lexicomp Online. Several investigations have confirmed sensitivity (87–100 %) and specificity (80–90 %) of Lexi-Interact software [6]. The detected drug-drug interactions by Lexi-Interact software are categorized as follows:

- Interaction Category A: There is no information about interactions.
- Interaction Category B: There is no need to change in patient's diet.
- Interactions Category C: Interactions are moderate and patients should be under the supervision of a physician during treatment.
- Interaction Category D: Interactions are intensive and drugs should be replaced to eliminate the interactions.
- Interaction Category X: The drug regimen should be change and prescribed drugs cannot be consumed together in any way.

Descriptive statistics was used to analyze recorded data (SPSS version 16.0). Quantitative and qualitative values are showed as mean ± standard deviation and frequency (percent), respectively. Also, Chi-2 and independent sample t-tests were used to analyze the correlation between variables.

3. Results and Discussion

In this study 48.55% of people were male (84) and 51.45% of them were female (89). The majority of subjects were aged 41-50 years. Most of the population have body mass index between 26-30 kg/m^2. There was at least one drug-drug interaction in 162 people (93.64%). There were no significant differences between incidence of drug-drug interactions with age and BMI (*P=0.85 and 0.87 respectively*).Hypertension and diabetes were first (56.1%) and second (30.6%) common underlying disease in patients, respectively (Table 1).

Based on our data most of patients had CKD at stage 5 (56.1%), in other words most people were hospitalized due to end stage renal disease (ESRD). The next stage with the most frequency was stage 4 (24.9%) (Table 2).

The maximum range of received drugs was between 6 and 10 items (Table 3). Statistical analysis showed that there was a meaningful correlation between the incidence of drug-drug

interactions and the number of received drugs (*P=0.01*).

The first common prescribed drug during hospitalization was pantoprazole (%87.9) (Table 4).

The most frequent drug-drug interaction was observed between atorvastatin and pantoprazole. The highest number of drug-drug interactions was related to type C (Table 5).

Data extracted from the following study revealed that there was no meaningful statistical difference between the two sexes in terms of drug-drug interaction (*P=0.76*).

There was a meaningful relation between the incidence of DDIs and the stage 5 of CKD (*P=0.02*).

Patients with kidney disease, especially those in end stage of disease, usually receive a variety of drug regimens. These patients should take several medications daily. Increasing in the number of prescribed drugs leads to increase in the probability of DDIs. Our results demonstrated that, the number of prescribed drugs and the stage of the disease are effective in DDIs incidence in CKD patients and type C was the greatest observed DDIs.

In the present study, most of the observed drug-drug interactions were related to type C (68.3%). In Chacko *et al.* (2016) study on renal nephrology patients, it has been shown that 66.80% of interactions are moderate in terms of severity [17]. In another study by Tavakoli *et al.* (2013) Intermediate drug-drug interactions were 59.65% of total interactions [18]. The results of these two studies are similar to our study. In a study performed by Van Li *et al.* (2013), 1359 drug-drug interactions were detected among 426 patients that moderate interactions were the most frequent type (67%) [19].

In our study, drug-drug interactions were observed in 92.9% of men and 94.4% of women. Drug-drug interactions were more prevalent in women than men, but there was no significant difference between two sexes. In Chacko *et al.* (2016) study, incidence of DDIs in men was more than that of women [16]. Also, in another study by Lubinagas *et al.* (2011), the frequency of interactions in women was higher than that of men [20].

In current study, most patients were aged between 59-61 (35.25%) and only 13 (7.5%) people were younger than 30 years old. In Chacko *et al.* (2016) study, the age between 61-70 years old was the most frequent age range [16]. In Lubinagas *et al.* (2011) study, the most frequent age range was 15-29 years old [20]. As can be seen, the results of these studies were not consistent with our study. Differences in age range in different studies can be due to differences in the quality of life and geographical conditions. It should be noted that kidney disease often occurs over 30.

Hypertension and diabetes were observed in 56.1% and 30.6% of patients. In most studies hypertension and diabetes have been recognized as two important risk factors for chronic kidney disease patients [21, 22]. Also, in Chacko *et al.* (2016) study, hypertension was present in 77.01% of patients [17].

In current study, the majority of patients were in stage 5 (ESRD). The ESRD is a stage

of disease that kidneys function is not more than 15% of their normal function and kidney transplantation or dialysis is essential [22-25]. In this study, 53.2% of patients were in stage 5 of the disease (92 patients out of 173) that there were drug-drug interactions in 97.8% (90 out of 92) of them. A significant correlation was observed between the stage 5 of chronic kidney disease and interaction probability. This result is consistent with Chacko *et al*. (2016) study that showed a significant correlation between the incidence of drug-drug interaction and the last stage of the kidney disease.[17] Also, this result is similar to another study by Mylapuram *et al*. (2012) [26].

The most important cause of drug-drug interaction is polypharmacy or multiple drugs prescription [27, 28]. According to the results of various studies the risk of drug-drug interactions in patients who received five drugs is 50%, while this risk is %100 in patients who received seven or more drugs [29]. In current study there was a significant correlation between drug-drug interaction and the number of received drugs. This finding is consistent with a study by Alessandra *et al*. (2013) [30].

In our study, the highest frequency of DDIs was observed between atorvastatin and pantoprazole (26%) which is type C in terms of severity. The mechanism of this interaction is inhibiting intestinal P-glycoprotein by pantoprazole, which reduces the secretion of atorvastatin into the intestinal lumen, so increases the plasma concentration of atorvastatin and leads to increase the risk of myopathy induced by atorvastatin. Another probable mechanism for this interaction is inhibiting metabolism of atorvastatin through cytochrome P450 3A4 by pantoprazole. The next frequent drug-drug interaction was observed between ferrous sulfate and pantoprazole (25.4%) which is type C in terms of severity. The mechanism of this interaction is reduction of iron salt absorption due to gastrointestinal pH elevation induced by pantoprazole. The third frequent drug-drug interaction was observed between ferrous sulfate and calcium carbonate (23.7%) which is type D in terms of severity. It should be noted that oral iron bioavailability decreases when administrates with antacids. Already, there is no specific mechanism for this interaction. It is possible that the solubility of iron decreases when simultaneously uses with calcium carbonate due to the elevation in pH and also its absorption maybe decrease due to the formation of complex. Based on available data, calcium carbonate can exert more effects than conventional antacids such as magnesium hydroxide and aluminum hydroxide. In order to prevent this interaction, oral iron must be used at least two hours apart from calcium carbonate. The serious drug-drug interaction was between atorvastatin and cyclosporine (4%) which is type X in terms of severity. Cyclosporine can increase the concentration of atorvastatin and its metabolites by inhibiting cytochrome P450 3A4, so lead to increasing risk of drug adverse effects (including hepatotoxicity and rhabdomyolysis). Rhabdomyolysis is a serious complication that can lead to kidney damage and death. The

general recommendation in this interaction is no use of these drugs together.

4. Conclusion

Identifying drug-drug interactions and evaluating the cause of them lead to reducing side effects of drugs, costs of treatment, and increasing life expectancy in patients, which finally result in improving the health of patients. There are several indirect and direct ways to reduce drug interactions:

Indirect Methods include elevation the knowledge of specialists and medical staff by holding seminars on drug-drug interactions and using prevention methods and suggesting effective treatments with the least complication.

Direct methods include participation of pharmacists in the field of treatment, evaluation of prescribed medications by designed software for possible drug-drug interactions and development of pharmaceutical databases. Pharmacists, especially clinical pharmacists, have an important role in increasing the efficacy of treatments and reducing side effects of DDIs.

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Tables:

Table 1. Distribution of age, body mass index and underlying disease in patients in cases participating in the study.

Age	Frequency	Percent (%)
<30	13	7.5
31-40	24	13.9
41-50	24	13.9
51-60	59	34.1
>60	53	30.6
BMI		
<18.5	4	2.3
18.5-25	51	29.5
26-30	70	40.5
>30	48	27.7
Underlying Disease in patients		
Hypertension	97	56.1
Diabetic mellitus (DM)	53	30.6
Ischemic heart disease	26	15
Coronary heart failure (CHF)	5	2.9
Hyperlipoproteinemia (HLP)	14	8.1
Hypothyroidism	7	4
Coronary artery bypass graft (CABG)	4	2.3
Chronic obstructive pulmonary disease (COPD)	2	1.2
Cerebrovascular accident (CVA)	1	0.6
Myocardial infarction (MI)	2	1.2

Table 2. Distribution of drug-drug interactions in relation to chronic kidney disease stages.

Disease stages	Drug-drug interaction (Yes)	Drug-drug interaction (No)	Total	Statistic Evaluation
Stage 1	5	1	6	NS (*P=0.33*)
Stage 2	8	0	8	NS (*P=1*)
Stage 3A	3	1	4	NS (*P=0.23*)
Stage 3B	13	2	15	NS (*P=0.24*)
Stage 4	38	5	43	NS (*P=0.46*)
Stage 5	95	2	97	S (*P=0.02*)
Total	162	11	173	

Table 3. Number of prescribed drugs and frequency of drug-drug interactions.

Number of prescribed drugs	Frequency	Percent (%)
0-5	22	12.7
6-10	86	49.7
11-15	54	31.2
15<	11	6.4
	173	100.0

Table 4. Distribution of prescribed drugs in patients during hospitalization.

Most frequent prescribed drugs during hospitalization	Frequency	Percent (%)
Pantoprazole	152	87.9
Calcium Carbonate	120	69.4
Calcitriol	95	54.9
Aspirin	54	31.2
Ferrous sulfate	67	38.7
Erythropoietin	46	26.6

Meropenem	51	29.5
Ondansetron	46	26.6
Atorvastatin	59	34.1
Metoprolol	54	31.2
Furosemide	46	26.6
Heparin	32	18.5
Ceftriaxone	50	28.9
Prednisolone	49	28.3
Carvedilol	35	20.2
Amlodipine	59	34.1

Table 5. Distribution of twenty first observed drug-drug interactions in patients during hospitalization.

Drug-drug interactions	**Interaction classification**	**Frequency**	**Percent (%)**
Atorvastatin + pantoprazole	C	45	26
Ferrous Sulfate + pantoprazole	C	44	25.4
Ferrous sulfate + CaCO3	D	41	23.7
Amlodipine + CaCO3	C	32	18.5
Atorvastatin + CaCO3	C	30	17.3
Prednisolone + CaCO3	D	28	16.2
Prednisolone + Cyclosporine	C	18	10.4
Atorvastatin + Carvedilol	C	17	9.8
Heparin + ASA	C	17	9.8
Mycophenolate + CaCO3	D	16	9.2
Ciprofloxacin + CaCO3	D	15	8.7
Mycophenolate + Pantoprazole	C	12	6.9
Calcitriol + Prednisolone	C	11	6.4
Carvedilol + Losartan	C	11	6.4

ASA + Furosemide	C	10	5.8
ASA + Clopidogrel	C	10	5.8
Ondansetron + Carvedilol	C	10	5.8
Mycophenolate + Cyclosporine	D	10	5.8
Atorvastatin + Cyclosporine	X	7	4
Allopurinol + CaCO3	D	7	4