Identifying potential drug interactions in chronic kidney disease patients

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Abstract

Introduction: Drug interactions (DIs) are common in clinical practice and are directly related to factors such as polypharmacy, aging, hepatic metabolism and decreased renal function. Individuals with chronic kidney disease (CKD) often require multiple classes of drugs being at important risk for the development of DIs. **Objective:** Identify potential interactions among drugs prescribed to patients with CKD on conservative treatment, and factors associated with their occurrence. **Methods:** Observational cross-sectional study, with analysis of 558 prescriptions. Potential DIs were identified by the database MICROMEDEX®, software that provides an internationally known pharmacopoeia. **Results:** There was a predominance of males (54.7%), seniors (69.4%), stage 3 CKD (47.5%), overweight and obese patients (66.7%). The most prevalent comorbidities were hypertension (68.5%) and diabetes mellitus (31.9%). Potential DIs were detected in 74.9% of prescriptions. Among the 1364 DIs diagnosed, 5 (0.4%) were contraindicated and 229 (16.8%) of greater severity, which need immediate intervention. Interactions of moderate and low severity were identified in 1049 (76.9%) and 81 (5.9%) prescriptions, respectively. The probability of one DI increased by 2.5 times for each additional drug (CI = 2.18 to 3.03). Obesity, hypertension, diabetes as well as advanced stage of CKD were risk factors strongly associated with DI occurrence. **Conclusion:** Drug associations in individuals with CKD were related to high prevalence of serious DIs, especially in the later stages of the disease.

Keywords: drug combinations; drug interactions; kidney failure, chronic.

Introduction

In clinical practice, multiple drugs are often combined in the treatment of patients with chronic diseases. These associations generally produce drug interactions (DI) with expected beneficial effects, but in some cases undesired outcomes may also occur, such as ineffective treatment and severe adverse events.[1,2] DI can be defined as the set of alterations introduced upon the therapeutic effect of a given drug stemming from the coadministration of one or more medications.[2,3] In this context, DI appear as the cause of a drug-related problem (DRP) which, when present, produces negative impacts on morbidity, mortality, length of hospitalization, quality of life, and cost of care.[4-7]

Despite the scarce reports of clinically evident cases of DI, knowledge of the pharmacodynamic and pharmacokinetic properties of different medications suggests the potential risks connected to drug interactions.[2,8,9] The occurrence of DI may be mitigated with preventive measures and intervention.[10-12] In this sense, the identification and classification of drug interactions by a pharmacist may optimize the clinical management of this type of event.[13,14]

The most frequently used classification for DI considers as contraindicated or significant the drug interactions that require immediate medical intervention due to imminent risk of death. In turn, minor and moderate drug interactions may produce limited clinical effect without the need to significantly change the therapy, in addition to calling for increased awareness from the medical staff in order not to compromise the treatment.[15]

When looking for possible occurrences of DI, one must pay attention to determining factors such as the chemical nature of the drugs, the number of drugs used, patient age, and the presence of liver and kidney involvement.[3,16]

The kidneys play a key role in the maintenance of homeostasis and in regulatory, excretory and endocrine functions. Therefore, the gradual decreases in the glomerular filtration rate (GFR) and/or loss of kidney function seen in chronic kidney disease (CKD) patients compromise the homeostasis of the entire body.[17,18]

In Brazil, the estimated number of patients on renal replacement therapy (RRT) grew from 42,000 in 2000 to more than 90,000 in late 2010.[19] The prevalence of dialysis in 2010 was 483 patients per million population (pmp), ranging from 265 pmp in Northern Brazil to 591 pmp in the Southeast. Hemodialysis was offered to 89.7% of the patients and peritoneal dialysis to 5.1%. Previous censuses revealed systemic hypertension (SH) was the most common etiologic diagnosis of CKD, followed by *diabetes mellitus* (DM).[19]

Based on the above, individuals with CKD constitute a population at high risk for potentially severe DI, as members of this group are predominantly elderly, hypertensive, diabetic, and experience impaired drug renal excretion.

This study looked into the profile of the most common types of DI in CKD patients undergoing conservative treatment.

Methods

This cross-sectional observational study was carried out at the clinic for CKD of the Centro Hiperdia Minas in Juiz de Fora and at the Interdisciplinary Center for Studies and Research in Nephrology (NIEPEN) of the Federal University of Juiz de Fora (UFJF). The database of prescriptions for individuals with CKD admitted between January and December 2011 for conservative treatment was analyzed. Patients aged 18 and above with complete medical records were enrolled.

Data collection was performed in two stages. In the first stage, the electronic charts of every patient enrolled in the study were analyzed for demographic, clinical, and prescription variables, including the drug names based on the Brazilian Common Denomination (DCB) and the Anatomical Therapeutical Chemical (ATC) classification systems, in order to establish the profile of the individuals seen in the clinic.

The second stage involved the identification of possible drug interactions. To that end, database MICROMEDEX® 2.0 (2011) was accessed through the journal portal of the Brazilian Federal Agency for the Support and Evaluation of Graduate Education (CAPES).

The MICROMEDEX® Health Series database contains information on medications, etiology, epidemiology, diagnosis and treatment. It provides access to internationally known pharmacopoeias such as Martindale and USP DI, in addition to some original systems made available only through the database, such as DRUGDEX® and DRUG-REAX®.[15]

Searches were carried out considering that the database provides descriptions of drug interactions for pairs of drugs, their likely mechanisms of interaction, scientific publications, severity, and indicated clinical management.

Statistical analysis

Descriptive analysis was performed using frequencies for categorical variables, and mean, median, standard deviation, and variance for quantitative variables.

Logistic regression analysis was applied to find the factors associated with potential drug interactions. Exposure to DI (yes/no) was the dependent variable in the model. Multivariate analysis was carried out for variables showing significant correlations.

Results were expressed as odds ratios (OR) and statistical significance was set at 5%.

Data sets were entered and treated on software packages Excel 1.0, STATA 11.0, and SPSS version 17.0.

The study was approved by the Ethics Committee of the Federal University of Juiz de Fora (CEP/UFJF) and given permit Nº. 328/2011.

Results

Pharmacotherapeutic profile

The first stage of the protocol consisted of a review of the pharmacotherapeutic profile of the 1,651 prescriptions issued to 850 CKD patients seen in 2011. A total of 10,023 medications with 289 different active ingredients were listed in the prescriptions.

Cardiovascular drugs were the most commonly prescribed class of medications (5,772/57.6%), followed by alimentary tract and metabolism medications (1,647/16.4%), and drugs affecting the blood and blood-forming organs (1,088/10.9%).

The ten most frequently prescribed medications were furosemide (8.4%), simvastatin (7.1%), losartan (7.1%), acetylsalicylic acid (5.2%), captopril (4.7%), hydrochlorothiazide (4.7%), omeprazole (4.5%), enalapril (4.1%), amlodipine besylate (3.3%), and nifedipine (3.1%).

Potential drug interactions

In the second stage of the study, 558 patients met the enrollment criteria and were analyzed for drug interactions. Subjects were predominantly male (54.7%), elderly (69.4%), overweight or obese (66.7%), and had stage 3 CKD (47.5%). The WHO criteria dictates that overweight individuals have a BMI between 25 and 29.99, while obese subjects have a BMI greater than or equal to 30.00. The most prevalent comorbidities were hypertension (68.5%) and DM (31.9%).

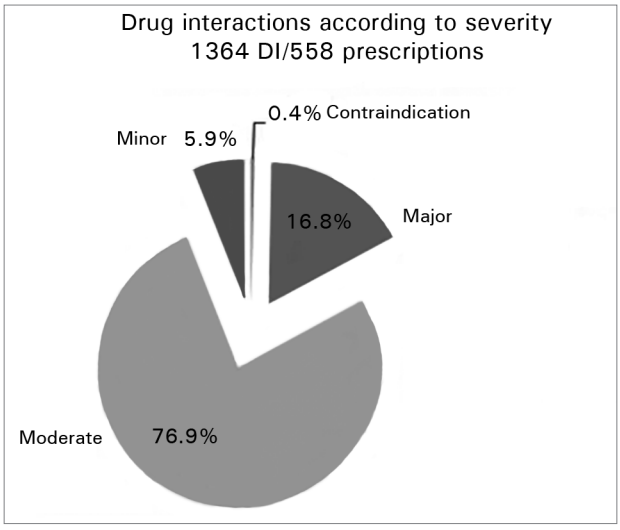
The prescriptions in effect used by the patients in their last visit at the clinic were assessed, as their records contained data from multiple visits to the clinic occurred throughout the year. Enrolled patients took a mean of 5.6 ± 3.2 drugs, and 418 (74.9%) of them had a potentially interacting pair of drugs in their prescriptions. A mean of 3.4 ± 2.3 drug interactions were observed in patients with some form of DI.

The assessment of the prescriptions on software program MICROMEDEX® revealed a total of 1,364 drug interactions. Figure 1 and Table 1 show the frequencies according to the severity of the drug interactions. Cases of absolute contraindication were seen in 0.4% of the patients; severe contraindications in 16.8%; moderate in 76.9%; and minor in 5.9% of the enrolled individuals.

Therefore, approximately a fifth of the identified drug interactions were absolute contraindications or severe cases of DI.

The five cases of absolute contraindication included prescriptions of a calcium channel blocker (nifedipine) and an anticonvulsant (carbamazepine, phenytoin, phenobarbital). Noteworthy severe drug interactions included the dual blockade of the renin-angiotensin system, accounting for 22% of the cases of severe DI, and prescriptions of an inhibitor of the renin-angiotensin system combined with a xanthine oxidase inhibitor (allopurinol).

Figure 1. Distribution of drug interactions according to severity.



Analysis of variables correlated with DI

Once the presence of a drug interaction was confirmed, the possibly correlated clinical variables and conditions were assessed.

In this study, the probability of occurrence of a drug interaction increased 2.5 fold for each drug added to the prescription (CI = 2.18 to 3.03) (Figure 2).

The analysis of risk factors for the occurrence of DI revealed that the variables more strongly correlated with the presence of drug interactions were age, stage of CKD, body mass index (BMI), hypertensive nephropathy, diabetic nephropathy, DM, and hypertension (Table 2).

These variables were then submitted to a multivariate logistic regression. The results of this analysis showed that advanced stage CKD, obesity, and diagnosis of DM and hypertension were the main risk factors for the occurrence of drug interactions (Table 3). Interestingly, the probability of occurrence of DI increased 4.7 fold in patients with stage 5 CKD when compared to individuals with CKD stages 1 and 2 (p = 0.003).

Discussion

This study included the prescriptions of 558 CKD patients treated conservatively at a nephrology service within one year. Potential drug interactions

Table 1 Distribution of the most common pairs of interacting drugs according to severity

Severity	PA1	PA2	Frequency (Percent)	Summary	Likely involved mechanism	Clinical management	%/DI (n = 1364)
Contraindication (n = 5)	Carbamazepine	Nifedipine	3 (60.0)	Reduces exposure to nifedipine.	Induction of nifedipine metabolism mediated by CYP3A4.	Alternative anti-hypertensive drug should be considered.	0.2
	Nifedipine	Phenytoin sodium	1 (20.0)	Reduces exposure to nifedipine and increases risk of toxicity by phenytoin (ataxia, hyperreflexia, tremor, nystagmus).	Induction of nifedipine metabolism mediated by CYP3A4 and reduction of phenytoin metabolism.	Alternative anti-hypertensive drug should be considered.	0.1
	Nifedipine	Phenobarbital	1 (20.0)	Reduces exposure to nifedipine.	Induction of nifedipine metabolism mediated by CYP3A4.	Alternative anti-hypertensive drug should be considered.	0.1
Major (n = 229)	Enalapril maleate	Losartan	50 (21.8)	Increased risk of adverse events (syncope, hypotension, hyperkalemia, altered renal function, acute kidney injury).	Dual blockade of the renin-angiotensin-aldosterone system	Closely monitor renal function if coadministration of ACE inhibitors and ARBs is needed.	3.7
	Allopurinol	Captopril	24 (10.5)	May result in hypersensitivity reaction (Stevens-Johnson syndrome, skin rash, coronary artery spasm with anaphylactic reaction).	Unknown	Monitor hypersensitivity reaction.	1.8
	Allopurinol	Enalapril	21 (9.2)	May result in hypersensitivity reaction (Stevens-Johnson syndrome, skin rash, coronary artery spasm with anaphylactic reaction).	Unknown	Monitor hypersensitivity reaction.	1.5
Moderate (n = 1049)	Furosemide	Acetylsalicylic acid	106 (10.1)	May result in reduced diuretic and anti-hypertensive effect.	Unknown	Monitor diuresis and creatinine clearance.	7.8

Continued Table 1.

	Enalapril	Furosemide	80 (7.6)	May result in postural hypotension (first dose).	Vasodilation and relative intravascular volume depletion.	Monitor hypotension, fluids, and body weight regularly for up to two weeks after dosage adjustments.	5.9
	Captopril	Furosemide	69 (6.6)	May result in postural hypotension (first dose).	Vasodilation and relative intravascular volume depletion.	Monitor hypotension, fluids, and body weight regularly for up to two weeks after dosage adjustments.	5.1
Minor (n = 81)	Metformin	Nifedipine	20 (24.7)	May increase metformin absorption.	Unknown	Monitor clinical signs of metformin toxicity, including diarrhea, nausea, and vomiting	1.5
	Furosemide	Hydralazine	18 (22.2)	May increase furosemide diuretic response.	Increased furosemide renal clearance.	Monitor diuretic response, serum electrolytes, and creatinine clearance. Adjust dosage if needed.	1.3
	Enalapril	Erythropoietin	10 (12.3)	May result in high maintenance dosages of erythropoietin to sustain hematocrit levels.	Unknown	Monitor patients given high doses of ACEi for erythropoietin effectiveness. When coadministered, higher dosages of erythropoietin may be needed administrados.	0.7

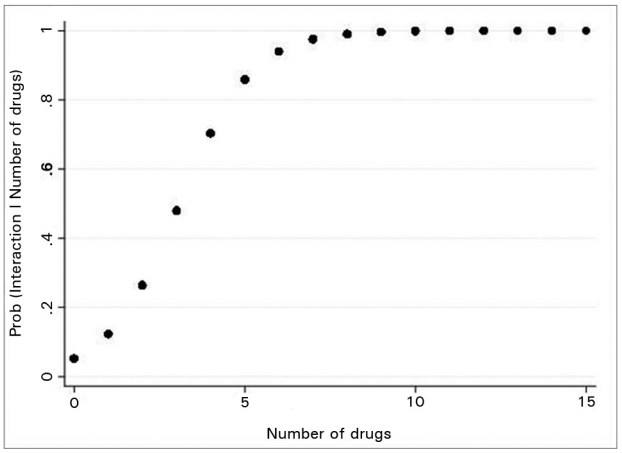
were detected in 418 patients and 74.9 % of the prescriptions. A grand total of 1,364 drug interactions were identified, with severe DI accounting for 16.8% of the cases and absolute contraindications for 0.4%. Risk factors for the occurrence of DI in the population were obesity, DM, hypertension, and advanced stage CKD.

DI is defined as a clinical event in which the coadministration of drugs alters the effect of one or both drugs. DI is a cause of DRP frequently seen in individuals exposed to polypharmacy, patients with liver disease, and subjects with impaired renal excretion, conditions that may worsen the processes of drug absorption, distribution, metabolism and excretion.

Software tool MICROMEDEX® Health Series is one of the most effective means to evaluate drug interactions. It is an established method in specialized literature used to promptly and reliably identify cases of DI.[1,13,16,20-22]

Drug-related problems are common to all stages of CKD.[4] However, most studies enroll patients with advanced stage CKD on hemodialysis.[4,23-25] A study with 395 patients on dialysis reported 1,593 cases of DRP. Inadequate workup monitoring (23.5%) topped the list of prevalent drug-related problems, followed by subtherapeutic dosage (11.2%) and overdosage (9.2%). The authors reported that only 4.5% of the patients suffered from drug interactions.[23]

Figure 2. Probability of drug interactions as a function of the number of prescribed medications; generated from logistic regression model. OR = 2.57 (2.18; 3.03) (for each additional medication, the chance of drug interaction increases 2.5 times).



Another study included 619 patients on conservative therapies and reported 'indication without corresponding drug prescription' as the most frequent DRP. Only 24% of the individuals with coronary disease were on HMG-CoA reductase inhibitors; only 58% of the subjects with DM and 23% if the individuals with proteinuria were on renin-angiotensin system blockers.[24] The authors did not report data on drug interactions.

Similarly, a prospective study on DRP in individuals with CKD treated conservatively reported 'indication without corresponding drug prescription' as the most frequent DRP. Again, the authors did not look into drug interactions.[25]

The prevalence of drug interactions among outpatients is known to be high in populations such as the elderly[26], individuals with chronic diseases[16], patients undergoing treatment for cancer[27], and subjects with liver disease.[28] However, searches with keywords 'drug interactions,' 'chronic kidney failure,' 'drug interaction and renal failure,' and 'drug related problems and kidney failure' failed to yield results on DI in individuals with CKD treated conservatively.

A recently published study looked into the prevalence of drug interactions in CKD inpatients by analyzing 205 prescriptions. A total of 474 (76.09%) cases of drug interactions were detected, with a mean of 2.7 interactions per prescription. Severe drug interactions involving cardiovascular medications were seen in 19.6% of the cases.[29] Although the study included hospitalized patients, its findings were similar to what was observed in our study, in which the mean number of drug interactions was 3.4 ± 2.3 and approximately 16% of the patients had severe drug interactions involving cardiovascular medications.

Severe drug interactions, along with absolute contraindications (0.4%), may pose significant risk to the health of patients, and hence require medical and/or pharmaceutical intervention to prevent against the occurrence of severe adverse effects.[15] Furthermore, a significant portion of the studied population (76.9%) had moderate drug interactions, which also require attention so as not to deteriorate the patients' condition.

Polypharmacy is one of the factors involved in the occurrence of drug interactions.[26,30] According to the literature, patients taking five drugs are 50% more likely to suffer from drug interactions, while subjects on seven or more medications are 100% more likely to experience the effects of drug interactions.[31]

Patients with CKD are at a high risk for cardiovascular and metabolic events, and consequently require the prescription of multiple drugs.[24,32,33] In our study, each patient took a mean of 5.6 ± 3.2 active ingredients as part of their drug regimen, in a situation which certainly implied greater risk of DI. Moreover, most of the individuals had CKD stages 3 and 4 and were on cardiovascular medication (57.6%), drugs acting on the alimentary tract and metabolism (16.4%), and drugs affecting the blood and blood-forming organs (10.9%). A recently published prospective study found similar percentages of use of medications in CKD patients undergoing conservative treatment.[25] Therefore, polypharmacy in this population has been associated with increased potential for drug interactions.

The use of cardiovascular drugs and medications acting on the metabolism as seen in our group of patients was consistent with the observed strong correlation between drug interactions and DM, hypertension and advanced CKD.

Another significant finding was the correlation between obesity and DI, which could stem from changes in the pharmacokinetics of lipophilic drugs secondary to the accumulation of adipose tissue,[34,35] as well as the increased propensity toward polypharmacy seen in this population. However, these mechanisms were not the object of this study.

Notwithstanding the limitations inherent to a single-center study, the results reported herein were promising and revealed the significant potential of clinically relevant drug interactions. Our findings call for the optimization

Table 2 Independent risk factors for the occurrence of drug interactions

Characteristic	N (Total = 558)	*p* - value	OR (95% CI)
Gender			
Male	305	-	Ref
Female	253	0.375	0.841 (0.57 - 1.23)
Age			
< or equal to 39	33	-	Ref
40 to 59	138	0.460	1.34 (0.61 - 2.94)
> or greater than 60	387	0.019	2.41 (1.15 - 5.06)
Smoking	196	0.866	0.96 (0.64 - 1.44)
Alcohol	87	0.098	0.65 (0.40 - 1.08)
Number of medications			
0 to 4	187	-	Ref
More than 5	371	0.000	36.80 (21.00 - 64.51)
CKD stage			
1 and 2	103	-	Ref
3a	107	0.000	3.24 (1.76 - 5.95)
3b	158	0.000	3.30 (1.90 - 5.71)
4	153	0.000	3.30 (1.90 - 5.74)
5	37	0.013	3.04 (1.27 - 7.28)
BMI, according to WHO			
Low and normal weight	162	-	Ref
Overweight	195	0.223	1.33 (0.84 - 2.11)
Obesity	185	0.001	2.47 (1.47 - 4.14)
Baseline disease			
Hypertensive nephropathy	213	0.007	1.76 (1.16 - 2.67)
Diabetic nephropathy	120	0.032	1.75 (1.05 - 2.94)
Ischemic nephropathy	25	0.290	1.79 (0.60 - 5.33)
Chronic glomerulonephritis	26	0.825	0.90 (0.37 - 2.20)
Reflux nephropathy	5	0.099	0.22 (0.03 - 1.32)
Unspecified	109	0.189	1.41 (0.84 - 2.35)
Comorbidities			
Diabetes mellitus	178	0.000	2.50 (1.56 - 4.01)
Hypertension	382	0.000	2.03 (1.36 - 3.02)
Coronary disease	37	0.373	1.46 (0.63 - 3.42)
Heart failure	29	0.073	3.02 (0.90 - 10.16)

**Note: the BMI was calculated based on weight and height measurements according to the formula BMI = body weight (kg)/height2 (cm). The cutoff points for the BMI described by the WHO were used in this study, as follows: low body weight (BMI < 18.5); normal body weight (BMI 18.5-24.99); overweight (BMI 25-29.99); and obesity (BMI ≥ 30.00).

Table 3 Multivariate logistic regression: analysis of risk factors correlated to potential drug interactions of patients with CKD

Factors	*p* - value	OR (95% CI)
Age		
< or equal to 39	0.064	Ref
40 to 59	0.907	0.94 (0.38 - 2.36)
> or greater than 60	0.253	1.65 (0.69 - 3.94)

Continued Table 3

CKD stage		
1 and 2	0.000	Ref
3a	0.001	3.12 (1.61 - 6.05)
3b	0.001	2.75 (1.51 - 5.02)
4	0.000	3.67 (1.97 - 6.83)
5	0.003	4.74 (1.68 - 13.30)
BMI		
Low and normal weight	0.004	Ref
Overweight	0.337	1.27 (0.77 - 2.10)
Obesity	0.001	2.58 (1.46 - 4.54)
DM	0.018	1.95 (1.12 - 3.41)
Systemic hypertension	0.013	1.80 (1.13 - 2.87)
CHF	0.173	2.81 (0.63 - 12.47)

of the drug regimens offered to CKD patients in order to prevent the incidence of DRP. Studies with larger numbers of patients may confirm this hypothesis.

Conclusion

A significant percentage of individuals with chronic kidney disease managed conservatively had potentially severe drug interactions in their prescriptions. In this population, the risk factors for the occurrence of drug interactions were diabetes mellitus, hypertension, obesity, and advanced chronic kidney disease.

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