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Evaluation of potential interactions of oral medications prescribed in a kidney and liver transplant unit

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Abstract

Objective: To identify, quantify and classify, according to severity degree potential drug interactions (PDIs) found in prescriptions of oral medications for patients admitted to a transplantation unit. **Methods:** This is a descriptive and retrospective cross-sectional study based on the prescriptions of patients admitted to a kidney and liver transplantation unit. The data were collected from 831 prescriptions and 223 were selected out of this total, which were submitted to screening for possible drug-drug interactions using the Micromedex® online tool. **Results:** The prescriptions selected had between 1 and 21 medications (mean of 8 ± 4), with 216 potential drug interactions identified; of this total, the following results were found regarding severity of these potential events: major (62.03%), moderate (31.94%) and minor (6.01%). Through the analysis carried out, a total of 66.66% (n=46) of the evaluated patients presented potential drug interactions in their prescriptions, with a mean of 3.13 PDIs per patient. It was possible to observe that more than 50% of the patients had potential drug interactions in their prescriptions, among which immunosuppressants were involved in 49.52% of all interactions. **Conclusion:** It was possible to observe that the high frequency of potential drug interactions in transplanted patients is possibly due to the number of drugs prescribed concomitantly due to the various comorbidities that these patients have, as the more drugs prescribed, the greater the probability of having this type of interaction. The most common PDIs were of major severity, which highlights the importance of patient monitoring for adequate decision-making by the clinical staff, promoting patient safety.

Keywords: Drug interactions; Medication prescriptions; Transplant; Polymedication.

Avaliação das potenciais interações de medicamentos orais prescritos em uma unidade de transplante renal e hepático

Resumo

Objetivo: Identificar, quantificar e classificar, de acordo com o grau de gravidade, as interações medicamentosas potenciais (IMP) presentes nas prescrições de medicamentos orais de pacientes internados em unidade de transplante. **Métodos:** Trata-se de um estudo transversal descritivo e retrospectivo realizado a partir das prescrições de pacientes internados em uma unidade de transplante renal e hepático. Onde foram coletados dados de 831 prescrições e deste total, selecionadas 223, as quais foram submetidas ao rastreamento de possíveis interações do tipo medicamento-medicamento pela ferramenta online *Micromedex*®. **Resultados:** As prescrições selecionadas apresentaram entre 1 e 21 medicamentos (média de 8 ± 4), sendo identificadas 216 interações medicamentosas potenciais; deste total, foram encontrados os seguintes resultados quanto à gravidade desses potenciais eventos: maior (62,03%), moderada (31,94%) e menor (6,01%). Através da análise realizada, um total de 66,66% (n=46) dos pacientes avaliados, apresentou potenciais interações medicamentosas em suas prescrições, com média de 3,13 IMP por paciente. Foi possível observar que mais de 50% dos pacientes obtiveram interações medicamentosas potenciais em suas prescrições, dentre as quais os imunossupressores foram envolvidos em 49,52% do total de interações. **Conclusão:** Foi possível observar que a alta frequência das interações medicamentosas potenciais nos pacientes transplantados ocorre possivelmente devido a quantidade de medicamentos prescritos concomitantemente, em razão das diversas comorbidades que estes pacientes apresentam, pois quanto maior o número de fármacos prescritos, maior a probabilidade de haver este tipo de interação. As IMP mais presentes foram de gravidade maior, o que ressalta a importância do monitoramento do paciente para a tomada de decisão adequada pelo corpo clínico promovendo segurança ao paciente.

Palavras-chave: Interações medicamentosas; Prescrições de medicamentos; Transplante; Polimedicação.

Introduction

Transplantation is a surgical technique that consists in replacing a diseased organ or tissue by another healthy one, which may come from a living or deceased donor, providing better quality of life to the recipient, who predominantly has chronic diseases of an irreversible nature, or in their final stages[1]. In this scenario, immunosuppressants have considerably favored the success of transplants by reducing the occurrence of acute and chronic rejections, thus providing greater graft survival[2,3].

The pharmacotherapy of transplanted patients is constantly susceptible to therapeutic regimens where there is concomitant use of immunosuppressants with other classes of medications, as these patients require several continuous-use drugs due to underlying diseases such as hypertension, diabetes and dyslipidemias, among others. Thus, the administration of multiple pharmacological agents is subjected to the occurrence of drug interactions, whose effects can be beneficial and to some extent expected but, in other cases, they may generate undesirable results, ranging from ineffectiveness of the treatment proposed to serious adverse events[4,5].

Drug interaction is defined as a pharmacological or clinical response caused by an interaction of the drug-drug, drug-food, drug-chemical substance, drug-laboratory and non-laboratory examination, and drug-medicinal plant types, whose final result can be an alteration in the desired effects or occurrence of adverse effects[6].

Occurrence of these interactions in the hospital environment is of major clinical and public health importance, as it can affect effectiveness of the pharmacotherapy and increase morbidity and mortality in transplanted patients. Such interactions are considered preventable adverse events, amenable to prevention and intervention[7,8,9]. In transplanted patients, potential drug interactions (PDIs) of the drug-drug type can play a prominent role in their clinical management.

In this perspective, the clinical pharmacists' role is highlighted, knowing the pharmacotherapy profile and identifying the main classes of medications prescribed and drug interactions, as this information enables health actions and strategies that can mitigate possible drug-related problems (DRPs), promoting rational use and optimization of the pharmacotherapy[10,11]. Therefore, this study aimed at identifying, quantifying and classifying according to severity degree, as well as through the tool chosen for analysis, the potential drug interactions found in the oral drug prescriptions of patients hospitalized in a transplantation unit.

Methods

This is a descriptive and retrospective cross-sectional study carried out based on the prescriptions of patients hospitalized from March to April 2022 in a kidney and liver transplantation unit of the University Hospital of the state of Ceará, a public institution that is a reference in transplant services, focusing on potential drug-drug interactions. It was approved by the Research Ethics Committee under CAAE 56178022.9.0000.5045 in accordance with resolution No. 466 of the National Health Council.

Data collection was carried out in the month following hospitalization of the patients, and the evaluation was made based on the *Micromedex®* system (a support tool for decision-making that consists of an instrument designed to support clinical work in the patient care space), which analyzes the data that were published, emphasizing evidence-based concepts found in peer-reviewed scientific studies, thus providing an evaluation of the documentation attributes[12].

After identification, the drug interactions were classified by severity degree, as follows: major, which can be fatal and/or require medical intervention to minimize or prevent serious effects; moderate, which can result in exacerbation of the patient's condition and/or require an alternative therapy; minor, which have limited clinical effects; and contraindicated, where the medications are contraindicated for concomitant use[13].

The analysis of potential drug interactions was performed per patient, and only medical prescriptions that were not repeated during hospitalization and that met the inclusion criteria for the use of oral medications in the forms of tablet, capsule, pill, solution, suspension and powder were selected. Prescriptions containing only drugs administered by other routes and medications prescribed that are not included in the database selected to evaluate possible interactions (vitamins from the B complex, dipyrone, bromopride, ornithine aspartate, gliclazide, magnesium chloride, calcium polystyrene sulfonate and ursodeoxycholic acid) were excluded.

Therefore, data were collected from 831 prescriptions and 223 were selected out of this total, which were submitted to screening in the *Micromedex®* online tool, and the classes of medications involved in potential drug interactions were identified through the ATC (Anatomic, Therapeutic, Chemical) classification[14]. Variables such as gender, age and medications prescribed orally in the electronic medical record system used by the institution were also collected.

Sample size was calculated using the following criteria: 95% confidence interval, 5% accuracy, and Z-statistic value of 1.96[15]. Thus, the minimum sample size for the number of prescriptions required to analyze the prevalence of potential drug interactions with 95% confidence was 217, a result achieved in the experimental design proposed.

The data collected were tabulated in a Microsoft Excel® 2010 version 5.0 spreadsheet. The continuous variables were expressed as mean ± standard deviation (SD) and the categorical variables, as percentages.

Results

The results obtained showed that all 223 prescriptions included in the analysis corresponded to 69 patients admitted to the unit. Of the 69 patients, 53.62% (n=37) were men and 46.37% (n=32) were women, aged from 19 to 81 years of (mean of 54 ± 14.7) (Table 1).

The selected prescriptions contained between 1 and 21 medications (mean of 8 ± 4), where 216 potential drug interactions were identified by the Micromedex® platform: 62.03% of major severity, 31.94% moderate and 6.01% minor (Table 2).

Table 1. Demographic characteristics of the patients admitted to a transplantation unit.

Characteristics	n (%)
Men	37 (53.62)
Women	32 (46.37%)
Age in years old	54 ± 14.7
Medications prescribed via oral route	8 ± 4
Total number of patients	69

Source: Prepared by the author.

Table 2. Classification of the potential drug interactions according to severity degree.

Potential Drug Interaction	n (%)
Major PDI	134 (62.03)
Moderate PDI	69 (31.94)
Minor PDI	13 (6.01)
Contraindicated	2 (0.93)
Total number of PDIs	216

Source: Prepared by the author.

In the prescriptions containing three or more medications, the incidence of potential drug interactions was 82.6%, whereas in those with less than three drugs, occurrence of PDIs was 5%. The Spearman's correlation matrix showed that the association between number of medications prescribed and number of PDIs was significant (p-value<0.001); the linear correlation coefficient was 0.797, considered strong, and the confidence interval used was 95%[16].

Through the analysis performed, a total of 66.66% (n=46) of the patients evaluated presented potential drug interactions in their prescriptions, with a mean of 3.13 PDIs per patient, distributed in all severity categories, consisting of a variation from 1 to 13 for major severity (mean of 1.94 ± 2.60 interactions/patient), from 1 to 6 for moderate (mean of 1 ± 1.57 interactions/patient) and from 1 to 2 for minor (mean of 0.18 ± 0.46 interactions/patient).

The percentage distribution of the main drug interactions contained in the prescriptions of the evaluated patients is represented in Tables 3 and 4.

Table 3. Prevalence of the potential drug interactions according to the major severity degree.

Potential drug interactions of major severity	n (%)
Sirolimus X Tacrolimus	114 (10.44)
Amlodipine X Tacrolimus	12 (8.95)
Acetylsalicylic acid X Tacrolimus	9 (6.71)
Omeprazole X Tacrolimus	8 (5.97)
Domperidone X Tacrolimus	7 (5.22)
Atenolol X Clonidine	6 (4.47)
Amiodarone X Tacrolimus	5 (3.73)
Amiodarone X Sulfamethoxazole+trimethoprim	4 (2.98)
Mycophenolate sodium X Pantoprazole	3 (2.23)
Acetylsalicylic acid X Furosemide	3 (2.23)

Table 4 . Prevalence of the potential drug interactions according to the moderate severity degree.

Potential drug interactions of moderate severity	n (%)
Sodium mycophenolate X ferrous sulfate	7 (10.14)
Pantoprazole X Ferrous Sulfate	7 (10.14)
Carvedilol X Clonidine	4 (5.79)
Levothyroxine X Pantoprazole	4 (5.79)
Acetylsalicylic acid X Carvedilol	3 (4.34)
Nifedipine X Tacrolimus	3 (4.34)
Sevelamer X Tacrolimus	3 (4.34)
Acetylsalicylic acid X Prednisone	2 (2.89)
Levothyroxine X Simvastatin	2 (2.89)
Pantoprazole X Warfarin	2 (2.89)

Among the most prescribed medications for the patients evaluated were tacrolimus (53.62%), sirolimus (20.28%), mycophenolate sodium (17.39), pantoprazole (23.18%), acetylsalicylic acid (17.39%) and amlodipine (15.94%).

Of the 92 drugs identified in the prescriptions, 56.52% (52/92) were involved in the PDIs detected, which equals 4.15 interactions/drug (216/52). Immunosuppressants are related to 49.54% (107/216) of these PDIs, standing out over the other medications, as shown in Table 5.

Table 5 . Use of the ATC classification to identify the drug classes most involved in potential drug interactions.

Medication	ATC Code	Pharmacological group	n (%)
Tacrolimus	L04	Immunosuppressant	77 (35.65)
Acetylsalicylic acid	N02	Analgesic	24 (11.11)
Amiodarone	A02	Cardiac therapy	21 (9.72)
Pantoprazole	A02	Acid-related disorder	20 (9.26)
Ferrous sulphate	B03	Antianemic preparations	19 (8.80)
Sirolimus	L04	Immunosuppressant	15 (6.94)
Sodium mycophenolate	L04	Immunosuppressant	15 (6.94)
Amlodipine	C08	Calcium channel blockers	14 (6.48)
Fluoxetine	N06	Psychoanaleptic	12 (5.56)
Clonidine	C02	Antihypertensive	11 (5.09)

Discussion

The analysis made it possible to assess the risks related to prescriptions with multiple medications that involve the potential drug-drug interactions inherent to a transplantation unit, which is due to the treatment of countless comorbidities in transplanted patients. It was possible to observe that the most prevalent type of interaction identified were of major severity, followed by moderate and minor.

The most frequent potential drug interaction of major severity was due to the association between sirolimus and tacrolimus. This combination has pharmacodynamic interaction, as they compete for the same cell binding protein (FKBP12); in addition, concomitant use of these two drugs may increase the risk of adverse events such as nephrotoxicity, hepatic artery thrombosis, reduced wound healing potential, hyperlipidemia and diabetes[17,18,19].

The second most common PDI of major severity corresponded to the amlodipine-tacrolimus combination. Simultaneous use of these two medications may influence pharmacokinetic factors, as calcium channel blockers, especially dihydropyridine (amlodipine), have CYP3A4 inhibitory action. In this circumstance, there may be a reduction in metabolism and, consequently, a possible increase in the tacrolimus serum level, which can contribute to significant clinical changes due to increased exposure to the immunosuppressant[20].

The association between omeprazole and tacrolimus was also found to be a PDI of major severity. The first one is a medication metabolized by CYP450, a process that can cause competitive inhibition of the enzyme and may interfere with the metabolism of other drugs such as tacrolimus, sirolimus and everolimus, and consequently increase the serum concentration of these immunosuppressants[21].

Regarding the potential drug interactions classified as moderate, the interaction related to the use of ferrous sulfate and pantoprazole stood out most frequently. In this case, there may be a possible pharmacokinetic change related to the reduction in iron absorption due to the increase in gastrointestinal pH upon pantoprazole administration[22].

As for the association between ferrous sulfate and sodium mycophenolate, responsible for the second most detected moderate PDI, no evidence was found in the literature to explain the mechanism of action involved. However, some studies show that administering iron with mycophenolate mofetil (a drug belonging to the same pharmacological class as mycophenolate sodium) did not generate significant changes in the plasma concentrations of the patients evaluated[23,24,25].

Concomitant oral administration of several medication is a significant problem related to safe pharmacotherapy. Polypharmacy mainly affects aged patients with chronic comorbidities, as well as those with prolonged hospitalization times[11,26]. Polypharmacy can favor the occurrence of drug-drug interactions, causing changes that can affect absorption, distribution and elimination of the drugs involved in the treatment, enhance the therapeutic effect, reduce efficacy of the medication or stimulate the appearance of adverse reactions [27].

Through the ATC classification, it was possible to observe that the drug classes involved in almost all potential drug-drug interactions found are also the most prescribed for transplanted patients. This shows the influence that these continuous-use medications may have, considering the risk of undesirable clinical changes. Therefore, the importance related to the prevalence of these PDIs in the transplantation unit is highlighted, emphasizing the relevance of the multidisciplinary team's work in preventing possible harms to the patient.

Thus, some interventions can be carried out by pharmacists, optimizing the clinical approach to adverse events related to PDIs, such as prior evaluation of the drugs' mechanism of action and their potential interactions, patient monitoring, adequate scheduling of the medications prescribed, suspension or substitution of drugs and dose adjustments in order to avoid harms to the patients' health.

Conclusion

Through this study it was possible to observe that the high frequency of potential drug interactions in transplanted patients is possibly due to the number of medications prescribed concomitantly due to the various comorbidities that these patients have, as the more drugs prescribed, the greater the probability of this type of interaction. Some computerized tools such as *Micromedex*® can be used to favor safe drug administration.

The most frequent PDIs were of major severity, which highlights the importance of patient monitoring for proper decision-making by the clinical staff. It is important to emphasize that studies carried out on medication use in a hospital environment with a focus on drug interactions can contribute significantly to the development of new strategies that can prevent or reduce harms to patients' health.

In this scenario, the multidisciplinary team performance is fundamental, highlighting the pharmacists' role in the clinical evaluation of the medications prescribed, identifying potential interactions of these drugs and promoting patient safety. In addition, it is valid to reinforce the importance of providing health education to the professionals in the hospital environment aiming at rational medication use.

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Collaborators

Authors GAS and ABO took part in elaboration of the project and in critical review of the intellectual content; GAS, ABFR and RFM contributed to data analysis and interpretation: and GAS, ABO, DTFM, JACS and LMO took part in writing of the article.

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Declaration of conflict of interests

The authors declare that there are no conflicts of interest in relation to this article.

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