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Araştırma Makalesi / Original Article

EVALUATION OF DRUG-DRUG INTERACTIONS IN RENAL TRANSPLANT PATIENTS

RENAL TRANSPLANT HASTALARINDA İLAÇ-İLAÇ ETKİLEŞİMLERİNİN DEĞERLENDİRİLMESİ

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ÖZET

Giriş: Dünya genelinde ve ülkemizde kronik böbrek yetmezlikli hasta sayısı her geçen gün artış göstermekte; bu hastaların artmış mortalite ve morbiditesinin olduğu da bilinmektedir. Bunun sonucu olarak renal replasman tedavisine ihtiyaç duyan hasta oranı da artmaktadır. Böbrek nakli renal replasman tedavileri içerisinde en normale yakın yaşam standardı sunan tedavi yöntemi olup bu grup hastanın düzenli immunsupresif tedaviyle birlikte pek çok ek ilaç kullanmakta olduğu da bilinmektedir. Bu çalışmada çoklu ilaç kullanımının olduğu renal transplantlı hastalardaki ilaç-ilaç etkileşimini araştırmayı planladık.

Yöntemler: Ocak - Aralık 2022 tarihleri arasında nefroloji polikliniğine başvuran renal transplant hastalarının reçeteleri geri dönük incelendi.

Bulgular: Çalışmaya 94 reçete dahil edildi. Araştırmada 94 reçetede toplam 21 majör, 34 orta ve 144 düşük seviyeli etkileşim tespit edildi.

Sonuç: Böbrek nakilli hastalarda ilaç-ilaç etkileşimi asımsanmayacak ölçüde sık görülmektedir. Bu durumun hastaları takip eden hekimler ve eczacılar tarafından bilinmesi ve yeni yazılması planlanan her ilacın ilaç-ilaç etkileşimine yol açıp açmadığının sorgulanması önem taşımaktadır.

Anahtar Kelimeler: Böbrek nakli, İlaç etkileşimleri, Nefroloji.

ABSTRACT

Introduction: The number of patients with chronic renal failure is increasing day by day throughout the world and in our country. It is also known that these patients have increased mortality and morbidity. As a result, the rate of patients requiring renal replacement therapy is also increasing. Renal transplantation is the treatment method that offers the closest standard of living among renal replacement treatments, and it is also known that this group of patients uses many additional medications along with regular immunosuppressive treatment. In this study, we planned to investigate drug-drug interactions in renal transplant patients with multiple drug use.

Methods: Prescriptions of renal transplant patients who applied to the nephrology outpatient clinic between January and December 2022 were analyzed retrospectively.

Results: 94 prescriptions were included in the study. In the study, a total of 21 major, 34 medium, and 144 low-level interactions were detected in 94 prescriptions.

Conclusion: Drug-drug interactions are extremely common in kidney transplant patients. It is important for physicians and pharmacists who follow the patients to be aware of this situation and to question whether each new drug planned to be prescribed causes drug-drug interaction.

Keywords: Renal transplantation, Drug interactions, Nephrology.

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INTRODUCTION

One of the leading causes of morbidity and mortality worldwide is end-stage renal disease. The prevalence of the disease and the use of renal replacement therapy worldwide are expected to increase sharply in the coming years (1). According to the data of the Tissue, Organ Transplantation and Dialysis Services Department under the Ministry of Health in Turkey, the total number of kidney transplants between 2008 and 2023 is 41,186 (2). The total number of kidney transplants between January and May 2023 is 1,160. Between 2002 and 2013, 20,431 kidney transplants took place (3).

Patients need close follow-up after transplantation as they must receive complex immunosuppressive regimens that make them susceptible to infection, malignancy, and cardiovascular disease. Additionally, patients often have multiple comorbidities, and therefore patients may have more complex clinical conditions (4).

After kidney transplantation, patients are administered lifelong immunosuppressive treatment regimens. Medications are an important part of kidney disease treatment. The treatment needed varies depending on the patient's kidney disease and associated comorbidities, as well as the treatment chosen. According to 2016 data, ion-binding agents, β-adrenergic blocking agents (beta blockers), antibiotics, analgesics, and lipid-lowering agents were most frequently prescribed to end-stage renal disease patients (5). Immunosuppressive therapy can be divided into induction and maintenance regimens. Induction therapy is administered at or around transplantation and is associated with greater immunosuppression than maintenance therapy. The goals of induction therapy are to prevent acute rejection and allow minimization or avoidance of maintenance immunosuppressive agents known to cause toxicity. Induction therapy typically consists of biological antibodies and high doses of glucocorticoids. Maintenance immunosuppression is usually initiated at the time of transplantation and continues long-term throughout the duration of the allograft. These agents vary in their effectiveness and side effect profiles (including the risk of infection, malignancy, cardiovascular disease, and post-transplant diabetes), and these factors should be considered when choosing a regimen for a particular patient (6). Many immunosuppressants taken after transplantation interact with various medications and should always be checked for interactions. It is also vital to avoid all medications that can impair kidney function (e.g., NSAIDs) (5).

Patients are a risky patient population in terms of the potential for drug-drug interactions and drug-related problems due to the large number of medications they use and the effect of kidney disease on drug metabolization and excretion (7). Due to the intensity and complications of the transplantation process, polypharmacy and drug interactions due to the use of many medications are inevitable. Renal transplant patients are a very sensitive group, so drug use in this patient group is quite different from other patient groups. In this study, prescriptions for renal transplant patients were examined. By carefully examining drug interactions in prescriptions, it was aimed to raise awareness that prescriptions commonly used in outpatient treatment may cause serious problems for patients.

METHODS

In the study, the prescriptions of patients who applied to the Nephrology Polyclinic as renal transplantation patients between January 2022 and December 2022 were retrospectively analyzed. Patients' demographic data were collected from patient files retrospectively. The number of drugs in the prescription was determined as a minimum of 4, prescriptions with 3 or fewer drugs were not included in the study. The drug interactions were analyzed by using RxMediaPharma™, a software program available for only medical professionals by purchasing. Drug interactions are classified into three levels, "Low", "Moderate" and "Major", according to the clinical severity of the interaction. Prescriptions suitable for the study design in the renal transplantation patients were included in the study.

Statistical analysis

Statistical Package for the Social Sciences (IBM SPSS) 21.0 program was used for statistical evaluation. A P-value lower than 0.05 was considered statistically significant. Data are given as numbers or %. The Chi-square test was used to compare categorical variables.

RESULTS

A total of 94 prescriptions were included in the study. 45.7% (n=43) of the prescriptions belonged to women and 54.3% (n=51) of them belonged to men. The average number of drugs in prescriptions was 6.8 (min 4 max 13). The average age of prescription holders was 69.44 years. The mean age of female patients was 42.8 (min 23, max 72); the mean age of male patients was 46.6 (min 21, max 70). There was no significant difference between the mean age of women and men (p=0.064).

Table 1. Drug interactions and classification

Interaction	**Number of interactions**
Major	
Tacrolimus x everolimus	21
Moderate	
Tacrolimus x Lansoprazole	34
Low	
Tacrolimus x Amlodipine	82
Tacrolimus x Nifedipin	34
Tacrolimus x Lercadipine	28

A total of 21 major, 34 moderate, and 144 low-level interactions were detected in 94 prescriptions in the study. The average interaction per prescription is 2.1. The

interaction contents are indicated in Table 1. When all interactions are examined, the most frequently interacting group of drugs is immunosuppressive drugs. In second place were antihypertensives; proton pump inhibitors (PPI) were in third place.

DISCUSSION

Drug-drug interactions change the effect of the drug due to simultaneous or recent use of drugs together. Concomitant use of two drugs may lead to toxicity with increased efficacy of the affected drug and therapeutic unresponsiveness with decreased efficacy. Predicting potential drug interactions poses some difficulties for the physician. It is important to detect potential drug-drug interactions that may lead to serious clinical consequences. Preventing drug interactions can be achieved by adjusting the dose and closely monitoring the patient's condition (8-9).

Due to the intensity and complications of the transplantation process, polypharmacy and drug interactions due to the use of many medications are inevitable. Particular attention should be paid to the effects that may occur due to the use of drugs with a narrow therapeutic index in combination with other drugs. According to a systematic review of drug interactions in patients in a study conducted in Canada; At least one potential drug interaction was identified in 63% of patients. 75% of these drug interactions were found to be moderate to serious in terms of clinical significance (10). In a study conducted in Brazil, 180 potential interactions were detected in 63 patients (11).

In the drug interaction study conducted by Moradi et al. in 2020 on renal transplantation patients, drug interactions were detected in 90% of the patients (12). In our study, interaction was observed in all prescriptions included (n = 94). This is because renal transplantation patients are exposed to potential drug-drug interactions as a result of multiple medications due to complex treatment protocols. Multiple drug use and treatment protocol types may increase the clinical significance of these potential drug-drug interactions and the associated risk of adverse reactions. Underestimating drug-drug interactions can also have a major impact on patients' quality of life.

The drug with the most interactions in our study was tacrolimus. Tacrolimus is an immunosuppressant agent with a narrow therapeutic range. Tacrolimus is mainly metabolized via liver and intestinal CYP3A4 and CYP3A5. CYP3A5 plays a more active role in the pharmacogenetics of tacrolimus (13). Since everolimus inhibits CYP3A4 just like tacrolimus, its immunosuppressant effect increases when used together, and therefore immunosuppression-related toxicity may increase (14).

There may be an interaction between tacrolimus and proton pump inhibitors, which irreversibly block gastric acid secretion by binding to and inhibiting the hydrogen-potassium ATPase pump on the luminal surface of the parietal cell membrane, and as a result, serum tacrolimus levels increase. This pathway occurs through CYP3A4 and CYP3A5 in renal transplant patients carrying CYP2C19 gene variants. In a renal transplant case study conducted by Homa et al., an increase in tacrolimus levels was detected after lansoprazole administration. In our study, tacrolimus and lansoprazole interactions were observed in 30 of 94 prescriptions, and this interaction was in the middle class in the drug information source used for evaluation purposes. Transplant physicians prescribing medium- and long-term PPIs to patients taking tacrolimus may consider monitoring immunosuppressant levels before starting or switching PPIs (15-16).

Many studies have reported that after kidney transplantation, patients develop systemic hypertension requiring medical treatment. The exact mechanism of the interaction between tacrolimus and amlodipine, which was observed in 82 prescriptions in our study, is unknown, but it is thought to be due to the inhibition of CYP450 3A5 metabolism by tacrolimus. Isolated case reports and a crossover study in healthy subjects have shown that the area under the curve (AUC) of tacrolimus may increase by 2.3-fold or more when taken concomitantly with amlodipine (17-18).

The mechanism of tacrolimus and nifedipine interaction seen in 34 prescriptions in our study is probably due to the nifedipine-induced inhibition of the hepatic metabolism of tacrolimus. Using tacrolimus together with nifedipine may increase the effects of tacrolimus (19-20).

Physicians and pharmacists should be more aware of these potential interactions, recognizing that not all drug-drug interactions are harmful. Collaboration may be considered for educational programs and counseling of patients to prevent inappropriate use of medications. Some drug-drug interactions may be clinically useful. Further research is needed to evaluate interaction outcomes on a patient-by-patient basis and minimize the prevalence of harmful interactions.

A limitation of our study is that due to the retrospective design of the study, the medications used by the patients and their duration of use could not be distinguished. Larger data can be obtained with longer periods and larger samples. Another limitation of the study is that it does not take into account herbal and over-the-counter medications.

CONCLUSION

In conclusion, the most important condition for preventing drug interactions and related problems is awareness. It is necessary to act with the awareness that prescribing medication for a renal transplant patient is as important as making a diagnosis and that we can benefit the patients without harming them. Considering that not every interaction is harmful, optimization of the treatment can be achieved.

Ethics Committee Approval: The study protocol was approved by the ethical committee of Eskisehir Osmangazi Medical Faculty (Protocol Number: 2023-257).

Informed Consent: This study was done retrospectively.

Authorship Contributions: Idea/Concept: RM, Design: RM, Supervision: SG, Data Collection or Processing: RM, Analysis or Interpretation: RM, SG, Literature Search: RM, SG, Writing: RM, SG, Critical Review: RM, SG, References and Fundings: -, Materials: RM, SG.

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