Assessment of Clinically Relevant Drug Interactions by Online Programs in Renal Transplant Recipients

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ABSTRACT

BACKGROUND: Potential drug-drug interactions (pDDIs) with immunosuppressive drugs are frequently observed in renal transplant recipients. Drug interaction programs are acknowledged as a fundamental tool to alert physicians to pDDIs, but there is a high concern about variation among different programs in terms of quality and reliability of information.

OBJECTIVES: To (a) characterize the difference in severity levels of pDDIs with tacrolimus and cyclosporine provided by 3 drug interaction programs and (b) identify clinically relevant DDIs with these immunosuppressive drugs in renal transplant recipients.

METHODS: This study was conducted in a nephrology outpatient clinic at the University Research & Training Hospital between November 2017 and February 2018. A clinical pharmacist attended clinic visits with physicians and evaluated drug interactions. Micromedex, Medscape, and Lexicomp drug interaction programs were used to identify pDDIs and their severities. Furthermore, Drug Interaction Probability Scale (DIPS) criteria were applied to identify clinically relevant drug interactions seen in clinic patients. Finally, a clinical pharmacist intervened to manage clinically relevant drug interactions identified by DIPS.

RESULTS: 80 patients (54 under tacrolimus; 26 under cyclosporine treatment) were included in this study. The 3 drug interaction programs generated 648 pDDIs, 63 of which were different drug interaction pairs. Ninety-eight pDDIs were common to all 3 drug interaction programs. Sixty-three different drug interaction pairs were evaluated according to severity level, and 3 drug interaction pairs were at the same level (moderate) among the programs. The Fleiss' kappa overall interrater agreement was poor. The kappa revealed a moderate agreement for interaction pairs with a "severe" rating and a slight agreement for interaction pairs with a "major" rating. According to the DIPS evaluation, 11 pDDIs were classified as "possible," and the percentage of clinically relevant drug-drug interactions was 4.0% (10/248), 4.2% (11/265), and 8.2% (11/135) for Medscape, Lexicomp, and Micromedex, respectively. Although daily doses of immunosuppressive drugs were not changed, the blood concentrations of these drugs increased after administration of an interacting drug. As a result, in order to maintain normal therapeutic range of concentrations, dose reduction or drug change was applied where appropriate.

CONCLUSIONS: Interaction checker programs are commonly used by health institutions, since they provide quick and summarized information on mechanism and management of drug interactions, when no clinical pharmacist is present to interpret. However, the likelihood of detecting clinically relevant DDIs by interaction checker programs is relatively low, and there are inconsistencies among different programs. Individualized patient monitoring should be maintained by a multidisciplinary health care team that includes a clinical pharmacist, and decision making should be based on professional assessment of the renal transplant patient.

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What is already known about this subject

- Renal transplant recipients are likely to be particularly vulnerable to adverse drug events caused by drug-drug interactions because of polypharmacy status and narrow therapeutic range of immunosuppressive drugs that are commonly used in this population.
- Drug interaction programs are known as a fundamental tool to alert physicians to drug-drug interactions.
- Previous studies have found considerable variation in the results provided by drug interaction programs for potential drug-drug interactions; however, only limited number of studies on clinically relevant drug-drug interactions have been undertaken.

What this study adds

- The percentage of clinically relevant drug-drug interactions for immunosuppressive drugs was 4.0%, 4.2%, and 8.2% for Medscape, Lexicomp, and Micromedex drug interaction programs, respectively.
- The Fleiss' kappa (κ) overall interrater agreement for the overall degree of interaction subcategories among Micromedex, Medscape, and Lexicomp drug interaction programs was poor ($\kappa = -0.0168$).
- A clinical pharmacist integrated into the multidisciplinary health care team may help to clarify clinically relevant drug interactions in renal transplant recipients when available information databases present any conflicts.

A potential drug-drug interaction (pDDI) is defined as the potential for modification of the effect of a drug when it is administered with another drug.¹ A clinically relevant DDI could either increase the toxicity or reduce the efficacy of a particular drug.²

Potential drug interactions with immunosuppressive drugs are frequently observed in practice. Cyclosporine and tacrolimus have long been considered among first-line options for maintenance immunosuppression in renal transplant recipients.³ These drugs have distinct pharmacokinetics but have narrow therapeutic ranges. Drug metabolism is mostly maintained by the cytochrome P450 (CYP3A4 and CYP3A5) enzymes and may be affected by pharmacogenetic polymorphisms.^{4,5} The combination of a drug using CYP450 metabolism and a patient with polymorphisms related to the metabolic route has

an increased risk of pDDI. Nephrotoxicity, neurotoxicity, or graft rejection can result as a consequence. Although the most potential interacting drugs with cyclosporine and tacrolimus are often quite similar, these 2 drugs do not always interact identically when administered with CYP inhibitors or inducers.⁶ The main reason is the difference between metabolism paths of tacrolimus and cyclosporine; the predominant enzyme in tacrolimus metabolism is CYP3A5 (and CYP3A4 with a lower extent for catalysis), whereas cyclosporine is mainly metabolised by CYP3A4.⁷

Approximately 10% of hospitals admissions of renal transplant recipients are related to probable adverse drug reactions. Renal transplant recipients are at high risk of DDI because of several comorbid conditions and the administration of many drugs concurrently (average of 5.6 interactions per patient).⁸ Drug interaction is associated with increased morbidity, mortality, length of hospital stay, and health care cost.⁹⁻¹¹

Therapeutic drug monitoring and assessment of pDDI are essential to decrease the risk of graft rejection and drug toxicity in patients receiving immunosuppressive drugs; consequently, pDDI should be routinely screened for all transplant recipients after transplantation and whenever a new drug is added to pre-existing immunosuppressive treatment. In order to maintain therapeutic efficacy with minimal side effects, the trough blood concentration of tacrolimus should be 8-12 ng/mL and second hour blood concentration of cyclosporine should be 800-1,000 ng/mL during the first 6 months of the post-transplant period based on our hospital protocols. After the 6 months, the trough blood concentration of tacrolimus is targeted as 5-8 ng/mL and second hour blood concentration of cyclosporine as 400-600 ng/mL.

Drug interaction programs are perceived as a fundamental tool to alert physicians to identify DDI. However, previous studies have found considerable variation in the results provided by drug interaction programs for pDDI.¹² A great number of pDDIs can be seen with drug interaction programs, but few studies have evaluated their clinical relevance. The purpose of this study was to characterize the difference in severity levels of pDDIs with tacrolimus and cyclosporine provided by 3 drug interaction programs and to identify clinically relevant DDIs with these immunosuppressive drugs in renal transplant.

Methods

Study Design, Setting, and Participants

A prospective study was conducted in a nephrology outpatient clinic that performs on average 50 renal transplants annually at the University Research & Training Hospital between November 2017 and February 2018. The study was approved by the Clinical Trials Ethics Committee (project no. KA-180008), which carried out the principles set forth in the Declaration of Helsinki 1975, revised Hong Kong 1989.

The renal transplant recipients who were aged between 18-70 years, were treated with tacrolimus or cyclosporine for at

TABLE 1 Categorization of Potential Drug-Drug Interactions According to Severity Indicated by Drug Interaction Programs

Severity of Interaction (Category)	Micromedex	Lexicomp	Medscape
Severe (5)	Contraindicated	(X) Avoid combination	Contraindicated
Major (4)	Major	(D) Consider therapy modification	Serious-use alternative
Moderate (3)	Moderate	(C) Monitor therapy	Monitor closely
Minor (2)	Minor	(B) No action needed	Minor
None (1)	Unknown	(A) No known interaction	No interactions found

least 12 months, had at least 2 laboratory findings of immunosuppressive drug concentrations, attended the outpatient clinic regularly during the study period, and gave written consent, were considered eligible and included in the study.

Study Procedure

A clinical pharmacist attended the clinic visits with physicians and reviewed patient demographics (age, gender, donor type, and pretransplant dialysis history), drug treatments, treatment modifications, and laboratory results within the previous month.

Initially, pDDIs and their severity levels were identified from a patient's drug treatment list using Micromedex, Medscape, and Lexicomp drug interaction programs. These 3 drug interaction programs are commonly used by physicians in the hospital. The Lexicomp (by Wolters Kluwer) and the Micromedex (by IBM) online databases require subscriptions to use for drug interactions.^{13,14} Medscape, however, is an open access program that is a part of the WebMD Network.¹⁵

As shown in Table 1, pDDIs were converted into 5 categories for the analysis: severe (contraindicated), major, moderate, minor, and none. If a drug interaction pair was defined with more than 1 category by the program, the most severe category was selected in order to compare among the Micromedex, Medscape, and Lexicomp programs. If the potential drug interaction was defined as severe/contraindicated, major, moderate or minor, in any program, a clinical relevance of drug interaction was verified by the patient's clinical status (such as change in immunosuppressive drug concentration), which may be a result of an identified pDDI.

Once a patient's clinical status was found to correspond with the consequences (associated signs and symptoms) of a pDDI, the Drug Interaction Probability Scale (DIPS) criteria was used for a causal evaluation of a particular interaction. Ultimately, a clinical pharmacist intervened to manage detected clinically relevant drug interactions with the DIPS, which consists of 10 questions that assess the probability of a causal relationship between an observed event and consequences of a drug

FIGURE 1 Cyclosporine and Tacrolimus Potential Drug-Drug Interaction Pairs Identified by the Micromedex, Medscape, and Lexicomp Drug Interaction Programs

interaction. The scale comprises the evaluation of DDI in terms of the following: (1) previous credible reports; consistency with the known properties of (2) precipitant or (3) object drug; (4) time course; (5) dechallenge; (6) rechallenge; (7) alternative causes; (8) concentration of object drug in blood or other fluids; (9) other objective evidence, other than drug concentration; and (10) change in the interaction with precipitant drug dose change. Each question can be answered with “yes,” “no,” or “unknown/not applicable” responses, with an assigned numeric score for each question. The final score translates into a qualitative scale that expresses the probability of the reaction actually being a drug interaction. A probability of drug interaction was categorized as doubtful (<2), possible (2-4), probable (5-8), or highly probable (>8).¹⁶

Statistical Analysis

Data were evaluated using descriptive statistics (mean, median, frequency, and percentages). SPSS version 22 (IBM, Armonk, NY) was used for the statistical analysis in the study. The Fleiss' kappa statistic was used to summarize the agreement in the category of pDDI provided by the 3 drug interaction programs. The Fleiss' kappa is a measure of interrater reliability that removes agreement expected by a chance and is suitable for 3 or more raters. A kappa value varies between -1 and 1, with 1 indicating perfect agreement, -1 indicating perfect disagreement, and 0 indicating agreement expected by a chance.¹⁶ The interpretation of Fleiss' kappa values is based on guidelines established by Landis and Koch, such that <0.0 is poor agreement; 0.0-0.2 is slight agreement; 0.21-0.40 is fair agreement; 0.41-0.60 is moderate agreement; 0.61-0.80 is substantial agreement; and 0.81-1.00 is almost perfect agreement.¹⁸

P values were calculated for the kappa, with a $P < 0.05$ meaning that rater agreement was unlikely to be because of chance. High agreement among raters does not always indicate that the answer is correct or vice versa. All Fleiss' kappa values were calculated using the R software package “irr,” version 0.84.1.¹⁹

Results

A total of 80 patients (54 under tacrolimus, 26 under cyclosporine treatment) were included in the study; 51.3% were male, and mean age was 41.5 ± 1.3 years. The median time since renal transplantation was 72.0 (95% confidence interval [CI] = 12.0-276.0) months. Majority of the transplantations had been performed from living donors ($n = 53$, 66.2%). Twelve transplants had been performed preemptively. The median number of medications per patient was 6 (95% CI = 3-15). The median daily drug dose was calculated as 2 mg (95% CI = 1-9) for tacrolimus and 100 mg (95% CI = 50-150) for cyclosporine.

The 3 drug interaction programs generated 648 pDDIs, involving 63 different drug interaction pairs. The total number of identified pDDIs with cyclosporine or tacrolimus alone in any drug interaction programs ranged from 135 to 265; only 98 pDDIs were common in all interaction programs. The Micromedex program had the least number of pDDIs (135 and 31 different pairs), followed by the Medscape program (248 and 36 different pairs) and the Lexicomp program (265 and 44 different pairs; Figure 1). The number of pDDIs according to severity level in the Lexicomp, Micromedex, and Medscape program are indicated in Table 2.

The overall Fleiss' kappa was found as -0.0168 (poor agreement) among the 3 interaction checker programs (Table 3). The kappa was 0.384 (moderate agreement) for interaction pairs

TABLE 2 Number of Potential Drug-Drug Interactions with Cyclosporine and Tacrolimus Identified by the Drug Interaction Programs

	Minor	Moderate	Major	Severe	Total pDDIs, n
Lexicomp	61	152	42	10	265
Medscape	8	152	82	6	248
Micromedex	0	84	46	5	135

pDDI = potential drug-drug interaction.

of severe category, and 0.006 (slight agreement) for interaction pairs of major category. Among 63 different pDDI pairs present in our patients, 3 were defined as the same category (moderate) by the programs. However, a drug interaction pair that was indicated as “none” by 1 program was indicated as severe (n=1), major (n=13), and moderate (n=29) by the other programs, which shows inconsistency for the rating of severity among the programs. For example, concomitant use of cyclosporine and lercanidipine was defined as “there is no interaction (none)” by Medscape, whereas the Lexicomp and the Micromedex programs defined the category of interaction as “severe.”

According to the DIPS evaluation (n=11 drug interactions total), cyclosporine-prednisolone (n=6), tacrolimus-lansoprazole (n=1), cyclosporine-lercanidipine (n=1), cyclosporine-amlodipine (n=1), cyclosporine-allopurinol (n=1) and cyclosporine-colchicine (n=1) interactions were classified as “possible (score=4)” by answering “yes” to the first (previous credible reports), second (consistency with the known properties of precipitant), third (consistency with the known properties of precipitant), and eighth (concentration of object drug in blood or other fluids) questions in the DIPS criteria (Table 4). Among observed 11 clinically relevant drug-drug interactions, 4.0% (10/248) were detected by Medscape, 4.2% (11/265) by Lexicomp, and 8.2% (11/135) by Micromedex.

Although daily doses of immunosuppressive drugs were not changed, the blood concentrations of these drugs increased after administration of an interacting drug. The clinical pharmacist made recommendations for clinically relevant drug interactions; as a result, the dose was reduced (cyclosporine) or drug was changed (lansoprazole was replaced by pantoprazole in a tacrolimus-lansoprazole interaction) where appropriate in order to maintain a normal therapeutic range of concentrations.

Discussion

Immunosuppressive drugs used in renal transplant patients have narrow therapeutic ranges and along with drug elimination is primarily maintained by the cytochrome P450 (CYP3A4 and CYP3A5) enzymes and the efflux pump P-glycoprotein. This combination elevates the risk of drug interactions in this

TABLE 3 Kappa Indices of Agreement Among 3 Drug Interaction Programs

Category	Kappa	P Value	Strength of Agreement ^a
None	0.003	0.967	Slight
Minor	-0.056	0.442	Poor
Moderate	-0.087	0.233	Poor
Major	0.006	0.932	Slight
Severe	0.384	0.000	Moderate
Overall ^b	-0.0168	0.722	Poor

^aLandis and Koch, 1977.¹⁸

^bFleiss' kappa.

population.⁴ In this study, drug interaction with immunosuppressive drugs were assessed by 3 commonly used drug interaction programs. The results revealed that these programs differ significantly in terms of identified number of pDDIs. The interrater reliability was moderate (kappa=0.384) for severe pDDI; however, the overall interrater reliability was only fair (kappa=-0.0168). The highest rate of identifying clinically relevant DDIs with tacrolimus and cyclosporine in renal transplant patients was found in the Micromedex program. Health care professionals should be aware of the diversity of pDDIs identified by different drug interaction programs.

Drug interaction programs extract information from the scientific and recent literature and allocate it in categories for health care professionals; however, a concern about variability of the quality and effectiveness of the information between the programs has emerged among health care professionals.^{12,20,21} Moreover, since a unique patient's characteristics cannot be integrated into those programs, they do not allow individualized dosing modification nor do they provide specific precautions to be taken by health care professionals.²²

In clinical practice, physicians are given a large number of pDDI alerts, and many of these can be quickly bypassed. Excessive alerts could disguise the importance of a particular DDI.²³ Therefore, a close monitoring of renal transplant patients by pharmacists can help to identify and prevent DDIs and may contribute to a patient's health outcomes. A study by Peng et al. (2003) showed that a clinical pharmacist's review reduced the incidence of potentially serious DDIs by an additional 80.6% in a large population of ambulatory patients.²⁴

Drug interactions observed with immunosuppressive drugs in renal transplant recipients may cause nephrotoxicity, neurotoxicity, or graft rejection as a consequence.⁶ Therefore, drug interactions with immunosuppressive drugs should be comprehensively assessed and then verified by health care professionals in renal transplant patients, using appropriate and validated tools such as DIPS in order to maintain effectiveness of the treatment. Another tool, known as the Naranjo algorithm, was also used in the literature,²⁵ which assesses

TABLE 4 Potential Drug-Drug Interactions for Tacrolimus and Cyclosporine Evaluated by Online Programs and the Drug Interaction Probability Scale

pDDI	Consequence of a Drug Interaction Observed in Patient	Severity in Lexicomp	Severity in Medscape	Severity in Micromedex	Clinical Relevance by DIPS
Tacrolimus-lansoprazole, n = 17	Increased tacrolimus concentration	Major	Moderate	Moderate	Possible (score = 4; n = 1)
Cyclosporine-prednisolone, n = 25	Increased cyclosporine concentration	Moderate	Moderate	Moderate	Possible (score = 4; n = 6)
Cyclosporine- allopurinol, n = 5	Increased cyclosporine levels	Moderate	Minor	Moderate	Possible (score = 4; n = 1)
Cyclosporine-lercanidipine, n = 4	Increase risk of cyclosporine and lercanidipine exposure	Severe	None	Severe	Possible (score = 4; n = 1)
Cyclosporine-amlodipine, n = 3	Increase risk of cyclosporine toxicity ^a	Moderate	Moderate	Major	Possible (score = 4; n = 1)
Cyclosporine-colchicine, n = 1	Increased colchicine and cyclosporine plasma concentration	Major	Major	Severe	Possible (score = 4; n = 1)

^aRenal dysfunction, cholestasis, and paresthesia.

DIPS = Drug Interaction Probability Scale; pDDI = potential drug-drug interaction.

the probability of adverse drug reactions rather than drug interactions. However, the DIPS algorithm is able to assist in the evaluation of causation in observed clinically relevant DDIs in an objective, reliable, and transparent manner.

Among identified pDDIs (135 from the Micromedex program, 248 from the Medscape program, and 265 from the Lexicomp program), only 4.2%, 4.3%, and 8.0%, respectively, were found to be clinically relevant. Among those interactions, 11 were found to be clinically relevant DDIs in this study; they were also acknowledged by previous studies and were managed by reducing the dose of immunosuppressive drugs or replacing the interacting drugs with alternate agents.^{6,26,27}

Limitations

This study has some limitations. A limited number of patients participated in the study for the planned period of time; however, the findings could have provided insight into the incidence of drug interactions, if more patients would have been included. Another limitation is the comparison of only categories pertaining to severity (severe, major, moderate, minor, and none) of potential DDIs. Other features, functions, and ease of use of the drug interaction programs were not investigated. In addition, in some of the cases, it was hard to differentiate whether the observed adverse reaction was caused by a DDI or by 1 drug alone. This limitation was mitigated by consensus decision on the certainty of DDI-related adverse reactions with the treating physician.

Conclusions

Potential drug interactions can be easily identified by using various interaction checker programs in routine clinical practice. However, severities can be indicated in different categories in the different programs. Regardless of which interaction program is preferred by a health institution, the likelihood of

detecting clinically relevant DDIs is relatively low. Therefore, patient monitoring should be maintained by a multidisciplinary health care team that includes a clinical pharmacist. The severity of a potential drug interaction that was provided by the programs should be interpreted by professionals, considering unique patient characteristics such as age, comorbidities, and treatment dose. Individualized decisions (e.g., alternative drug changes, dose changes, or only monitoring only) should be made in the treatment of renal transplant patients.

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