ABSTRACT

Healthcare organizations continue to adopt information technologies with clinical decision support (CDS) to prevent potential medication-related adverse drug events. End-users who are unfamiliar with certain high-risk patient populations are at an increased risk of unknowingly causing medication errors. The following case describes a heart transplant recipient exposed to supra-therapeutic concentrations of tacrolimus during co-administration of ritonavir as a result of vendor supplied CDS tools that omitted an interaction alert. After review of 4692 potential tacrolimus-based DDIs between 329 different drug pairs supplied by vendor CDS, the severity of 20 DDIs were downgraded and the severity of 62 were upgraded. The need for institution-specific customization of vendor-provided CDS is paramount to ensure avoidance of medication errors. Individualized care will become more important as patient populations and institutions become more specialized. In the future, vendors providing integrated CDS tools must be proactive in developing institution-specific and easily customizable CDS tools.

INTRODUCTION

Medication errors and adverse drug events lead to significant morbidity, mortality, and increased cost for hospitalized patients.1,2 Healthcare organizations increasingly use information technologies with clinical decision support (CDS) to prevent potential medication-related adverse drug events.3 Technologies such as computerized prescriber order entry and pharmacy information systems with optimized CDS enhance efficiency, quality, and safety of medication therapy management for effective patient care.4-5

Solid organ transplant recipients are at particularly high risk for medication errors resulting from drug–drug interactions (DDIs) owing to complex medication regimens with narrow therapeutic indexes.6-7 Calcineurin inhibitors (CNIs), cyclosporine and tacrolimus, are the most commonly used maintenance immunosuppressive agents in solid organ transplantation.7 As substrates of cytochrome P-450 isoenzyme 3A4 (CYP3A4) and the P-glycoprotein (PGP) efflux pump, the CNIs are associated with numerous DDIs.6 The care of transplant recipients is further complicated among individuals infected with HIV who require treatment with highly active antiretroviral therapy (HAART).8-9 Owing to similar affinity to, and effect on, CYP3A4 and PGP, the concomitant administration of HAART and CNI regimens is of significant concern. Co-administration and resulting DDIs may result in profound medication errors and, ultimately, patient harm. Herein we describe the treatment of an HIV-infected heart transplant recipient to examine the use of healthcare information technology, with a focus on lessons learnt.

PATIENT CASE

A 58-year-old man, diagnosed with HIV, presented for orthotopic heart transplant, secondary to ischemic cardiomyopathy. At the time of transplant, the patient was maintained on a stable HAART regimen consisting of emtricitabine 200 mg once daily, tenofovir 300 mg once daily, and ritonavir 100 mg twice daily. Three months before transplantation, the patient’s CD4 count and HIV viral load were 492 cells/mm3 and <50 copies of HIV-1 RNA/ml, respectively.

Immunosuppressive therapy at the time of transplantation included intraoperative intravenous methylprednisolone 1000 mg, followed by an oral prednisone taper to 5 mg daily, mycophenolate mofetil 1500 mg twice daily, and tacrolimus (goal whole blood trough concentration [C0]: 10–12 ng/ml). Sublingual tacrolimus was started on the morning of postoperative day (POD) 2 at a dose of 1 mg every 12 h. Subsequent tacrolimus dosing during the patient’s hospital course is outlined in figure 1. Notably, on POD 5, a tacrolimus concentration of 45 ng/ml was misinterpreted as a peak value; therefore, an additional 1 mg of oral tacrolimus was administered on the evening of POD 5. Upon appropriate identification of an elevated tacrolimus concentration on POD 6 (52 ng/ml), administration of tacrolimus was discontinued until POD 8. At this time, the tacrolimus concentration declined from 37.3 ng/ml to 14.7 ng/ml, and a one-time dose of 0.5 mg oral tacrolimus was given. On POD 9 the tacrolimus concentration increased to 33.8 ng/ml. The patient did not receive any additional tacrolimus doses during the remainder of his inpatient stay. The patient’s HAART remained uninterrupted throughout the patient’s course and it was determined that the combination of ritonavir and tacrolimus resulted in supratherapeutic tacrolimus concentrations.

The presence of persistently elevated tacrolimus concentrations is especially concerning owing to significant and potentially irreversible side effects from the medication. The most severe adverse effects associated with tacrolimus are acute renal failure, infectious complications, tremors, headaches,
delirium, and coma. At baseline, the patient’s serum creatinine (SCr) was 1.2 mg/dl. The patient’s highest recorded SCr was 2 mg/dl on POD 6, correlating directly with the highest tacrolimus concentration, 52.4 ng/dl (figure 1). At the time of discharge, SCr had stabilized at 1.5 ng/ml. Additional signs and symptoms of tacrolimus toxicity included confusion, tremor, and headaches, all of which resolved by POD 10. The patient was discharged on POD 31 with a tacrolimus concentration of 11.1 ng/ml and a plan to dose tacrolimus at 0.5 mg orally every 14 days.

**IMPLEMENTATION**

After this patient case, workflow analysis identified that the electronic health record (EHR) vendor had set the default for a DDI resulting in a moderate severity for the combination of HAART and CNI therapies. It is important to note that classification of DDI severity is often contracted to EHR suppliers by clinical drug-database vendors. The CDS tools supplied by clinical drug-database vendors may not be modified by EHR vendors for their clients. Only major-severity DDIs, as defined by our institution’s CDS committee, were programmed to present an alert to clinicians; therefore, no electronic alert was produced in this patient case. The CDS committee’s decision to present major-severity alerts to clinicians was based on an attempt to reduce alert fatigue and the expectation that major-severity alerts were the most clinically significant. Identification of the clinically inappropriate vendor default severity settings prompted our institution’s CDS committee and transplant pharmacy team to review and modify the standard DDI defaults for tacrolimus. The team reviewed 4692 potential DDIs related to tacrolimus, reflected in 329 drug pairs at all severities (minor, moderate, and major) and, based on literature review and clinical expertise, 82 pairs were modified. A total of 20 DDI pairs originally programmed as a major severity were downgraded to either minor severity or moderate severity (box 1), while 62 DDI pairs of minor severity or moderate severity were upgraded to the major-severity category (box 2). The team recommended additional CDS tools to incorporate human factor interactions—such as, non-interruptive display of relevant laboratory value results (serum drug concentrations and timing of sample obtained). These additional CDS components will be displayed within the order entry screen for immunosuppressive agents that require therapeutic drug monitoring. To ensure a comprehensive review, an identical process for cyclosporine DDIs is ongoing.

**DISCUSSION**

Publications exploring the impact of healthcare information technology (IT) in solid organ transplantation are scarce. A comprehensive understanding of the process of medication use (prescriber order, pharmacist review, dispensing of the medication, and administration) is essential for implementing effective electronic error prevention strategies. Distinct and complex

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**Box 1 Selected tacrolimus drug–drug interaction downgrades from major severity to moderate severity**

- Aspirin
- Bacitracin
- Immune globulin 10%
- Leflunomide
- Mesalamine
- Methadone
- Olsalazine
- Pentamidine inhaled solution
- Sulfasalazine
- Vancomycin

**Box 2 Selected tacrolimus drug-drug interaction upgrades from moderate- to major-severity**

- Amikacin sulfate
- Amiodarone
- Amphotericin B
- Amprenavir
- Atazanavir
- Bromocriptine
- Carbamazepine
- Chloramphenicol
- Cimetidine
- Clarithromycin
- Colistimethate
- Darunavir
- Delavirdine
- Dexamethasone
- Diltiazem extended release
- Efavirenz
- Erythromycin
- Etravirine
- Mephenobarbital
- Nelfinavir
- Nicardipine
- Oxcarbazepine
- Pentobarbital
- Phenytoin
- Polymyxin B
- Posaconazole
- Propafenone sustained release
- Quinapril
- Ritonavir
- Tipranavir
- Tobramycin
- Verapamil
- Voriconazole
patient populations require evidence-based client customization. Owing to the narrow therapeutic category of immunosuppressive agents and their pharmacokinetic profiles, solid organ transplant recipients are at particularly high risk for medication errors that result from DDIs. Commercially available EHR systems provide standardized alerting modules from contracted vendors to their clients as a CDS tool. A lack of appropriately designed CDS electronic alerts and provider awareness resulted in the development of tacrolimus-specific toxicities and prolonged hospitalization for this patient.

The potential impact of information technologies on avoidance and reduction of medication errors through safeguards at all points of the medication use process is profound. Maintaining, customizing, and continuously evaluating all CDS systems within a vendor-supplied EHR is vital to ensure that the most applicable data are provided for patient care and safety. In our experience, the most effective CDS tools are customized alerts that include clinical pathways, which integrate pertinent patient data and hospital guidelines in ‘real time’. This case is a compelling example of the need for institution-specific customization of vendor-provided DDI alerts. Vendor-supplied DDI databases and systems are extensive; an internal, comprehensive review of DDIs most pertinent to patients served by individual institutions is imperative in tailoring institution-specific medical logic modules. Appropriate configuration of DDI alerts can facilitate and prioritize critical events that lead to patient harm, while at the same time ensuring that prescribers are not overburdened with all possible DDIs, thus minimizing alert fatigue. In general, healthcare institutions focus on enhancing the specificity of alerts in order to reduce alert fatigue. Therefore, our multidisciplinary team’s recommendations to increase the alert severity of 62 medications, potentially generating more alerts to end-users, were unexpected, yet deemed appropriate.

Review of DDI settings should be multifaceted and may include an evaluation of alerts triggered by end-users. A review of frequently over-ridden drug pairs and medications associated with serious adverse drug events would allow vendors to refine standard settings to target their clients’ patient populations according to different levels of patient acuity and disease states. Additionally, vendors should provide standard reports that allow clients to evaluate and further customize CDS settings as deemed necessary. Client-specific customization becomes most effective when sites have the capability to automatically track, generate, and evaluate user responses to alerts. This is a particular challenge for organizations that may not have the necessary resources for proficient IT departments and personnel.

The process is further complicated for clients who review and augment custom settings individually based on whether the drugs are listed as an object or precipitant (e.g., tacrolimus—ritonavir, ritonavir—tacrolimus). Objects and precipitant medications from vendor-supplied DDI lists were not always present for the reciprocal combination—for example, tacrolimus—ritonavir was reported as a potential DDI, whereas ritonavir—tacrolimus was not. Moreover, manual database customization does not allow an option to apply changes in severity setting to all or selective dosage forms of the objective and precipitant drugs. For example, in order to capture a change in DDI severity alert between tacrolimus and acyclovir, one must consider the intravenous, capsule, suspension, and topical formulations of tacrolimus, as well as the intravenous, tablet, topical, and liquid formulations of acyclovir (a total of 32 different DDI alert combinations). The process of reviewing tacrolimus DDIs by the multidisciplinary CDS committee highlights the repetitiveness of identical DDIs and their differing dosage forms: of the original 4693 pairs, approximately 60 individual agents were reviewed. This redundancy also extends to the IT analysts who often use manual change processes to customize DDI settings, and is further magnified in organizations with multiple production environments. The development of processes for editing CDS tools must be simplified by EHR vendors so that updates and maintenance of settings are less burdensome.

Additionally, studies suggest that the potential for unintended consequences of CDS is due to a lack of specificity and clinical relevance. Integrating human factor interaction within CDS warning displays may enhance end-user response. Plans to tailor alert messages to promote end-user response rate, including the use of colors, font, text size, and consolidating information, should be implemented. System configuration options and tools for customization should be a focus for EHR vendors to improve human–computer interactions.

CONCLUSION

The balancing act between meaningful uses of EHRs and non-specific and interruptive DDIs highlights the need for greater partnership between client sites, end-users, EHR vendors, and medical information companies providing CDS content. All EHR system vendors are responsible for pursuing and facilitating collaborative relationships with users to achieve meaningful use of technology. During system design, implementation, and upgrade of EHR systems, vendors should provide recommendations to clients that optimize CDS tools with clinical work-flow considerations. This will require a less consultative position and greater partnership to ensure that clients optimize functionality and operation of purchased EHRs. Continuous updates of vendor products are essential to ensure optimal patient safety and care. Healthcare organizations relying on vendor products should be informed of all changes to the EHR databases with the clinical rationale provided. All parties are responsible for encouraging transparency and communication so that medical information companies can provide evidence-based decisions to modify product standards. The ongoing exchange of modifications made to clinical decision support tools will enhance the future of meaningful EHR systems for patient care.

Acknowledgments The authors would like to thank Anastasia Anamisis, Pharm.D. BCPS, Keith Fester, Pharm.D., Jennifer McDermott (Walker), Pharm.D. BCPS, and Jenna Schefert, Pharm.D. for their clinical input.

Contributors All authors contributed to the conception, design, and acquisition of data for analysis and interpretation in the manuscript. All authors took part in drafting the manuscript, including critical revisions for intellectual content. All authors approved the final version for publication.

Competing interests None.

Ethics approval Columbia University Medical Center.

Provenance and peer review Not commissioned; externally peer reviewed.

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