Multifactorial Causes of Tacrolimus Errors: Confusion With Strength/Formulation, Look-Alike Names, Preparation Errors, and More Ensuring Safety of Recipes for Drug Compounding

Please, no more teaspoon dosing

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A recent string of errors associated with tacrolimus, an immunosuppressant used primarily to prevent rejection in transplant recipients, prompted ISMP to review the literature and analyze related events reported to the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) and the ISMP National Medication Errors Reporting Program (MERP). We found that tacrolimus has been involved in many reported errors during the past decade that have been caused by a wide variety of factors, the most common of which are described below.

Tacrolimus Availability

Tacrolimus is commercially available for oral use in the United States in 0.5 mg, 1 mg, and 5 mg capsules (immediate-release **PROGRAF** and generics, extended-release **ASTAGRAF XL**), and 0.75 mg, 1 mg, and 4 mg tablets (extended-release **ENVARSUS XR**). The drug is also available in 5 mg/mL, 1 mL ampuls (Prograf) for intravenous (IV) use after dilution only in patients who are unable to take oral medications, as anaphylactoid reactions have been reported with IV administration. Sublingual administration (off-label) of the immediate-release formulation (at approximately 50% of the oral dose) is suggested in some drug references (eg, Lexicomp) for patients unable to take oral medications. If an oral liquid formulation is needed, it must be compounded.

Types and Causes of Errors

Drug Strengths That Differ by a Factor of 10

Mix-ups between drug strengths that differ by a factor of 10 are a common type of dosing error among products available in 10-fold increments (eg, **ARIP**iprazole, 2 mg and 20 mg; warfarin 1 mg and 10 mg; predni**SONE** 5 mg and 50 mg; buprenorphine 75 µg and 750 µg; **EPINEPH**rine 0.1 mg/mL and 1 mg/mL). So, it is not surprising that many mix-ups have been reported between the 0.5 mg and 5 mg strengths of tacrolimus. Most of the reported errors involved dispensing and administration of the 5 mg strength instead of the 0.5 mg strength. These may have been precipitated by the unsafe practice of not including a leading zero (ie, .5 mg) when prescribing or displaying the 0.5 mg strength.

Some of the errors resulted in patient harm. For example, a nephrologist treating a patient who had been hospitalized with an elevated serum creatinine after a kidney transplant reported that the cause of the acute kidney injury was a tacrolimus overdose. The overdose was caused by a dispensing error in which the 5 mg capsules were provided instead of the 0.5 mg capsules. The patient had been taking 5 mg twice daily (10 mg) instead of 0.5 mg twice daily (1 mg) for approximately 1 month before hospitalization.

Various Release Formulations

Mix-ups between regular-release and extended-release tacrolimus formulations were another frequently observed theme during our review, again reflecting a common error type among the many drugs available in both conventional (immediate-release, regular-release) and modified (eg, delayed-release, extended-release) formulations.

ADVAGRAF, an extended-release tacrolimus product marketed outside of the United States by Astellas but later approved in the United States under the trade name Astagraf XL, was the drug most frequently involved in mix-ups with regular-release tacrolimus. More than 60 reports of errors with this drug were submitted to FDA by the manufacturer (FDA receives both foreign and domestic reports from manufacturers). Leading up

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to the approval of Astagraf XL in the United States, the manufacturer and FDA carefully assessed the error experiences with Advagraf to develop labeling and naming strategies to help mitigate confusion. For example, XL was added to the trade name Astagraf in the United States to help draw attention to its extended-release formulation.

However, we can still learn from these cases and others, as the way tacrolimus appeared on electronic prescribing system screens frequently contributed to these errors, as it often does in the United States. In one case, a physician mistakenly ordered “tacrolimus MR 0.5 mg capsules” when he intended to select “tacrolimus 0.5 mg” on the screen (“MR” means modified-release). When drugs are listed by their generic names, and different formulations exist, the eyes typically capture the name of the drug first, and then may miss any evidence that one may be selecting the wrong formulation.

Look-Alike Medication Names

ISMP has documented more than 800 confused drug name pairs that have been published in our newsletters. One name pair that we have recently been asked to consider including on our list of confused drug names is tacrolimus and tamsulosin, an α_1 blocker used to treat benign prostatic hyperplasia (and off-label to treat bladder outlet obstruction symptoms and distal ureteral calculi expulsion). Although the available strengths differ, we discovered that several mix-ups between tacrolimus 0.5 mg and tamsulosin 0.4 mg have been reported, some leading to patient harm.

For example, a liver transplant coordinator reported 2 incidences where outpatient pharmacies had dispensed tamsulosin 0.4 mg to patients who had been prescribed tacrolimus 0.5 mg. Tragically, both reported cases were believed to have contributed to the rejection of the transplanted liver. In another case, a patient had been hospitalized with symptoms of organ transplant rejection. During collection of a home medication list, a nurse noticed that the capsules in the patient’s vial of medication labeled as tacrolimus 0.5 mg were quite different in color than she expected. She contacted a pharmacist, who identified the capsules as tamsulosin 0.4 mg.

Confusion among brand names has been reported less frequently. In one case, it was discovered that a patient with a high tacrolimus serum level had been given Prograf 5 mg capsules, intended for another family member, instead of his prescribed **PROSCAR** (finasteride) 5 mg. Apparently, the Prograf had been placed in the patient’s dosing pill box by a family member in error instead of Proscar. Fortunately, the patient’s creatinine remained stable and he was not harmed by the error.

Confusion When Dispensing More Than One Strength for the Patient’s Dose

With variable tacrolimus dosing based on the patient’s weight, type of organ transplant, response to therapy, adjuvant immunosuppressants, and other factors, any of the available capsule

or tablet strengths might be needed to fill a prescription. However, the pharmacy may not stock all strengths, and/or several strengths of the drug may be needed to accommodate the patient’s total daily dose. This can lead to dosing confusion, particularly during the dispensing and administration phases of the medication-use process.

For example, dispensing errors have involved a mismatch between the total prescribed dose and the capsule or tablet strengths dispensed to provide each dose. In one case, the prescriber ordered tacrolimus 5 mg orally every 12 hours (10 mg daily). However, the pharmacy only stocked the 0.5 mg strength and a limited supply of the 1 mg strength. The prescription was mistakenly filled with the 0.5 mg capsules, with directions to take 2 capsules by mouth every 12 hours, along with 1 mg capsules, with directions to take 3 capsules by mouth every 12 hours. This resulted in the patient receiving only 8 mg of the drug daily.

Patient confusion is also a concern when various strength capsules or tablets are dispensed. For example, a postrenal transplant patient was prescribed tacrolimus 6 mg orally every 12 hours. The initial prescription was partially filled with 1 mg capsules, with directions to take 6 capsules for each dose every 12 hours, until the supply of 5 mg capsules could be ordered to lower the cost of the prescription medication. Once the 5-mg capsules arrived in the pharmacy, the remainder of the prescription was filled using 5 mg capsules along with 1 mg capsules to achieve each 6 mg dose. A pharmacist had placed a note on the bag containing the medication in the will-call area as a reminder to talk to the patient about the change in capsule strength and the new directions for use. However, the note was not noticed, and patient counseling never occurred.

Although new directions had been provided on the labels of the 2 newly dispensed vials, the patient combined all the capsules into the initial prescription vial. The patient then took 6 capsules in the morning and 6 at night, as indicated on the label instructions. A month later, a very high serum tacrolimus level was obtained. Inspection of the patient’s supply of tacrolimus showed the 2 strengths commingled in the vial, with the 1 mg capsules predominantly on the bottom (meaning the patient took mostly the 5 mg capsules each day, up to 60 mg daily).

Manufacturer Label Confusion

One of the extended-release formulations of tacrolimus, Astagraf XL, comes in a bottle with a label that has occasionally confused patients who were dispensed the product in the sealed manufacturer’s (Astellas Pharma US) container. In 1 case, a patient who was previously taking immediate-release tacrolimus 3 mg every 12 hours had just been converted to 6 mg of the extended-release product Astagraf XL daily. The new prescription for Astagraf XL had been filled using sealed manufacturers’ bottles of the 1 mg capsules, onto which pharmacy labels had been applied, directing the patient to take 6 capsules daily. However, 1 week later, lab work showed that the tacrolimus trough had dropped to an

Figure 1. “ONCE-DAILY” has been misinterpreted by patients as meaning take only 1 capsule per dose, rather than following the directions on the prescription label.

undetectable level. The patient had been taking only 1 mg of the drug daily, not the 6 mg dose. Instead of following the correct directions on the pharmacy label, the patient had been following what she thought were directions for use on the manufacturer’s label that stated, “ONCE-DAILY,” listed right below the drug name and dose (Figure 1).

Compounding Errors

Errors during the compounding of tacrolimus oral liquid formulations were also reported, including 10-fold overdoses and underdoses when the incorrect capsule strength was used for preparation (ie, 0.5 mg instead of 5 mg), inappropriate substitution of a generic product for a brand name product, incorrect preparation of the suspension, and incorrect storage conditions. In 2 of the cases, a tacrolimus suspension was created using the wrong suspending agent. Tacrolimus is poorly soluble in water, so it is recommended to compound an oral suspension using Ora-Plus and Simple Syrup.¹ Ora-Plus contains suspending agents, which prevent drug particles from aggregating and settling. This allows for the creation of a homogeneous suspension and uniform concentration. One of the patients who received an incorrectly compounded suspension, for which Ora-Plus was not used, experienced problems with extreme fluctuations in his tacrolimus levels. The outcome for the second patient is unknown.

Safe Practice Recommendations

Standardize Compounding Concentrations and Recipes

If oral liquid formulations of tacrolimus must be compounded, establish a standard concentration for pediatrics

and adults and provide staff with clear recipes that include the oral suspension vehicle (eg, Ora-Plus and Simple Syrup, not water) to use along with detailed directions for preparing the suspension. A Michigan statewide initiative has created recipes with standardized concentrations for pediatric oral compounded liquids.² These recipes, including one for tacrolimus, are freely available at: <http://www.mipedscompounds.org/standard-formulation>. They include directions for preparation, data on stability, and storage information. The American Society of Health-System Pharmacists is also currently working on a project to provide standardized concentrations for intravenous and oral liquid medications (<https://www.ashp.org/-/media/assets/pharmacy-practice/s4s/docs/s4s-ashp-oral-compound-liquids.ashx>).

Avoid Leading Decimal Point Doses

Always include a leading zero when expressing tacrolimus doses less than 1 mg on computer screens, device screens, pharmacy labels, shelf markers, and other paper and electronic formats. Whenever possible, avoid fraction doses greater than 1 mg by rounding the dose to the nearest whole number.

Monitor Patients Frequently

Tacrolimus has a narrow therapeutic index, so trough levels should be obtained for monitoring to prevent organ rejection (from levels that are subtherapeutic) and nephrotoxicity (from supratherapeutic levels).

Use Brand Names

Display the brand name of tacrolimus extended-release formulations (ie, Astagraf XL, Envarsus XR) on drug ordering and verification screens to help differentiate these formulations from regular-release tacrolimus (ie, Prograf, generics). When prescribing regular-release tacrolimus, use only the brand or generic name, *without* any modifiers such as “IR” for immediate-release.

Add to Look-Alike List

Consider including tacrolimus and tamsulosin on your organization’s look-alike drug name list, and increase the situational awareness of staff regarding the risk of potential mix-ups. (The drug name pair will be added to *ISMP’s List of Confused Drug Names* with the next update.)

Stock Needed Strengths

Stock all available strengths of tacrolimus that might be prescribed in your facility and use the simplest single strength or combination of strengths to match the patient’s prescribed dose when dispensing the product.

Educate Prior to Discharge

Educate patients regarding the directions for taking the correct dose of tacrolimus, how to manage dose changes, and the importance of monitoring drug levels. Ensure that patients can repeat back the specific directions for taking each prescribed dose. Provide patients with information about the common types of errors that may happen with tacrolimus and how to prevent and detect these errors.

Conduct Outpatient Counseling

Establish a fail-safe mechanism to ensure that patients are counseled when picking up prescriptions for tacrolimus, particularly for the first prescription and whenever the dose, dosage strength, or formulation is changed.

Recommendations for FDA and Drug Companies

We call upon FDA and drug companies to avoid the availability of doses in 10-fold increments whenever possible. We also call upon the manufacturer of Astagraf XL (Astellas) and FDA to evaluate whether labeling changes are necessary given consumer confusion with the term “ONCE-DAILY.”

ISMP thanks Staley Lawes, PharmD, BCPS, FISM, for her contribution to this article.

Ensuring Safety of Recipes for Drug Compounding

During a biannual update of drug compounding recipes, one of the pharmacy's recipes for a cloNIDine formulation was updated incorrectly. Based on information found on an online pharmacy help site, the hospital's recipe for preparing a cloNIDine suspension was updated. The new recipe was intended to prepare a 0.1 mg/mL suspension; however, the directions from the previous recipe were left in place accidentally, which correlated with a 0.01 mg/mL concentration. Thus, the final concentration using the updated recipe would be 10-fold lower than the recipe indicated.

The recipe change was made by a pharmacist without an independent double check, which was the pharmacist's usual practice but not a required element of the recipe updating process. The error led to administering a 10-fold underdose to an infant in a neonatal intensive care unit.

Errors made in drug compounding recipes can affect multiple patients, so it is important to always have a second individual perform an independent double check of all the information in listed recipes. The pharmacy has now instituted this as a required practice to ensure that all parts of the recipes match, including the concentration it yields. Fortunately, only one patient received the incorrectly prepared suspension after the recipe error was made. Based on a chart review, a pharmacist's consult note, and follow-up after 4 months, there was no apparent harm from the underdosing that occurred with this patient.

Please, No More Teaspoon Dosing

Some community or ambulatory care pharmacists mistakenly believe it is helpful to “translate” prescription liquid dosing instructions for patients from metric (eg, milliliters [mL]) to household measures (eg, teaspoon). When they receive a prescription with dosing in mL, they change it to teaspoon dosing or list both teaspoons and mL (in parentheses) on the label, believing most consumers are more familiar with household measures than metric dosing.

Unfortunately, pharmacy staff have inadvertently typed the number of mL in the teaspoons field, sometimes resulting in patient hospitalization. A close call occurred recently when **AUGMENTIN ES-600** (amoxicillin and clavulanate) suspension was prescribed for a child with otitis media. When the child's mother picked up the medication, a pharmacist provided counseling about how often to give each dose, to discard the medication in 10 days, and that it may cause diarrhea. However, the actual volume required for each dose was not discussed. Later, when the child's parent read the label at home, it said, “Give 5 teaspoons by mouth twice daily for 10 days.” Wondering if this was accurate, she logged into an electronic patient portal to view a summary of her child's office visit and saw that the dose should have been 5 mL, not 5 teaspoons.

Mix-ups between mL and teaspoon have been a long-standing problem, first discussed by ISMP in this publication in 2000. In recent years, there has been considerable movement toward the use of the metric system for all over-the-counter (OTC) and prescription liquid medications. Most oral dosing devices now display a mL scale, some exclusively. Thus, “translating” mL doses to teaspoons, or listing both teaspoons and mL on labels, should cease, as it is not helpful to patients and creates confusion. The National Council for Prescription Drug Programs (NCPDP) published *Recommendations and Guidance for Standardizing the Dosing Designations on Prescription Container Labels of Oral Liquid Medications* in 2014, calling upon stakeholders, particularly pharmacy leadership, to adopt mL dosing as the standard (<https://www.ncdp.org/NCPDP/media/pdf/wp/DosingDesignations-OralLiquid-MedicationLabels.pdf>). This is needed for all patient instructions on pharmacy labels and in computer systems. Also, always provide an appropriate metric dosing device and ensure that patients or caregivers know how to measure the dose in mL, using “teach back” to confirm understanding.

References

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