

Nurse AdviseERR®

Educating the Healthcare Community About Safe Medication Practices

Severe harm and death associated with errors and drug interactions involving low-dose methotrexate

For patients with severe, disabling rheumatoid arthritis (RA), oral methotrexate is often the preferred disease-modifying antirheumatic drug, unless it is specifically contraindicated.^{1,3} Compared to dosing for antineoplastic indications, methotrexate for RA is administered once weekly as low-dose therapy.³ According to official prescribing information, the recommended starting dose is a single oral dose of 7.5 mg once weekly or divided oral doses of 2.5 mg every 12 hours for 3 doses per week. The dosing schedule may be adjusted to achieve optimal response, with doses up to about 25 mg weekly.

Since early 1996 and as recently as May 2015, harmful or fatal errors with low-dose oral methotrexate have been reported to ISMP and published in more than 50 of our newsletters. Most errors involved accidental daily dosing of oral methotrexate that was intended for weekly administration. In 2004, we published a study of methotrexate errors over a 4-year period that resulted in 25 deaths and 48 serious outcomes, many due to daily dosing.⁴ Our sister organization, ISMP Canada, has also received multiple reports of severe harm or death in patients taking low-dose methotrexate for RA and other autoimmune diseases. Two of the three recent incidents highlighted in the September 30, 2015, *ISMP Canada Safety Bulletin*⁵ involved patients who were taking no more than 20 mg of methotrexate weekly, yet they died of severe methotrexate toxic effects due to other risk factors, including drug interactions that increased the serum concentration of methotrexate. The third event is very similar to many other methotrexate errors, with patients taking the medication daily instead of weekly. The findings and recommendations from these three selected cases reported to ISMP Canada are shared here to highlight system-based opportunities to further improve safety with low-dose methotrexate therapy.

Medication Incidents

Incident 1. A patient with renal dysfunction and hypoalbuminemia was experiencing worsening RA symptoms. To address these symptoms, the patient decided to double his weekly methotrexate dose from 10 mg to 20 mg, a change that happened to coincide with the end of a treatment course of amoxicillin for an infection. The next day, the rheumatologist prescribed an additional disease-modifying antirheumatic drug, leflunomide. Within a week, the patient was admitted to the hospital with pancytopenia, and despite aggressive treatment, he died. The patient's baseline risk factors for methotrexate toxicity, the intentional doubling of the methotrexate dose by the patient without the prescriber's knowledge, and drug interactions related to the concomitant use of amoxicillin and leflunomide with methotrexate, all contributed to the development of severe toxic effects.

Incident 2. An elderly patient with RA was admitted to the hospital to treat a fracture. In the hospital, the patient's weekly dose of methotrexate 20 mg was continued and diclofenac was started. The patient developed renal failure (possibly from diclofenac use) and pancytopenia, and subsequently died. It was later determined that the severe interaction between methotrexate and diclofenac was not addressed when diclofenac was initiated, possibly because of the lack of interaction specificity (i.e., presence of numerous alerts) when the order was entered, and an incorrect assumption that the patient had been taking diclofenac at home prior to hospitalization. The patient died as a result of methotrexate toxicity.

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check it out

Consider the following recommendations to improve the safety of low-dose methotrexate therapy.

Computer System Administrators

- Design the computer order entry system for both pharmacy and physicians to default to a weekly (rather than daily) dosing schedule for oral methotrexate orders.¹⁵
- Require a hard stop verification and mandatory entry of an appropriate oncologic indication when the clinician selects a daily schedule for oral methotrexate orders.¹⁵
- In hospital systems and electronic medication administration records (eMARs), link methotrexate order entry and verification to laboratory results (e.g., CBC, serum creatinine, liver enzymes), to prompt review of renal function and other monitoring parameters by pharmacists, nurses, and prescribers.
- Include a robust drug–drug and drug–disease interaction module for methotrexate, with links to laboratory results where possible, so prescribers and pharmacists can effectively evaluate the potential for toxic effects.

Prescribers

- Before initiating oral methotrexate therapy, screen for risk factors by obtaining baseline values, including CBC, chest radiograph, and indicators of liver and renal function, to identify patients for whom methotrexate is not a safe therapy; an electronic health record (EHR) that prompts for this information is an asset.
- Repeat CBC, liver function (especially albumin level), and serum creatinine every 2-4 weeks for 3 months after initiating methotrexate and every 8-12 weeks thereafter for patients with RA.²

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Incident 3. Methotrexate 15 mg once weekly was prescribed for treatment of an autoimmune disorder in an elderly patient. The community pharmacy dispensed a 3-month quantity of medication, but provided instructions on the label to take 15 mg (6 x 2.5 mg tablets) once daily. The error was discovered during patient counseling with a pharmacist when the patient requested a refill 3 weeks later. The error resulted in severe harm, which led to a long hospital stay, including treatment with the rescue agent leucovorin calcium.

Background

Some of the most common toxic effects with low-dose methotrexate are gastrointestinal, hematological, and hepatic.⁶ Severe adverse effects are more common with the higher doses of methotrexate used for antineoplastic indications. However, hematological toxicity is reported to occur in up to 3% of patients treated with long-term, low-dose methotrexate for RA and other autoimmune disorders.⁷ Severe toxic effects, such as myelosuppression, pulmonary complications, central nervous system toxicity, hepatotoxicity, and mucositis, have led to hospital admissions and even death.⁸ Prescribing guidelines recommend obtaining a complete blood count (CBC), creatinine levels, and liver enzymes before methotrexate is initiated.^{1,2} It is also recommended that these tests be repeated at regular intervals for the duration of therapy² and that practitioners address any rapid, unusual changes in these parameters, as well as any consistent upward or downward trends.⁹

Hypoalbuminemia, renal dysfunction, and certain concomitant medications, including nonsteroidal anti-inflammatory drugs and proton pump inhibitors, all increase a patient's risk of developing toxic effects from methotrexate.⁸ Interacting medications are often prescribed with methotrexate and can be used together safely, provided regular monitoring takes place. To reduce gastrointestinal and hepatic toxic effects, folate supplementation may be recommended for patients who are receiving low-dose methotrexate.¹⁰

ISMP has identified methotrexate as a high-alert medication¹¹ in both hospital and community settings, even when used for non-oncologic purposes such as RA. As with all high-alert medications, there is a heightened risk of significant patient harm when this drug is used in error. ISMP and ISMP Canada have both previously published concerns about inadvertent daily, rather than weekly, administration of methotrexate.¹²⁻¹⁴ Since 2014, a bundle of three strategies to help prevent these types of errors have been highly promoted as one of the *ISMP Targeted Medication Safety Best Practices for Hospitals*—using a weekly dosage regimen default when oral methotrexate orders are entered, requiring a hard stop verification of an appropriate oncologic reason for all daily oral methotrexate orders, and educating patients and/or family members prior to discharge.¹⁵ While we have seen some significant gains with implementing these strategies since 2014, less than half of hospitals participating in a recent survey reported full compliance.

This article highlights the importance of initial screening for risk factors and ongoing monitoring for methotrexate toxicity. Even when this drug is prescribed at low doses, extra safeguards are needed when it is prescribed, dispensed, and administered, regardless of the setting, dose, or indication for use. While severe harm and fatalities have occurred during hospitalization, many of the adverse outcomes occurred after discharge. It is important for hospitals to ensure that the proper dosage regimen is administered during hospitalization, and to implement effective, proactive strategies so the proper dosage regimen is maintained after discharge. Likewise, it is imperative for outpatient pharmacists to ensure correct instructions are on the label of methotrexate prescription bottles, that patients are counseled, and that they understand the directions for use. Healthcare providers are urged to implement the recommended system safeguards listed in the **check it out!** column on the right, starting on page 1, to improve the safety of low-dose methotrexate therapy.

ISMP gratefully acknowledges ISMP Canada for providing this article, which was adapted from the September 30, 2015 article in the *ISMP Canada Safety Bulletin*.⁵

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- Screen for Hepatitis B and C, and in high-risk patients, test for HIV, as recommended in some guidelines, prior to initiating methotrexate.¹
- Consider folate supplementation for patients starting methotrexate therapy.
- When prescribing methotrexate for weekly administration, specify a particular day of the week in the directions to reduce the risk that the patient will receive instructions for daily use. Avoid Monday as the day to take the weekly dose, since this might be misread as “morning”
- Limit the prescription quantity to be dispensed to a 4-week (28-day) supply.
- Ask patients about their use of specific prescription and over-the-counter medications that could increase the risk for methotrexate toxicity.
- When a dosing error is discovered, ensure the patient receives immediate medical attention. Although serum levels of methotrexate can be measured, they are not an accurate predictor of either the degree of toxicity or the outcome for the patient, because of the drug's pharmacokinetic and pharmacodynamic properties.^{8,16}

Nurses and Pharmacists

- If folate has not been prescribed, follow up with the prescriber to determine if initiation of this supplement is desired.
- Ensure that every patient receives education or counseling when discharged on oral methotrexate or when filling a prescription for oral methotrexate.
- Double check all printed medication lists and discharge instructions to ensure that they indicate the correct dosage regimen for oral methotrexate prior to providing them to the patient.
- Ensure that the process for providing education or counseling for oral methotrexate includes clear verbal **AND** written instructions. Ideally, EHRs should automatically generate continued on page 3—**check it out** >

> **Methotrexate**—continued from page 2**References**

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FDA Advise-ERR:**Avoid using the error-prone abbreviation, TPA**

The US Food and Drug Administration (FDA) and ISMP continue to receive reports of medication errors involving wrong drug errors between **ACTIVASE** (alteplase) and **TNKASE** (tenecteplase). The reported errors are related to the use of the abbreviation, “t-PA” or “TPA.” In October 2015, we wrote about a wrong drug error where a nurse typed “t” in the automated dispensing cabinet and selected tenecteplase on the screen instead of alteplase because “alteplase was commonly referred to as tPA.”¹

Activase is a tissue plasminogen activator that FDA approved in 1987 for use in the management of acute myocardial infarction and later for acute ischemic stroke and pulmonary embolism. TNKase, also a tissue plasminogen activator, was FDA approved in 2000 for the management of acute myocardial infarction only. Because Activase was the first tissue plasminogen activator approved, it has commonly been referred to as “t-PA” or “TPA” by healthcare providers. Unfortunately, the use of the abbreviations “t-PA” or “TPA” has led to confusion with the use of shorthand “TNK” for TNKase, leading to wrong drug errors.

Two cases of wrong drug errors resulting in mix ups between Activase and TNKase were initially reported in the May 29, 2003, ISMP acute care newsletter.² The errors stemmed from medication orders that were written as an initial dose of “t-PA 8 mg IV” and “t-PA 7 mg IV” for acute ischemic stroke. Nurses involved in these cases assumed t-PA was shorthand for TNKase, and gave patients 8 mg and 7 mg of TNKase, respectively, instead of the intended drug, Activase.

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ate this written information upon discharge for patients receiving oral methotrexate.

- Specifically review the dosing schedule with patients, explain that taking extra doses is dangerous (and why), and discuss that the medication is not to be used “as needed” for symptom control.
- Have the patient repeat back the instructions to validate that he or she understands the dosing schedule and toxicities of the medication if taken more frequently than prescribed.
- When available, dispense low-dose methotrexate for non-oncologic indications as a dose pack (e.g., Rheumatrex), which helps guide patients to take the proper dose weekly. (Such manufacturer’s packaging should be required.)
- Provide all patients with a copy of the free ISMP high-alert medication consumer leaflet on oral methotrexate (found at: www.ismp.org/AHRO/default.asp).¹⁷
- Emphasize the need to adhere to the prescribed dose and to obtain all the monitoring tests ordered by the prescriber as scheduled.
- Ask the patient or caregivers about the use of specific prescription and over-the-counter medications that may interact with methotrexate.

SAFETY wire

Reminder: Eliminating ratio expressions. According to USP39-NF34 (The US Pharmacopeia [USP] and The National Formulary [NF]), which became official on May 1, 2016, ratio expressions on single entity drug products are no longer acceptable. Manufacturers should only display **EPINEPHrine** 1:1,000 injection as 1 mg/mL, and 1:10,000 must only be displayed as 0.1 mg/mL. The total content per volume in the container will be prominently labeled along with the per mL content. Ratio expressions for neostigmine and isoproterenol are also unacceptable. Some manufacturers have been making the change for a while or have already

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Since the initial reports, we continue to receive cases of confusion between these two products. In 2014, a patient who experienced an ischemic stroke received TNKase instead of the intended drug, Activase. Although it was unclear whether the abbreviation “tPA” was used in the order, the reporter attributed the wrong drug error to confusion between the abbreviations “TNK” and “TPA” because Activase was frequently called “TPA.”

Wrong drug errors between TNKase and Activase can be attributed to the fact that both have similar settings of use (emergency departments, critical care areas) and patient populations (cardiovascular events). However, the use of the abbreviation “TPA” is a significant contributing factor that led to the wrong drug errors. The abbreviations “TPA,” “tPA,” and “TNK” are listed on the Drug Name Abbreviation section of the ISMP List of *Error-Prone Abbreviations, Symbols, and Dose Designations*.³ Despite ISMP’s recommendations⁴ to avoid abbreviating drug names, the continued use of the abbreviation “TPA” has led to confusion between Activase and TNKase. Likewise, the continued use of the abbreviation “TPA” may also stem from frequent but inappropriate use of the abbreviations “tPA,” “TPA,” and “rt-PA” in published medical literature when referring specifically to Activase.⁵

The consequences of giving patients with ischemic stroke TNKase instead of Activase include the failure to administer a drug known to be effective (Activase) and the potential for an overdose—the dose for Activase (0.9 mg/kg)⁶ is often higher than the maximum labeled TNKase dose for acute myocardial infarction. An overdose of TNKase may increase the risk of intracranial hemorrhage, retroperitoneal bleed, extended hospitalization, and death.

Since Activase, TNKase, and **RETAVERSE** (reteplase), are all tissue plasminogen activators, referring to any one of these products as “TPA” may lead to confusion regarding the intended product. Therefore, we recommend the following:

1. Never use abbreviations for drug names.
2. Do not use the abbreviation “TPA.” Refer to all three tissue plasminogen activators by their brand names (Activase, TNKase, Retavase), established/generic names (alteplase, tenecteplase, reteplase), or both in all verbal and written communications.
3. Do not use “TNK” as an abbreviation for TNKase.
4. Remove the abbreviation “TPA” and “TNK” from all standardized order sets, computerized provider order entry screens, and treatment protocols to avoid confusion.
5. Since Activase, but not TNKase or Retavase, is approved for use in the management of ischemic stroke and pulmonary embolism, prescribers should state the indication on prescription orders to help ensure the correct drug is ordered and dispensed.
6. Consider the use of alerts for TNKase in electronic prescriber order entry systems and/or automatic dispensing cabinets (e.g., “Warning: Frequently confused with Activase [alteplase], verify the correct drug for the appropriate indication”).

An FDA video on this topic is available at: www.medscape.com/viewarticle/850514.

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begin conversion (**Figure 1**), but complete inventory turnover will likely take some time. Still, it’s not too early to let practitioners know about the changes, and encourage them to begin using only metric dosing. Product labels currently express the strength both ways. Ratio



Figure 1. Hospira’s EPINEPHrine ampul label before (left) and after (right) the change to metric only.

expressions are a known cause of errors (www.ismp.org/sc?id=1718), and continued prescribing in terms of a ratio expression, after product labels no longer mention that, could lead to confusion and calculation errors.

Be sure to educate staff who continue to use ratio expressions. Review order sets, policies, procedures, codes carts, and other emergency kit listings, and all databases that may need to be changed. Drug storage labels should also communicate strengths in metric weights to avoid confusion. The ratio expression for local anesthetics that have more than one ingredient, such as lidocaine 1% and **EPINEPH**rine 1:100,000 injections, will retain ratio expressions for the **EPI-NEPH**rine component because a decimal notation for such a low strength could easily be misread.

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