Severe Harm and Death Associated With Errors and Drug Interactions Involving Low-Dose Methotrexate

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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 the full 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 three doses per week. The dosing schedule may be adjusted to achieve optimal response, with doses up to about 25 mg weekly.

Since early 1996, harmful or fatal errors with low-dose oral methotrexate have been reported to the Institute for Safe Medication Practices (ISMP) and published in more than 50 of its newsletters. Most errors involved accidental daily dosing of oral methotrexate that was intended for weekly administration. In 2004, ISMP published a study of methotrexate errors over a four-year period that resulted in 25 deaths and 48 serious outcomes, many due to daily dosing.[4] Its 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 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 for treatment of a fracture caused by a fall. While in the hospital, the patient's weekly dose of methotrexate 20 mg was continued and diclofenac was started. The patient developed renal failure (possibly precipitated by diclofenac use) and pancytopenia, and subsequently died. It was later determined that the known 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 including noncritical interactions) when the order was initially 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.

Incident 3. Methotrexate 15 mg once weekly was prescribed for treatment of an autoimmune disorder in an elderly patient. The community pharmacy dispensed a three-month quantity of medication, but provided instructions on the label to take 15 mg (six 2.5-mg tablets) once daily. The error was discovered during patient counseling with a pharmacist when the patient requested a refill three 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 a low-dose regimen of methotrexate are gastrointestinal, hematologic, and hepatic.[6] Severe adverse effects are more common with the higher doses of methotrexate used for antineoplastic indications. However, hematologic 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), and creatinine and liver enzyme levels, before methotrexate is initiated.[1,2] In addition, it is recommended that measurement of these parameters be repeated at regular intervals for the duration of therapy[2] 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 develop-

ing 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 medication[11] in both hospital and community settings, even when used for nononcological 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 has 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 oncological reason for all daily oral methotrexate orders, and educating patients and/or family members prior to discharge.[15]

SAFE PRACTICE RECOMMENDATIONS

The following considerations are suggested for drug-related computer software administrators, prescribers, pharmacists, and nurses to reduce the risk of incidents similar to those described above.

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 oncological indication when the clinician selects a daily schedule for oral methotrexate orders.[15]
- In hospital systems and electronic medication administration records, 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.
- For computer systems lacking some of the above functionalities, work with the software vendors to implement these safety features.

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 testing every two to four weeks for three months after initiating methotrexate and every eight to 12 weeks thereafter for patients with RA.[2]
- Screen for hepatitis B and C, and in high-risk patients, test for human immunodeficiency virus, 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 because this might be misread as "morning."
- Limit the prescription quantity to be dispensed to a four-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]

Pharmacists

- Create a forcing function to ensure that every oral methotrexate prescription is reviewed with the patient or a family member prior to discharge from the hospital and when a prescription is presented or refills are processed in a community pharmacy.
- If folate has not been prescribed, follow up with the prescriber to suggest initiation of this supplement.
- Ensure that any drug interaction alerts generated during order entry and verification are communicated to and resolved with the prescriber and/or the patient when indicated.
- When possible, dispense only a four-week supply of methotrexate at a time.
- When available, dispense low-dose methotrexate for nononcological indications as a dose pack (e.g., Rheumatrex, Dava Pharmaceuticals), which helps guide patients to take the proper dose weekly. (Such manufacturer packaging should be required.)

Nurses and Pharmacists

- 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 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 discuss that the medication is not to be used "as needed" for symptom control.

continued on page 248

continued from page 192

- 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.
- Provide all patients with a copy of the free ISMP high-alert medication consumer leaflet on oral methotrexate (available at: www.ismp.org/AHRQ/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.

CONCLUSION

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. Methotrexate is a high-alert drug, and extra safeguards are needed whenever 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 have occurred after discharge. It is important for hospitals not only to ensure that the proper dosage regimen is administered during hospitalization, but also to implement effective proactive strategies so that the proper dosage regimen is maintained after discharge. Likewise, it is imperative for outpatient pharmacists to ensure that correct instructions are on the label of methotrexate prescription bottles, that patients are counseled, and that they understand the directions for use. Health care providers are urged to implement these recommended system safeguards to improve the safety of low-dose methotrexate therapy.

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REFERENCES

1. Bykerk VP, Akhavan P, Hazlewood GS, et al. Canadian Rheumatology Association recommendations for pharmacological management of rheumatoid arthritis with traditional and biologic disease-modifying antirheumatic drugs. *J Rheumatol* 2012;39(8):1559–1582.
2. Saag KG, Teng GG, Patkar NM, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum* 2008;59(6):762–784.
3. Singh JA, Furst DE, Bharat A, et al. 2012 update of the 2008 American College of Rheumatology (ACR) recommendations for the use of disease-modifying antirheumatic drugs and biologics in the treatment of rheumatoid arthritis (RA). *Arthritis Care Res* 2012;64(5):625–639.
4. Moore TJ, Walsh CS, Cohen MR. Reported medication errors associated with methotrexate. *Am J Health Syst Pharm* 2004;61(13):1380–1384.
5. ISMP Canada. Severe harm and deaths associated with incidents involving low-dose methotrexate. *ISMP Canada Safety Bulletin* 2015;15(9):1–5.
6. Salliot C, van der Heijde D. Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: a systematic literature research. *Ann Rheum Dis* 2009;68(7):1100–1104.
7. Lim AY, Gaffney K, Scott DG. Methotrexate-induced pancytopenia: serious and under-reported? Our experience of 25 cases in 5 years. *Rheumatology (Oxford)* 2005;44(8):1051–1055.
8. Kivity S, Zafrir Y, Loebstein R, et al. Clinical characteristics and risk factors for low-dose methotrexate toxicity: a cohort of 28 patients. *Autoimmun Rev* 2014;13(11):1109–1113.
9. Chakravarty K, McDonald H, Pullar T, et al. BSR/BHPR guideline for disease-modifying antirheumatic drug (DMARD) therapy in consultation with the British Association of Dermatologists. *Rheumatology (Oxford)* 2008;47(6):924–925.
10. Shea B, Swinden MV, Ghogomu ET, et al. Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis. *J Rheumatol* 2014;41(6):1049–1060.
11. Institute for Safe Medication Practices. ISMP high-alert medications. 2011, 2014. Available at: www.ismp.org/sc?id=624. Accessed February 19, 2018.
12. ISMP Canada. Incidents of inadvertent daily administration of methotrexate. *ISMP Canada Safety Bulletin* 2008;8(2):1–3.
13. Blinova E, Volling J, Koczmara C, Greenall J. Oral methotrexate: preventing inadvertent daily administration. *Can J Hosp Pharm* 2008;61(4):275–277.
14. ISMP. Small effort, big payoff… automated maximum dose alerts with hard stops. *ISMP Medication Safety Alert* 2013;18(19):1–4.
15. Institute for Safe Medication Practices. 2014-2015 targeted medication safety best practices for hospitals. 2014. Available at: www.ismp.org/sc?id=625. Accessed February 19, 2018.
16. Inoue K, Yuasa H. Molecular basis for pharmacokinetics and pharmacodynamics of methotrexate in rheumatoid arthritis therapy. *Drug Metab Pharmacokinet* 2014;29(1):12–19.
17. Institute for Safe Medication Practices. Read this important information before taking: methotrexate. 2012. Available at: www.ismp.org/sc?id=626. Accessed February 19, 2018.

The reports described in this column were received through the ISMP Medication Errors Reporting Program (MERP). Errors, close calls, or hazardous conditions may be reported on the ISMP website (www.ismp.org) or communicated directly to ISMP by calling 1-800-FAIL-SAFE or via email at ismpinfo@ismp.org. ■