**Erroneous Dosing of Oral Methotrexate**

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**PROBLEM:** The use of methotrexate is well established in oncology. For many years, it has also been prescribed in low doses for immunomodulation in rheumatoid arthritis, asthma, psoriasis, inflammatory bowel disease, myasthenia gravis, and inflammatory myositis, and these uses are continually increasing. Unfortunately, the perils of low-dose oral methotrexate are clearly evident from the dozens of fatalities that have been reported when this cytotoxic agent is prescribed for these alternative conditions.

When oral methotrexate is used for some of these purposes, the dose is administered once weekly or twice a week. However, mistakes have been all too frequent, because relatively few medications are administered on a weekly basis. Clinicians and patients are much more familiar with daily dosing.

In one reported case submitted to the Institute for Safe Medication Practices, a prescription for the vasodilator minoxidil (e.g., Loniten®, Pfizer) at 2.5 mg four times daily was dispensed as methotrexate for an 86-year-old patient. In another instance, a physician prescribed methotrexate 15 mg daily rather than the weekly dose for a 79-year-old patient. The patient received nine doses before the error was discovered. The patient later died.

Another patient died after he misunderstood the directions for the agent’s use and took methotrexate 2.5 mg every 12 hours for six consecutive days instead of 2.5 mg every 12 hours for three doses each week. Still another patient died after he misread the prescription on the container and took 10 mg every morning instead of every Monday.

Errors have also occurred in hospitals. In one case, the physician had properly recorded that a patient had been taking methotrexate 7.5 mg weekly as an outpatient. However, when the physician prescribed three 2.5-mg tablets weekly, it was transcribed incorrectly as three times daily. Upon the patient’s transfer to a different unit, the dose was transcribed incorrectly as three times weekly. In each case, the errors were detected during a pharmacy review of the order before the patient could be harmed.

Similar errors have been reported overseas. In Australia, a patient took extra doses of methotrexate, as needed, to relieve arthritic symptoms. Three elderly patients took the medication daily despite clearly written instructions to take it weekly. Two other cases involved incorrect transcription of the dosing schedule with hospitalized patients. Three of the six patients died as a result of the errors.

**SAFE PRACTICE RECOMMENDATION:** Because of the number of fatalities from errors with oral methotrexate, clinicians should consider it a “high-alert” medication. Several measures can help reduce the risk of mistakes when oral methotrexate is prescribed:

1. Alerts should be built into electronic prescribing systems and pharmacy computers to warn clinicians whenever doses of oral methotrexate have been entered. The alert can also be used to remind the staff to check the indication with patients in retail settings.

2. The electronic system should be configured in such a way as to avoid defaulting to a daily dosing schedule.

3. Pharmacists should conduct a prospective drug utilization review (DUR) before dispensing oral methotrexate to determine its indication for use, to verify proper dosing, to confirm the correct dosing schedule on medication administration records (MARs) and prescription labels, to instruct the staff and patients, and to promote appropriate patient monitoring.

4. A system should be established to ensure that outpatients receive counseling when they pick up new prescriptions and refills of this drug. For example, the bag can be marked with a red flag to alert the clerical staff that counseling is mandatory, not optional.

5. Patients should receive clearly written instructions that name a specific day of the week for taking methotrexate tablets. When possible, Monday should be avoided because it can be misread as “morning.”

6. Instructions should be typed in large print to assist elderly patients with poor eyesight.

7. Patients should be advised to contact their physicians if they forget to take a dose, and they should be informed that a flare-up of the disease is unlikely with one missed dose.

8. Written drug information leaflets should be given to patients. The leaflets should contain clear advice about the weekly dosage schedule, not a daily dosing schedule.

9. It should be explained to patients that taking extra doses is dangerous.

10. Feedback from patients should be encouraged to ensure that they understand the weekly dosing schedule and that the medication should not be used “as needed” for symptom control.

11. Help can be solicited from a responsible caregiver if patients appear to have cognitive or severe sensory difficulties.

12. Prescribing oral methotrexate as a dose pack (e.g., Rheumatrex® [Lederle/Wyeth]) helps to reinforce the weekly dosing schedule.

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