Oral Methotrexate: Preventing Inadvertent Daily Administration

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BACKGROUND

Methotrexate, a folic acid antagonist, is classified as a cytotoxic antimetabolite. It has been used for many years in the treatment of various types of cancer and is also used to treat autoimmune disorders such as rheumatoid arthritis and psoriasis.[1] In the treatment of autoimmune conditions, methotrexate is typically given once weekly, but numerous errors involving methotrexate that has been inadvertently prescribed, dispensed, administered, or taken once daily have been reported worldwide.[2-5] Because of the immunosuppressive properties that make this drug so valuable in the treatment of autoimmune disorders, daily dosing can lead to serious patient harm. Daily administration, even if doses are low, can cause severe adverse effects involving the bone marrow, liver, and other organ systems.[1,6] Recently, a cluster of cases were reported to ISMP Canada in which methotrexate was taken or administered daily rather than weekly, resulting in serious adverse effects or death.[3] This article includes (with permission) excerpts from a recent issue of the *ISMP Canada Safety Bulletin* describing inadvertent daily administration of methotrexate,[3] along with case summaries from other publications. This article aims to raise awareness of the consequences of daily instead of weekly dosing of methotrexate, to highlight some of the contributing factors that have led to the improper use of methotrexate, and to suggest strategies to enhance the safety of methotrexate use.

CASE EXAMPLES FROM ISMP CANADA

The following examples were voluntarily reported to ISMP Canada by Canadian health care professionals and are quoted from a recent issue of the *ISMP Canada Safety Bulletin*.[3]

An elderly patient was taking methotrexate 5 mg orally once per week and prednisone 5 mg twice daily for rheumatoid arthritis. After an accidental fall and fracture requiring convalescence, the patient inadvertently received methotrexate 5 mg daily. About 2 weeks later, the patient was admitted to hospital with pancytopenia and a pulmonary infection. The patient died several days later because of complications.

Methotrexate, to be taken once weekly, was prescribed for an adult patient with a type of vasculitis. Although the prescription label stated the correct instructions in the patient's preferred language, the patient took the methotrexate daily for 2 weeks (the patient had received over 3 months' supply of the medication). The patient presented to an emergency

department and was admitted for treatment of methotrexate toxicity. Fortunately, the patient gradually recovered and was discharged home.

An adult patient was prescribed methotrexate 7.5 mg orally per day for 2 weeks then 10 mg per day for the treatment of an autoimmune disorder. The patient presented to an emergency department with pancytopenia and oral thrush. The patient was admitted for treatment, which included folinic acid to counteract the methotrexate. Fortunately the patient gradually improved and was eventually discharged home.

CASE EXAMPLES FROM OUTSIDE CANADA

Cases of methotrexate toxicity related to daily rather than weekly dosing have also been reported in other publications.

One report described a patient who was given methotrexate for rheumatoid arthritis.[5] She was taking seven 2.5 mg tablets once a week on Sundays for a total dose of 17.5 mg weekly. At a visit with her family physician, a request was made to reduce her pill burden by changing to one 10 mg and three 2.5 mg methotrexate tablets. The physician inadvertently entered an order into the computer system for the methotrexate 10 mg to be taken daily instead of the intended "as directed" instruction. The community pharmacist dispensed methotrexate 10 mg tablets to be taken once daily, and the patient took the drug as directed. About 1 week later, the patient began to feel unwell, and she was admitted to hospital several days later. The methotrexate error was identified on the fourth day in hospital. The patient died approximately 1 week later from complications related to methotrexate toxicity.

Another report described 2 deaths that resulted from misinterpreted instructions.[4] One patient took methotrexate 2.5 mg every 12 h for 6 consecutive days, instead of 2.5 mg every 12 h for 3 doses each week. Another patient misread the directions on a prescription bottle and took 10 mg every "morning" instead of every "Monday".

The same report described transcription errors involving methotrexate.[4] A physician recorded that a patient had been taking methotrexate 7.5 mg weekly as an outpatient and wrote an order for the patient to receive three 2.5 mg tablets weekly. However, the order was incorrectly transcribed as methotrexate 2.5 mg orally three times daily. When the patient was transferred to another unit, the medication was again transcribed incorrectly but this time as methotrexate 2.5 mg 3 times a week. Fortunately, these errors were caught during pharmacy review of the orders, and neither reached the patient.[4]

POSSIBLE CONTRIBUTING FACTORS

Errors with methotrexate can occur for a variety of reasons. The following are some possible contributing factors[3]:

- lack of information about (or misunderstanding of) the dosing schedule
- lack of information at the point of care to assist practitioners in identifying the correct dosing schedule
- relative infrequency of weekly dosing (most oral medications are typically given on a daily basis)

OPPORTUNITIES FOR PHARMACIST INTERVENTION

Possible strategies that hospital-based pharmacists might implement to prevent dosing errors with methotrexate include the following:

- Exercise extreme caution when obtaining the best possible medication history for patients who are taking methotrexate at the time they are admitted to hospital. Whenever there is an indication that methotrexate is being taken daily or an order for daily administration is received, take further steps before dispensing the medication to ensure that the correct dose, strength, route, frequency, and directions for administration have been identified.
- Implement automated alerts (e.g., in electronic prescribing systems and pharmacy information systems) that will prompt practitioners to review the indication and dosing frequency whenever methotrexate is entered.[3,4,7]
- Include explicit dosing instructions for methotrexate, such as day of the week, on the pharmacy-generated medication administration record.[3,4]
- Provide patient counselling for any patient receiving a new or modified methotrexate prescription before discharge.
    - Ensure that the patient understands how many tablets to take and when and how to take them. Also ensure that the patient is aware of the signs and symptoms of toxicity and the importance of laboratory monitoring and follow-up care with the prescriber.[7,8] (Notably, a study about lack of patient understanding has suggested the need to reinforce key messages related to methotrexate therapy.[9])

- Provide written information to supplement verbal counselling and ensure that the documentation contains only information applicable to autoimmune disorders and weekly dosing schedule.[3,7,8,10]
- Give the patient a calendar suitable for recording doses of medication administered, as well as any dosage changes and blood test results.[8,10]
- Use the predischarge patient counselling session as an opportunity to double-check methotrexate discharge prescriptions for accurate dose, strength, route, frequency, and directions.[10]

- Ensure that appropriate physician follow-up has been arranged and ensure that the patient understands the significance of this follow-up (e.g., the potential need for laboratory testing).[8]
- Educate practitioners:
  - Suggest appropriate strategies to prescribers, such as including the indication for oral methotrexate on the prescription; choosing, in consultation with the patient, a day of the week for dosing (avoiding Monday, which has been misinterpreted as "morning")[4]; and limiting dispensed quantities of oral methotrexate to a 1-month supply whenever possible.[3]
  - Share examples of errors that have occurred with methotrexate and highlight the significant patient harm that can occur if this medication is incorrectly prescribed, dispensed, administered, or taken daily instead of weekly.

CONCLUSIONS

Use of oral methotrexate in the treatment of patients with autoimmune conditions necessitates heightened awareness on the part of the practitioners involved in their care. A review of medication errors reported to the US Food and Drug Administration indicated that the largest proportion of preventable events involving methotrexate and causing injuries or death were due to the distinctive dosing schedule.[7] Furthermore, 52% of the reported errors involved some kind of overdose, with the most common problem identified as daily rather than weekly dosing. Interdisciplinary communication is key to ensuring that pharmacists, nurses, and physicians work collaboratively to prevent these errors. In addition, pharmacists have an important role to play in encouraging patients to become more involved in their own care by learning about their medications and asking questions when the information they receive is unclear.

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- through the secure web portal at http://www.ismp-canada.org/err_report.htm
- by telephone at 416.733.3131 or toll-free at 1.866.544.7672 (1.866.54.ISMPC)