

# Patient Safety Tip of the Week

## June 21, 2016    Methotrexate Errors in Australia

We've now done multiple columns on errors with methotrexate therapy. The basic problem is that methotrexate is used in different doses and different regimens when used for oncological indications or immunomodulating indications for conditions like rheumatoid arthritis, psoriasis, and inflammatory bowel disease. For the latter conditions, low dose methotrexate is used (typically administered weekly in doses that might be in the 7.5-25 mg range).

Now the Australian experience with serious methotrexate errors has been published ([Cairns 2016](#)). Cairns and colleagues analyzed 3 separate databases over a 10-14 year period and found numerous cases, including fatalities, of errors related to methotrexate dosing. An important point noted was that there was almost no overlap of cases reported to these three databases, suggesting that there is likely overall underreporting of such cases. And especially concerning was that there appeared to be a significant increase in calls to their poison information center about methotrexate over the last two years.

In one database they identified 22 cases where methotrexate was listed as a cause of death, including 7 cases that had dosing errors recorded and showed patients had taken methotrexate for between three and ten days consecutively. Of the 7 cases where dosing errors were recorded, three were due to dosette packaging errors by pharmacists, one to a prescribing error, one to mistaking methotrexate for another medication, one to an error by a carer, and one to prescriber-patient miscommunication.

In a second database they found 16 reports of methotrexate-related adverse events, including 5 deaths, and again found unintended daily dosing in 10 cases. In those cases where reasons for errors were available, 11 cases involved mistaking methotrexate for another medication (most often folic acid or prednisone). Five cases were due to error by a carer or nursing home. Other reasons noted were newly prescribed methotrexate, dosette packing errors by pharmacists, misunderstood instructions, prescribing error, dispensing/labeling error, and one case where the patient believed it would improve efficacy.

The authors note that guidelines in place had already recommended extended patient counselling, designating a specific day of the week to take methotrexate, and use of smaller drug packs. Australia introduced smaller pack sizes for methotrexate (10 mg x 15 tablets) but most methotrexate remains dispensed in the larger (10mg x 50 tablets) packs.

The study emphasized that taking methotrexate daily for even 3 consecutive days could be fatal but noted wide variability in the duration of daily dosing before toxic effects

occurred. Some patients took it daily for weeks before toxicity became apparent. Possible contributory factors cited included increasing patient age, renal function and hydration status.

The authors also noted that folate and methotrexate are both small yellow tablets, likely increasing the chance the two might be mixed up. They suggested that formulating methotrexate as a distinctively colored tablet might help. They also recommend clear labeling that the medication is taken weekly and that taking it daily could be harmful. Another recommendation was to co-package with folate in a manner akin to the way contraceptives and sugar pills are packaged. Both these potential solutions would require manufacturers/suppliers to implement changes. But don't hold your breath - drug manufacturers have little incentive to change packaging, etc. because methotrexate is now a low cost drug.

And, of course, they recommend that clinical decision support tools be utilized in both CPOE/e-prescribing systems and pharmacy IT systems to provide alerts aimed at preventing daily dosing errors.

Since first-time users and older patients appear to be at greater risk, they emphasize the importance of taking time to counsel these patients. The authors also note that in addition to physiologic changes that might alter methotrexate metabolism and excretion, the elderly may have other problems like confusion, memory impairment, visual decline, and others that could put them at increased risk of dosing errors. Regarding counselling of patients and/or caregivers, we'd also like to reiterate that ISMP provides a great [consumer leaflet with safety tips for patients taking methotrexate](#).

We are not surprised that the Australian researchers found some errors related to nursing homes. In our What's New in the Patient Safety World columns for July 2011 "[More Problems With Methotrexate](#)" and February 2016 "[Avoiding Methotrexate Errors](#)" we noted that the **patient in a long-term care facility may be especially vulnerable**. In such cases, the original order for methotrexate is usually written by a specialist. The patient is then followed in the LTC facility typically by a primary care physician who may be less knowledgeable about the particular use of methotrexate for that condition. Also, the LTC patient may not be seen by a physician for periods as long as a month. And many LTC patients have cognitive impairments that might prevent them from understanding issues about their medications. So if a medication reconciliation error has occurred and a patient intended for once weekly dosing is now on daily dosing, the opportunity for toxicity is greatly increased. So LTC facilities should take steps to ensure that any of their residents taking methotrexate get the same level of supervision and protections that non-LTC patients would get.

Not mentioned in the Australian study are drug-drug interactions. Our February 2016 What's New in the Patient Safety World column "[Avoiding Methotrexate Errors](#)" noted examples of such drug-drug interactions in leading to methotrexate toxicity (like NSAID's and proton pump inhibitors, amoxicillin and leflunomide) ([ISMP Canada](#))

[2015](#)). That ISMP Canada article also noted predisposing factors such as hypoalbuminemia and renal dysfunction in leading to methotrexate toxicity.

In several of our columns on patients receiving lethal doses of chemotherapy we have questioned why one would ever prescribe or dispense or administer a dose of a drug that could be potentially lethal if the total dose were inadvertently given. Most of those have pertained to patients receiving IV chemotherapy where a dose intended to be administered over several days ran in instead over one day or even just hours. But the same argument applies to oral methotrexate. Imagine if an ordering physician or dispensing pharmacist was required to tell a patient each time “I am ordering/dispensing for you a potentially lethal dose of this medication”. How many patients do you think would say “that’s ok, I’d rather have the convenience of not having to refill my prescription once a month”? That’s a point also made in the editorial ([MacKee 2016](#)) accompanying the Australian study which quoted one professor of clinical pharmacology as recommending providing only a 1-month supply to prevent dosing errors. He said “It is difficult to have a five-times overdose of methotrexate when you only have four tablets in a month.”

A very real problem here, of course, is that we have a drug that is used in very different doses and regimens for two different conditions. If we were just starting to use a new drug for two potentially very different conditions requiring such differences in dosing and regimens, we might well consider giving the drug two different names. For example, we might name one methotrexate and use it for conditions like rheumatoid arthritis, psoriasis, inflammatory bowel disease, etc. And the one for oncology we might name something like “Folic acid inhibitor X”. The two pills could be manufactured as pills of different colors. Could we do such a thing now? We don’t think so. Trying to do this today would likely lead to unintended consequences that would cause more harm than good.

Restrictive formularies could be a potential solution. For hospitalized patients, restrictions can be put in place so that only oncologists can order daily methotrexate. On the outpatient side, managed care organizations often have restrictive medication practices in which certain drugs can only be prescribed by certain specialists. So why cannot they require prior authorization for prescriptions for more than “x” amount of methotrexate if ordered by someone other than an oncologist? They could, but that solution obviously would apply to only a minority of patients being prescribed methotrexate.

But keep in mind that, in the Australian experience, some patients developed toxicity even when taking methotrexate as few as 3 days consecutively. So even if you were to restrict dispensing of methotrexate to only 4 tablets at a time (supposedly a month’s total dose), a patient theoretically could still develop toxicity if they took the 4 tablets on consecutive days rather than one a week. But limiting dispensing to just a one month supply would certainly go a long way to reducing the chance of inadvertent daily dosing errors with serious or fatal outcomes.

It's worth repeating here the several practical recommendations made by ISMP Canada ([ISMP Canada 2015](#)) discussed in our February 2016 What's New in the Patient Safety World column "[Avoiding Methotrexate Errors](#)" for IT systems, prescribers, and pharmacists.

On the **IT side**, it recommends that CPOE and pharmacy IT systems should **default to a weekly dose**. If a daily dose is ordered there should be a hard stop requiring input of the **indication and duration** of treatment. It recommends provision of an **alert** about potential serious adverse effects of daily dosing, particularly in patients with some of the above risk factors or taking any of the interacting medications, with suggestions for monitoring. It also suggests **linking lab results** to order entry for methotrexate (eg. CBC, LFT's, albumin, creatinine) so the prescriber and pharmacist can be reminded to check for risk factors and be reminded of parameters they may need to monitor.

It also recommends a **robust drug-drug and drug-disease interaction module** for methotrexate. That one is the most problematic. We already know that drug-drug and drug-disease and drug-food alerts are among the alerts most often ignored by prescribers. Many EHR's and CPOE or e-prescribing systems allow for configuration of alerts to allow only certain more serious alerts to be shown. But some do not allow selective enabling of these alerts (i.e. allowing drug-drug or drug-disease alerts for just high alert medications as opposed to all medications).

On the **prescriber side** it recommends **baseline values** for parameters that may need to be monitored during therapy (eg. CBC, LFT's, creatinine) and notes that a good order entry system could **prompt the provider to order these** at the time methotrexate is being ordered. It also has recommendations for **frequency of monitoring** these parameters, screening for hepatitis B and C and HIV prior to initiating therapy, and considering **folate** supplementation.

It has 2 excellent recommendations to avoid the error of patients getting daily methotrexate rather than intended once weekly methotrexate:

1. **Specify one particular day of the week** the patient should take it (and avoid Monday since "Monday" might be mistaken for "morning").
2. **Limit the prescription to a 4-week supply.**

It also reminds the prescriber to **ask the patient about specific prescription and any OTC medications** they may be taking that could increase the likelihood of methotrexate toxicity.

On the **pharmacist side** it recommends a **forcing function be developed to ensure that every prescription of methotrexate is reviewed** with the patient (or caregiver). The patient should be **counselled** and given **written information** about methotrexate and stress the importance of adhering to the prescribed dose and monitoring. If **folate** supplementation has not been prescribed the pharmacist should contact the prescriber. The pharmacist should **follow up on any drug interaction alerts** that may appear and discuss with the prescriber and patient. Specific **discussion about OTC medications** or

other medications known to interact with methotrexate should occur. And, again, the **supply dispensed should only be for 4 weeks.**

Most of the same recommendations appear in an article in the rheumatology literature ([Blank 2015](#)). This article has a couple more practical recommendations. It notes that use of a **“dose pack”** may help guide patients to take the proper weekly dose for non-oncologic indications. When reviewing the dosing schedule with patients it is important to explain that taking extra doses is dangerous 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.

By the way, did you notice we did not use the abbreviation “MTX” for methotrexate? That abbreviation is on the [ISMP “Do not use” list of abbreviations](#) because it may be confused with mitoxantrone. So use of that abbreviation would be another potential error involving methotrexate. Is “MTX” on your “Do not use” abbreviation list?

#### **Our prior columns related to methotrexate issues:**

- July 2010 “[Methotrexate Overdose Due to Prescribing Error](#)”
- July 2011 “[More Problems With Methotrexate](#)”
- February 2016 “[Avoiding Methotrexate Errors](#)”

#### **Our prior columns related to chemotherapy safety:**

- September 11, 2007 “[Root Cause Analysis of Chemotherapy Overdose](#)”
- April 2010 “[Medication Incidents Related to Cancer Chemotherapy](#)”
- April 6, 2010 “[Cancer Chemotherapy Accidents](#)”
- July 2010 “[Methotrexate Overdose Due to Prescribing Error](#)”
- July 2011 “[More Problems with Methotrexate](#)”
- May 7, 2013 “[Drug Errors in the Home](#)”
- May 5, 2015 “[Errors with Oral Oncology Drugs](#)”
- September 15, 2015 “[Another Possible Good Use of a Checklist](#)”
- February 2016 “[Avoiding Methotrexate Errors](#)”
- April 19, 2016 “[Independent Double Checks and Oral Chemotherapy](#)”

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