What's New in the Patient Safety World

February 2016

Avoiding Methotrexate Errors

We've done several columns on problems with methotrexate (see our What's New in the Patient Safety World columns of July 2010 "Methotrexate Overdose Due to Prescribing Error" and July 2011 "More Problems With Methotrexate"). But most of the issues have focused on the erroneous prescription and administration of daily doses of methotrexate (as are used for oncological indications) instead of once weekly doses that are used for rheumatoid arthritis (RA) or other autoimmune diseases.

There are actually several other dangers associated with low-dose methotrexate, as outlined by a recent ISMP Canada Safety Bulletin (ISMP Canada 2015). They provide details of 3 incidents of methotrexate toxicity in patients with RA or other autoimmune diseases.

In the first incident a patient with RA and renal dysfunction and hypoalbuminemia doubled his weekly methotrexate dose (without his prescriber's knowledge). This coincided with a course of amoxicillin and initiation of leflunomide therapy. The patient developed severe pancytopenia and died. The severe methotrexate toxicity was attributed to the doubled dose, the underlying risk factors (renal disease and hypoalbuminemia), and the drug interactions with amoxicillin and leflunomide.

In the second incident a patient on weekly methotrexate for RA was hospitalized with a fracture and was begun on diclofenac. Renal failure, pancytopenia, and death followed.

In the third incident a patient with an autoimmune disorder was prescribed a once weekly dose of methotrexate but the pharmacy dispensed a 3-month supply with instructions to take the medication daily. The patient developed severe harm necessitating prolonged hospitalization.

The ISMP Canada safety bulletin notes **risk factors** for methotrexate toxicity as renal dysfunction, hypoalbuminemia, and **certain concomitant medications** (like NSAID's and proton pump inhibitors). They stress the importance of careful monitoring if one of these medications must be used. They also note that folate supplementation be considered to reduce GI and hepatic side effects.

The ISMP Canada article has several very practical recommendations 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 a recent 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.

In our July 2011 What's New in the Patient Safety World column "More Problems With Methotrexate" 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.

Methotrexate can be a very effective drug for RA and other autoimmune diseases and is usually well tolerated. But, as the above examples demonstrate, even low-dose methotrexate can be associated with severe toxicity in certain circumstances. It is thus for good reasons that ISMP (US) includes methotrexate on its list of high alert medications. ISMP also provides a great consumer leaflet with safety tips for patients taking methotrexate.

References:

ISMP Canada. Severe Harm and Deaths Associated with Incidents Involving Low-Dose Methotrexate. ISMP Canada Safety Bulletin 2015; 15(9): 1-5 http://www.ismp-canada.org/download/safetyBulletins/2015/ISMPCSB2015-09_Methotrexate.pdf

Blank C. 10 Ways to Avoid Fatal Methotrexate Errors. Rheumatology Network 2015; December 2, 2015 http://www.rheumatologynetwork.com/rheumatoid-arthritis/10-ways-avoid-fatal-methotrexate-errors

ISMP (Institute for Safe Medication Practices). ISMP List of High-Alert Medications in Community/Ambulatory Healthcare.
http://www.ismp.org/communityRx/tools/ambulatoryhighalert.asp

ISMP (Institute for Safe Medication Practices). Consumer Leaflet with Safety Tips for Methotrexate. 2013
http://www.ismp.org/tools/highalertMedications/methotrexate.pdf