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Patient Safety Tip of the Week

October 18, 2022

Methotrexate Again, With a Twist

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 in once-a-week doses.

Nimkar et al. (Nimkar 2022) recently described a case of an unintentional overdose of methotrexate in a patient with psoriasis, resulting in severe myelosuppression and mucositis. The patient was a 65-year-old woman with a past medical history of psoriasis for 10 years. She was taken to the emergency department by her family with a complaint of increased skin lesions, bleeding from the lesions, and painful mouth ulcers for the last 15 days. She also had high-grade fever and shivering for the last three days and black-colored stools for the last two days. She had stopped taking food due to painful ulcerations in her mouth.

Exam showed multiple ulcerated and necrotic psoriatic plaques with redness and tenderness on various parts of the body, with signs of active bleeding from the skin lesions. There was also blood in the stool. Her hemoglobin was 7.7, leukocyte count $100/mm^3$, and platelets $48{,}000/mm^3$. She continued to deteriorate in the hospital and, despite multiple medical interventions, she died.

The patient had a long history of psoriasis and had been taking methotrexate 7.5 mg once a week and folic acid 5 mg once a day for 10 years. However, for the last 15 days, a relative had accidentally gave her methotrexate 7.5 mg once daily and folic acid 5 mg once a week, after which signs of toxicity appeared.

Obviously, in this case, the family relative transposed the dosing frequency of methotrexate and folate. But it raises a key question we have raised with other medication issues, particularly IV infusions. That question is "**Why would you ever allow a potentially lethal dose of a medication to be given if it were to be given over a much shorter time frame than intended?**" We've raised that question in cases where IV infusions of 5-Fluorouracil (5-FU), intended to be infused over several days, instead get infused over several hours. But the concept here is similar – **why should a patient have**

a supply of methotrexate large enough to be lethal if taken daily by accident? The monthly supply of methotrexate for these patients should only be 4-5 tablets. We don't know details of how the methotrexate was prescribed or dispensed in the current case. Perhaps the patient was given a 90-day supply, which could have allowed for the 15 daily doses she received.

In the study highlighted in our June 21, 2016 Patient Safety Tip of the Week "Methotrexate Errors in Australia" Cairns et al. (Cairns 2016) noted that folate and methotrexate were both small yellow tablets, likely increasing the chance the two might be mixed up. We wonder whether that might have been a factor in the current case (such detail was not provided in the current case).

In 2018, ISMP issued a "Call to Action" to prevent accidental daily methotrexate dosing (ISMP 2018), noting that harmful or fatal errors with daily oral methotrexate for nononcologic use had been reported to ISMP and published in more than 60 ISMP Medication Safety Alert! Newsletters since early 1996.

The fundamental problem is that relatively few medications are dosed weekly. So, it is not surprising that accidental daily dosing of oral methotrexate might occur. ISMP notes that this type of wrong frequency error has originated in all stages of the medication use process, from prescribing to self-administration.

IMSP notes that titrated methotrexate doses or divided weekly doses have often caused confusion. Patients may misunderstand complex regimens. ISMP (ISMP 2018) gave such an example. An 8-week supply of 2.5 mg tablets (30 tablets) had been dispensed with label instructions that said, "Take 3 tablets by mouth one day for 2 weeks then increase to 4 tablets by mouth 1 day per week thereafter." Despite counseling, the patient was confused by the label instructions and took 3 tablets (7.5 mg) daily for 5 days before serious symptoms led his doctor to identify the error.

ISMP also notes that computer order entry systems may contribute to this type of incorrect dosing. They noted that some systems present common orders for oral methotrexate in both daily and weekly dosing frequencies. A clinician may pick the first choice that matches the desired dose, without noticing that the frequency of administration listed is daily, not weekly. Methotrexate today is far more often used for non-oncologic conditions, so it makes sense that CPOE or ePrescribing systems should default to weekly dosing rather than daily dosing.

ISMP has the following recommendations:

- **Defaulting to a weekly dosing schedule** in prescriber and pharmacy order entry systems
- Requiring verification and entry of an appropriate oncologic indication in order entry systems for daily orders
- Educating patients and providing them with verbal and written instructions that specify the weekly dosing schedule and emphasize the danger with taking daily or extra doses

- Asking patients to repeat back the instructions for taking oral methotrexate to validate understanding
- Verifying the dose and frequency of all medication lists and discharge instructions
- **Limiting the prescription quantity to a 30-day supply** (e.g., dispensing just eight 2.5 mg tablets for a 5 mg weekly dose would reduce the risk of a serious overdose)

ISMP also encourages the FDA to require manufacturers to package oral methotrexate for nononcologic use in **patient dose packs that direct consumers to the correct weekly dosing**. They note that, in Spain, blister packs of oral methotrexate limit the quantity of tablets available to patients. The outer carton and blister packs include the nononcologic indications and a specific warning that the dose is once a week for these approved indications.

ISMP's 2022-2023 ISMP Targeted Medication Safety Best Practices for Hospitals (ISMP 2022) includes BEST PRACTICE 2:

a) Use a weekly dosage regimen default for oral methotrexate in electronic systems when medication orders are entered.
b) Require a hard stop verification of an appropriate oncologic indication for all daily oral methotrexate orders.
    i) For manual systems and electronic order entry systems that cannot provide a hard stop, clarify all daily orders for methotrexate if the patient does not have a documented appropriate oncologic diagnosis.
    ii) Hospitals need to work with their software vendors and information technology departments to ensure that this hard stop is available. Software vendors need to ensure that their order entry systems are capable of this hard stop as an important patient safety component of their systems.
c) Provide specific patient and/or family education for all oral methotrexate discharge orders.
    i) 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.
    ii) Ensure that the process for providing discharge instructions for oral methotrexate includes clear written instructions AND clear verbal instructions that specifically review the dosing schedule, emphasize the danger with taking extra doses, and specify that the medication should not be taken "as needed" for symptom control.
    iii) Require the patient to repeat back the instructions to validate that the patient understands the dosing schedule and toxicities of the medication if taken more frequently than prescribed.
    iv) Provide all patients with a copy of the free ISMP high-alert medication consumer leaflet on oral methotrexate.

Our June 21, 2016 Patient Safety Tip of the Week "Methotrexate Errors in Australia" highlighted a study by Cairns and colleagues (Cairns 2016) on methotrexate-related

adverse events. Unintended daily dosing was the predominant contributing factor. Mistaking methotrexate for another medication (most often folic acid or prednisone) was another common contributing factor. Several cases were due to error by a caregiver 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.

That 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. Possible contributory factors cited included increasing patient age, renal function and hydration status. Since first-time users and older patients appear to be at greater risk, they emphasized 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.

ISMP's QuarterWatch™ (ISMP 2019) noted that even 1 week of daily administration of methotrexate can result in many painful and severe adverse effects, including death. They reviewed 14 cases of methotrexate overdoses, all of which occurred in patients age 65 and older. In 6 of the cases, the error was made by the patient. They note that an older population is likely to take multiple daily medications and have trouble reading the instructions on medication labels; thus, it is not surprising some patients became confused. That's especially the case if the "weekly" dose is ordered in 3 smaller divided doses taken 12 hours apart. Patients have also been confused by directions for escalating doses. In the other 8 cases, the oral methotrexate was ordered, labeled, or dispensed incorrectly.

That QuarterWatch™ notes that the warning against daily administration is buried about halfway through the Patient Information label and fails to effectively communicate the potentially fatal consequences of non-adherence to weekly administration. ISMP's high-alert medication consumer leaflet on oral methotrexate is a much better tool for conveying to patients the risks of methotrexate.

An article by ISMP's Matthew Grissinger (Grissinger 2018), based on an ISMP Canada Safety Bulletin (ISMP Canada 2015) discusses most of the points made in the above resources, but also reminds us that computer systems should 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. He also suggests that, if folate has not been prescribed, the pharmacist should follow up with the prescriber to suggest initiation of this supplement.

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. It's especially likely

to occur when an LTC patient gets admitted to a hospital and then gets transferred back to the LTC unit. 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.

We've often harped on the **need to include the indication** when we order or prescribe a medication. In our August 2019 What's New in the Patient Safety World column "Including Indications for Medications: We Are Failing" we gave a methotrexate example. We said if a pharmacist saw an order for daily methotrexate and the indication was "rheumatoid arthritis" (or other non-oncologic indication), the pharmacist might recognize the dosing error.

One recommendation that appeared in some of the older studies but seems to have disappeared was to tell the patient to take the methotrexate on a specific day of the week (but avoid "every Monday", since that may be confused with "every morning") in order to emphasize that the medication is to be taken weekly rather than daily. We've always liked that recommendation.

The twist in the current case is what a relative did. That relative probably never received any education or counselling about methotrexate dosing. Of all the actions and interventions we've talked about in this and our previous columns, probably the only one that might have prevented this catastrophe would have been **limiting the number of methotrexate tablets available** to the patient. Perhaps that is the most important lesson here. With more than 1 million patients currently taking methotrexate in the US (ISMP 2019), the risks of this type of accidental overdose remain substantial.

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"
- June 21, 2016 "Methotrexate Errors in Australia"

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https://www.ismp.org/sites/default/files/attachments/2018-11/Methotrexatefinal.pdf

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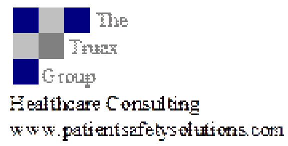

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