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CMIRPS Canadian Medication Incident Reporting and Prevention System
SCDPIM Système canadien de déclaration et de prévention des incidents médicamenteux

ISMP Canada Safety Bulletin

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Severe Harm and Deaths Associated with Incidents Involving Low-Dose Methotrexate

Computer System Administrators

For methotrexate tablets and injection, set up defaults in pharmacy and prescriber order-entry systems to prepopulate the dosing frequency as "weekly". If daily use is required, require entry of an appropriate indication, as well as a stop date.

Prescribers

When prescribing weekly methotrexate, consider the patient's baseline risk factors for toxic effects and ask about the patient's use of other prescription and over-the-counter medications. Continue ongoing monitoring to identify changes in risk factors. Ideally, prompts will be integrated in the prescribing system or process.

Pharmacists

Create a system forcing function that ensures review of every methotrexate prescription with the patient or designate. Carefully evaluate and address any drug–drug or drug–disease interactions that are identified.

For patients with the autoimmune disease rheumatoid arthritis (RA), oral or parenteral methotrexate is the preferred disease-modifying antirheumatic drug with respect to efficacy and safety, unless it is specifically contraindicated.[1,2] In contrast to dosing for antineoplastic indications, methotrexate for RA is administered once weekly as low-dose therapy.[3] ISMP Canada has received multiple reports of severe harm or death in patients taking methotrexate for RA and other autoimmune diseases. The findings and recommendations from selected recent case reports are shared here to highlight system-based opportunities to improve safety.

Medication Incidents

Incident 1: A patient with renal dysfunction and hypoalbuminemia was experiencing worsening RA symptoms. To address these symptoms, the patient doubled his weekly methotrexate dose from 10 mg to 20 mg, a change that happened to coincide with the end of a treatment course of amoxicillin for an infection. The next day, the rheumatologist started another disease-modifying antirheumatic drug, leflunomide. Within a week, the patient presented to hospital with pancytopenia, and despite aggressive treatment, he died. The patient's baseline risk factors for methotrexate toxicity, the intentional doubling of the methotrexate dose by the patient without the prescriber's knowledge, and drug interactions related to the concomitant use of amoxicillin and leflunomide all contributed to the development of severe toxic effects.

Incident 2: An elderly patient with RA was admitted to hospital for treatment of a fracture caused by a fall.

While in hospital, the patient's weekly dose of methotrexate 20 mg was continued and diclofenac was started. The patient developed renal failure (possibly precipitated by diclofenac use) and pancytopenia and subsequently died. It was later determined that the known severe interaction between methotrexate and diclofenac was not addressed when the second drug was initiated, possibly because of the lack of interaction specificity (i.e., presence of numerous alerts including non-critical interactions) when the order was initially entered and there was an incorrect assumption that the patient had been taking diclofenac in the community. The patient died as a result of methotrexate toxicity.

Incident 3: Methotrexate 15 mg once weekly was prescribed for treatment of an autoimmune disorder in an elderly patient. The community pharmacy dispensed a 3-month quantity of medication, but gave instructions to take 15 mg (6 x 2.5 mg tablets) once daily. The error was discovered during pharmacist counselling when the patient requested a refill 3 weeks later. The error resulted in severe harm, which led to a long hospital stay, including treatment with the antidote folinic acid.

Background

For the treatment of RA, low-dose methotrexate is recommended, typically with doses up to 25 mg weekly.[1] Some of the most common toxic effects with a low-dose regimen are gastrointestinal, hematological, and hepatic.[4] Severe adverse effects are more common with the higher doses of methotrexate used for antineoplastic indications. However, hematological toxicity is reported to occur in up to 3% of patients treated with long-term, low-dose methotrexate for RA and other autoimmune disorders,[5] and severe adverse events, such as myelosuppression, pulmonary complications, central nervous system toxicity, hepatotoxicity, and mucositis, have led to hospital admissions and even death.[6] RA prescribing guidelines recommend that a complete blood count (CBC) be obtained and liver enzyme and creatinine levels measured before methotrexate is initiated.[1,2] In addition, it is recommended that measurement of these parameters be repeated at regular intervals for the duration of therapy[2] and that practitioners address any rapid, unusual changes in these parameters, as well as any consistent upward or downward trends.[7]

Hypoalbuminemia, renal dysfunction, and certain concomitant medications, including nonsteroidal anti-inflammatory drugs and proton pump inhibitors, all increase a patient's risk of developing toxic effects from methotrexate.[6] Interacting medications are often prescribed with methotrexate and can be used together safely, provided regular monitoring is taking place. To reduce gastrointestinal and hepatic toxic effects, folate supplementation may be recommended for patients who are receiving low-dose methotrexate.[8]

The US Institute for Safe Medication Practices (ISMP) has identified methotrexate as a high-alert medication[9] in the community setting, even when used for non-oncologic purposes such as RA. As with all high-alert medications, there is a heightened risk of significant patient harm when this drug is used in error. ISMP Canada has previously published concerns about inadvertent daily, rather than weekly, administration of methotrexate.[10,11] When a dosing error is discovered, it is important that the patient receive immediate medical attention. Although serum levels of methotrexate can be measured, they are not an accurate predictor of either the degree of toxicity or the outcome for the patient, because of the drug's pharmacokinetic and pharmacodynamic properties.[6,12]

Recommendations

The following considerations are suggested to reduce the risk of incidents similar to those described above.

Computer System Administrators

- Design the computer order-entry screen for both pharmacy and physician systems to default to a weekly (rather than daily) dosage schedule for all methotrexate orders.[13]
- Require a hard stop or mandatory entry of clinical indication and duration of treatment when the clinician selects a daily schedule for methotrexate orders.
- Add an alert either at order entry or in the clinical decision support system, to indicate that serious adverse effects, including death, can result from

daily administration of the methotrexate,[10] especially if the patient has risk factors for toxic effects or is taking concomitant interacting medications. Note that this risk can be mitigated with appropriate monitoring.
- In hospital and electronic medication record (EMR) systems, link methotrexate order entry to laboratory results (e.g., serum creatinine, CBC, liver enzymes), to prompt review of renal function and other monitoring parameters by both pharmacists and prescribers.
- 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.
- For computer systems lacking some of the above functionalities, work with the software vendors to implement these safety features.

Prescribers

- Before initiating methotrexate therapy, obtain baseline values for monitoring parameters, including CBC, chest radiograph, and indicators of liver and kidney function, to screen for risk factors; an EMR that prompts for this information is an asset.
- Repeat CBC, liver function (especially albumin level), and serum creatinine every 2-4 weeks for 3 months after initiating methotrexate and every 8-12 weeks thereafter for patients with RA.[2]
- Screen for Hepatitis B and C and, in high-risk patients, test for HIV, as recommended in some guidelines, prior to initiating methotrexate.[1]
- Consider folate supplementation for patients starting methotrexate therapy.
- When prescribing methotrexate for weekly administration, specify a particular day of the week in the directions, to reduce the risk that the patient will receive instructions for daily use. Do not specify Monday as the day to take the weekly dose, since this might be misread as "morning".
- Limit the prescription quantity to be dispensed to a 4-week (28-day) supply.
- Ask patients about their use of specific prescription and over-the-counter medications that could influence the risk for methotrexate toxicity.

Pharmacists

- Create a forcing function to ensure that *every* methotrexate prescription is reviewed with the patient or a designate when the prescription is presented.
- Ensure that every patient receives counselling and written information (e.g., the methotrexate information sheet from ISMP[14]). Ideally, pharmacy computer systems should automatically generate this information for all new and refill prescriptions.
- If folate has not been prescribed, follow up with the prescriber to suggest initiation of this supplement.
- Ensure that any drug interaction alerts generated during order entry are communicated to and resolved with the prescriber and/or the patient when indicated.
- Emphasize the need to adhere to the prescribed dose and to obtain all the monitoring tests ordered by the prescriber as scheduled.
- When possible, dispense only 4-week supply of methotrexate at a time.
- Ask the patient or caregivers about the use of specific prescription and over-the-counter medications that can influence methotrexate toxicity.

Conclusion

This bulletin highlights the importance of initial screening for risk factors and ongoing monitoring for methotrexate toxicity, even when this drug is prescribed at low doses. Methotrexate is a high-alert drug, and extra safeguards are needed whenever it is prescribed or dispensed, regardless of the dose or indication for use. Healthcare providers are urged to implement recommended system safeguards recommended for software administrators, prescribers, and pharmacists to improve the safety of low-dose methotrexate therapy.

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Health Canada Releases a Safety Advisory Regarding BD Syringes

Last week Health Canada released a safety advisory about the use of Becton-Dickinson (BD) sterile disposable plastic syringes for the purposes of storing compounded or repackaged medications. Some medications stored in these syringes have been reported to lose potency if not used promptly after filling. The issue appears to stem from new material in the rubber stoppers used in certain lots of these syringes. Health Canada recommends that any medications stored in these syringes not be administered unless there is no other alternative.

ISMP Canada recognizes the impact this safety information has on organizations and is working with national and provincial stakeholders to identify practical solutions.

The full advisory can be found on the Health Canada website at: http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2015/55044a-eng.php and information from BD is available on their website at: http://www1.bd.com/ca/alerts-notices

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CMIRPS SCDPIM
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The Canadian Medication Incident Reporting and Prevention System (CMIRPS) is a collaborative pan-Canadian program of Health Canada, the Canadian Institute for Health Information (CIHI), the Institute for Safe Medication Practices Canada (ISMP Canada) and the Canadian Patient Safety Institute (CPSI). The goal of CMIRPS is to reduce and prevent harmful medication incidents in Canada.

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ISMP CANADA

The Institute for Safe Medication Practices Canada (ISMP Canada) is an independent national not-for-profit organization committed to the advancement of medication safety in all healthcare settings. ISMP Canada's mandate includes analyzing medication incidents, making recommendations for the prevention of harmful medication incidents, and facilitating quality improvement initiatives.

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