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CMIRPS Canadian Medication Incident Reporting and Prevention System
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ISMP Canada Safety Bulletin

Volume 22 • Issue 3 • March 17, 2022

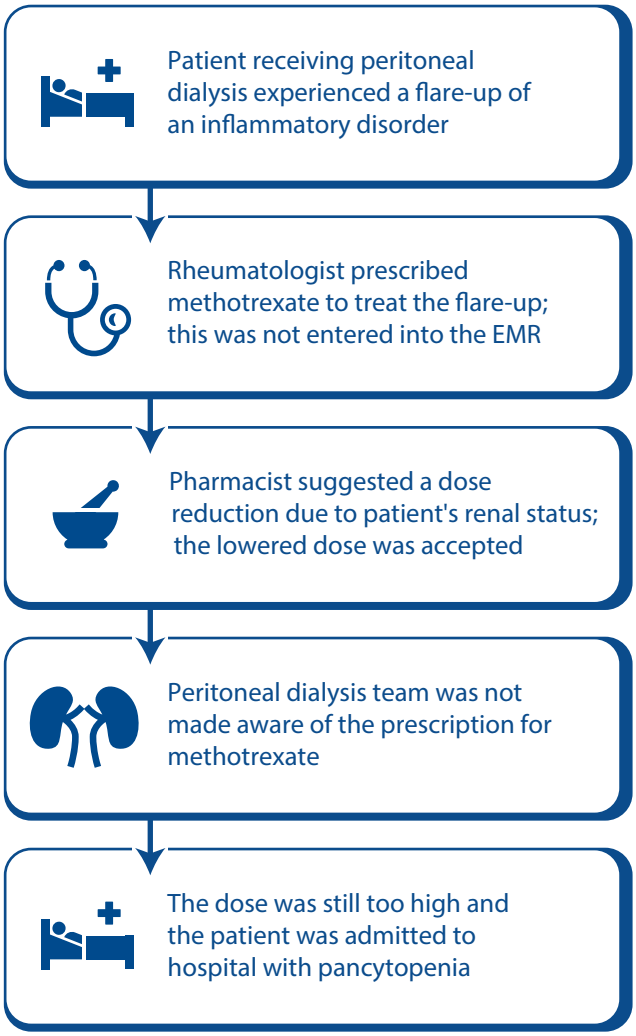
Heightened Risk of Methotrexate Toxicity in End-Stage Renal Disease

Chronic kidney disease resulting from a decline in renal function affects approximately 3% of Canadians.[1] End-stage renal disease, typically leading to the need for dialysis or kidney transplant, may develop as a patient's renal function worsens.[2] Many medications should be avoided by or prescribed at a lower dose for patients with impaired renal function to prevent toxicity.[3] Prescribing can be further complicated by polypharmacy and comorbid illnesses, such as liver dysfunction.[4] This bulletin describes findings from 2 harmful incidents involving patients for whom methotrexate was prescribed while they were receiving dialysis.

INCIDENT EXAMPLES

Incident #1 (Figure 1)**:** A patient who was receiving peritoneal dialysis experienced a flare-up of an inflammatory disorder, and a rheumatologist prescribed methotrexate to treat the flare-up. The methotrexate was not entered in the patient's electronic medical record (EMR), and the peritoneal dialysis team was not made aware that the medication had been started. Before dispensing the prescription, the community pharmacist, who was aware of the patient's renal status, contacted the rheumatologist to suggest that the dose of methotrexate be reduced; the rheumatologist agreed with the dose reduction. However, the dose was still too high and the patient experienced pancytopenia and mucositis and was admitted to the hospital.

Figure 1. Patient journey (Incident #1)



Incident #2: A patient who was receiving hemodialysis died soon after starting methotrexate. The patient's death was attributed to an infection resulting from methotrexate-induced pancytopenia.

BACKGROUND

Peritoneal dialysis or hemodialysis is typically initiated for patients with end-stage renal disease. Patients who are undergoing dialysis are supported by specialized, highly skilled interdisciplinary care teams.[5] Because the dialysis team provides guidance to patients about managing their medications, it is important that patients (and health care providers within the circle of care) inform the team whenever a change is made to a medication regimen, particularly when a new medication is initiated.

Methotrexate is an antineoplastic and immunosuppressant drug. It is indicated for the treatment of certain neoplastic diseases and as a disease-modifying antirheumatic drug (DMARD) for the treatment of specific arthritis disorders; it is sometimes used off-label for various other disorders involving the immune system.[6] The main route of elimination for methotrexate is through the kidneys, therefore dosage adjustments are needed for patients with impaired renal function.[6] Accumulation of methotrexate in the body is associated with an increased incidence of adverse reactions such as mucositis, stomatitis, liver damage, and hematologic effects, including anemia, thrombocytopenia, pancytopenia, and bone marrow suppression.[6]

DISCUSSION

Analysis of these 2 incidents identified several factors that contributed to inappropriate dosing of methotrexate for patients who were receiving dialysis. Health care providers may encounter similar issues when other medications that require dose adjustment are prescribed for patients who have impaired renal function.

- **Communication challenges within the patient's circle of care**

  In both incidents, the patient for whom methotrexate was prescribed was receiving dialysis. The prescriber was not in communication with the patient's nephrologist or dialysis team before initiating therapy with this high-alert medication.[7]

  In the first incident, the community pharmacist recognized the risk of toxicity related to renal dysfunction and recommended a dosage change to the prescribing rheumatologist; the peritoneal dialysis team was not included in the communications.

  In the second incident, it is unclear whether the community pharmacist that dispensed the methotrexate was aware that the patient was receiving dialysis. A Canadian survey conducted by a renal clinic found that more than two-thirds of community pharmacy respondents did not know that renal clinic patients came to their pharmacies.[8]

- **Lack of familiarity with renal dosing considerations for methotrexate**

  In both incidents, the health care providers might not have recognized that methotrexate was contraindicated or would require dose adjustment when administered to patients with end-stage renal disease.[6,9]

  There is inconsistent messaging in the resources available to health care providers. For example, according to current Canadian product monographs, methotrexate is contraindicated for patients with severe renal impairment including end-stage renal disease with or without dialysis.[10-12] However, at the time of the incident, other resources provided less explicit cautions or did not highlight methotrexate as a drug of concern for patients receiving dialysis.

- **Underdeveloped software for checking drug-disease interactions**

  Software designed to check drug-disease interactions is not available in all systems and may not be consistently used. Users (both prescribers and pharmacists) often rely on the patient to communicate their medical conditions, allergies, and medication lists. There is opportunity for improved use of technology to support communication of medication information.

In the first incident, the methotrexate prescription was not entered into the EMR. Consequently, it would not have been possible for interaction-checking software to generate a drug-disease interaction alert.

RECOMMENDATIONS

All health care providers

- For a patient with end-stage renal disease:
  - regularly review their medications, particularly when a new medication is initiated;
  - document all medication changes in the patient's medical/pharmacy record and EMR; and
  - confirm the appropriateness of any new medications with a nephrologist or renal pharmacist.
- Share the updated medication list with all providers within the patient's circle of care.

Prescribers

- When considering a new medication for a patient with end-stage renal disease (particularly a high-alert medication), verify its appropriateness[5] and/or need for dose adjustments with a member of the patient's renal/dialysis team before prescribing the medication.
  - Include information about the patient's renal function on the prescription.
- When methotrexate is prescribed, create a monitoring plan for nephrotoxicity, hepatotoxicity, and myelosuppression.

Renal/dialysis team members

- Consider opportunities to support improved communication within the patient's circle of care, including community pharmacists.[8]
- Ask patients with end-stage renal disease, regardless of dialysis status, to:
  - communicate this medical condition when seeking treatment from a health care provider who is not a member of the renal/dialysis team; and
  - contact the renal/dialysis team before taking a new medication.

Community pharmacists and pharmacy staff

- Standardize processes for entering new prescriptions to ensure that patients are asked about changes in their health, including changes in renal function.
- Enable or refine the drug-disease interaction-checking function in the pharmacy software system.
- For any patient whose medication profile suggests kidney disease, ask about renal function whenever prescriptions are filled. Typically, patients with end-stage renal disease are taking supplements such as vitamin D analogues (e.g., calcitriol, alphacalcidol), iron, phosphate binders (e.g., calcium, sevelamer), erythropoietin, and vitamins (e.g., Replavite).[13]
- Identify patients at risk of kidney disease (e.g., those with hypertension or diabetes mellitus) and periodically ask about their renal function.

Pharmacy/EMR software vendors

- Incorporate comprehensive lists of medical diagnoses and treatment modalities (e.g., "chronic kidney disease" and "dialysis") in drop-down selection lists for medical conditions.
- Consult specialty references for comprehensive information about common conditions, such as chronic kidney disease, that allow for graded levels to indicate the severity of interactions with certain medications (similar to the mild, moderate, and severe risk ratings for drug-drug interaction-checking systems).

Drug information providers

- To support health care providers, optimize the information presented in drug information resources (e.g., product monographs, specialty renal dosing references) for safe medication use in renal impairment.

CONCLUSION

Appropriate medication dosage adjustments in patients with impaired renal function continue to be a challenge. The analysis findings described in this bulletin highlight the need to consult with/refer to key resources (e.g., nephrologist, renal pharmacist, lists of medications to avoid in end-stage renal disease and dialysis) and the importance of communication among health care providers and patients. Increased utilization of supports and functions in software systems (i.e., in clinics, prescriber offices, and pharmacies) can assist in identifying medications that are contraindicated or require dose adjustments for patients with end-stage renal disease.

ACKNOWLEDGEMENTS

ISMP Canada gratefully acknowledges expert review of this bulletin by several individuals, including (in alphabetical order): Kathy Denesyk BSP, B.Ed., ACPR, CDE; Edward Welsh MD, FRCPC Internal Medicine and Nephrology.

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National Poison Prevention Week
March 20 to 26, 2022

Unintentional poisoning is the third leading cause of injury-related death in Canada, with children being especially vulnerable to these preventable events.[1] ISMP Canada—along with Parachute and many other injury and poison prevention partners—is raising awareness about the prevention of unintentional poisonings through the annual National Poison Prevention Week, running from March 20 to 26, 2022. Resources for health care practitioners to share with their patients are available at https://parachute.ca/en/program/poison-prevention-week/.

ISMP Canada has previously shared information, through consumer newsletters, safety bulletins, webinars, and social media, about the risks associated with 2 of the campaign's targeted substances that cause poisonings: cannabis products (especially those that mimic common children's candies) and hand sanitizers (packaged in containers that resemble beverage bottles and children's food pouches).

Analyses of reported incidents involving medication overdoses have identified opportunities to increase awareness among health care practitioners of the additional support and guidance that can be provided by the local poison control centre.

An updated list of poison control centres is available at https://infopoison.ca/centres/.

Reference

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CMIRPS SCDPIM
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ismp CANADA

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