The Institute for Safe Medication Practices Canada (ISMP Canada) is an independent national nonprofit agency established for the collection and analysis of medication error reports and the development of recommendations for the enhancement of patient safety.

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Incidents of Inadvertent Daily Administration of Methotrexate

Methotrexate, a folic acid antagonist, was initially introduced as a chemotherapy agent and has been used for many years in the treatment of such cancers as leukemias, lymphomas, and solid tumours of the breast and lung. In addition, methotrexate has immunosuppressive properties and is therefore also used in the treatment of autoimmune disorders, such as severe psoriasis and rheumatoid arthritis.[1] *When used for these autoimmune conditions, methotrexate is typically given once weekly.*[1,2] Numerous publications,[3,4] a review of a death in the United Kingdom,[5] and alerts published in countries outside of Canada[6,7,8,9] have highlighted incidents in which methotrexate has been inadvertently prescribed, dispensed, or administered on a daily basis, instead of the intended weekly basis, resulting in death. In a review of the US Food and Drug Administration reports involving methotrexate, confusion related to once-weekly dosing was identified as one of the most common types of error, often resulting in death or other serious adverse effects.[10]

This bulletin highlights examples from a cluster of cases reported to ISMP Canada in which methotrexate was taken or administered daily rather than weekly, often with serious adverse effects.

Cases

An elderly patient was taking methotrexate 5 mg orally once per week and prednisone 5 mg twice daily for rheumatoid arthritis. After an accidental fall and fracture requiring convalescence, the patient inadvertently received methotrexate 5 mg daily. About 2 weeks later, the patient was admitted to hospital with pancytopenia and a pulmonary infection. The patient died several days later because of complications.

An adult patient had been receiving methotrexate for rheumatoid arthritis; the weekly dose was divided for three times weekly administration. (The product monograph indicates that, in the treatment of autoimmune disorders such as rheumatoid arthritis, the weekly dose can be divided into 3 doses and given at 12-hour intervals, i.e., over a 24-hour period, once a week.[2]) The family physician inadvertently wrote a repeat prescription for methotrexate to be taken 3 times per day. The error was eventually discovered by a family member. The patient was admitted to hospital but died despite treatment. The cause of death included methotrexate toxicity.

An adult patient was prescribed methotrexate 7.5 mg orally per day for two weeks then 10 mg per day for the treatment of an autoimmune disorder. The patient presented to an emergency department with pancytopenia and oral thrush. The patient was admitted for treatment, which included folinic acid to counteract the methotrexate. Fortunately, the patient gradually improved and was eventually discharged home.

Methotrexate, to be taken once weekly, was prescribed for an adult patient with a type of vasculitis. Although the prescription label stated the correct instructions in the patient's preferred language, the patient took the methotrexate daily for 2 weeks (the patient had received over 3 months' supply of the medication). The patient presented to an emergency department and was admitted for treatment of methotrexate toxicity. Fortunately, the patient gradually recovered and was discharged home.

Possible Contributing Factors

The following factors were identified as possibly contributing to these incidents:

- lack of understanding (or misunderstanding) of the dosing schedule;
- lack of information at the point of care to assist practitioners in identifying the correct dosing schedule;
- most oral medications are routinely dosed on a daily basis, weekly dosing is relatively infrequent.

Recommendations

The following measures are suggested to reduce the possibility of inadvertent medication incidents associated with weekly oral methotrexate therapy.

Prescribers:

- Provide clear dosing instructions, avoiding phrases such as "use as directed". In consultation with the patient, choose a particular day of the week when the medication is to be taken, and specify this day on the

prescription. However, avoid choosing Monday as the designated day, as this word has reportedly been misinterpreted as "morning".[4]

- Consider including the indication for methotrexate use on prescriptions, as helpful information for other health care providers (e.g., pharmacists and nurses).
- When possible, for patients living in the community, consider limiting quantities to be dispensed to a one month supply at a time.

Nurses and pharmacists:

- If methotrexate is ordered with a dosing frequency more often than weekly, and the indication is unclear, contact the prescriber to verify the appropriateness of the dosing schedule.

Pharmacists:

- Ensure that a pharmacist reviews every methotrexate order before the medication is dispensed.
- Include explicit dosing instructions for methotrexate administration, such as the day of the week, on pharmacy-generated medication labels, medication administration records, and other forms.
- Ensure that written information provided to the patient about the use of methotrexate in the treatment of autoimmune disorders contains *only* the information applicable to such treatment.[11,12]
- In addition, in community pharmacies:
  - Implement a system that requires pharmacist counselling for *all* methotrexate prescriptions, including refills, to ensure that patients are reminded of once-weekly dosing.
  - Encourage patients to keep track of the day when they take each dose of methotrexate, e.g., by marking off the date on a calendar.
  - When possible, dispense only one month's supply of methotrexate at a time to prompt a review and follow-up if the patient makes a refill request sooner than anticipated.

In general:

- Ensure that all practitioners involved in the care of patients receiving methotrexate for autoimmune disorders are aware of the high-alert nature of this medication and the potential for harm if it is administered incorrectly.
- Encourage patients to become active participants in their own care. During counselling sessions, ensure that patients understand the information provided, for example, by asking them to describe their understanding of the information provided. (Notably, a study about lack of patient understanding has suggested the need to reinforce key messages related to methotrexate therapy.[13])
- Build alerts in electronic prescribing systems and pharmacy information systems prompting practitioners to review the indication and dosing frequency for methotrexate orders.

As illustrated by the cases described above, weekly dosing schedules can easily be misinterpreted by prescribers, pharmacists, nurses, patients and patient caregivers. It is hoped that sharing information about reported cases will raise awareness and lead to system enhancements to ensure the safe use of oral methotrexate.

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References

1. MicroMedex Healthcare Series. DRUGEX evaluations: Methotrexate. 2008. Greenwood Village (CO): Thomson Scientific and Healthcare.
2. Methotrexate monograph. In Compendium of Pharmaceuticals and Specialties. 2008:1375-79. Ottawa (ON): Canadian Pharmacists Association.
3. Moisa A, Fritz P, Benz D, Wehner HD. Iatrogenically-related, fatal methotrexate intoxication: a series of four cases. Forensic Sci Int. 2006;156: 154-157.
4. Institute for Safe Medication Practices. Beware of erroneous daily oral methotrexate dosing. ISMP Med Saf Alert. 2002 [cited 2008 Feb 4];7(7):1-2. Available from: http://www.ismp.org/newsletters/acutecare/articles/20020403.asp

5. Methotrexate toxicity. An inquiry into the death of a Cambridgeshire patient in April 2000. Cambridgeshire (UK): Cambridgeshire NHS Health Authority; 2000 Jul [cited 2008 Feb 4]. Available from: http://www.blacktriangle.org/methotrexate-toxicity.pdf
6. Special alert. Methotrexate overdose due to inadvertent administration daily instead of weekly. Huntingdon (PA): Institute for Safe Medication Practices; 2002 Dec 3 [cited 2008 Feb 4]. Available from: http://www.ismp.org/hazardalerts/ha.pdf
7. National Patient Safety Agency. Patient safety alert. Improving compliance with oral methotrexate guidelines. 2006 Jun 1 [cited 2008 Mar 18]. Available from: http://www.npsa.nhs.uk/EasySiteWeb/GatewayLink.aspx?alId=1494
8. National Patient Safety Agency. Patient briefing. Making sure you take oral methotrexate safely. 2006 June 1 [cited 2008 Mar 18]. Available from: http://www.npsa.nhs.uk/EasySiteWeb/GatewayLink.aspx?alId=5329
9. Adverse Drug Reactions Advisory Committee of the Australian Drug Evaluation Committee. Methotrexate–name the day. Aust Adv Drug React Bull. 1998 [cited 2008 Feb 04];17(2):3. Available from: http://www.tga.health.gov.au/adr/aadrb/aadr9805.htm
10. Moore TJ, Walsh, CS, Cohen MR. Reported medication errors associated with methotrexate. Am J Health Sys Pharm. 2004;61:1380-1384.
11. National Patient Safety Agency. Methotrexate treatment. Oral methotrexate pre-treatment patient information leaflet. Update 2006 [cited 2008 Mar 18]. Available from: http://www.npsa.nhs.uk/EasySiteWeb/GatewayLink.aspx?alId=1582
12. National Patient Safety Agency. Methotrexate treatment. Patient-held blood monitoring and dosage record booklet. Update 2006 [cited 2008 Mar 18]. Available from: http://www.npsa.nhs.uk/EasySiteWeb/GatewayLink.aspx?alId=5324
13. Kerr KL, Higham C, Cox AR, Situnayake R. A determination of patient awareness of the safety issues surrounding treatment with methotrexate. Pharm J. 2003;270:900-901.

World Health Organization Recommendations for Vincristine

Vincristine, a chemotherapy agent, should always be administered intravenously, never by any other route. On July 7, 2007, a 21-year-old woman died in Hong Kong after this drug was inadvertently administered by the spinal route. According to the World Health Organization (WHO), since 1968 this error has been reported a total of 55 times from a variety of settings around the world. In response to the Hong Kong incident, the WHO issued an international alert (see http://www.who.int/patientsafety/highlights/PS_alert_115_vincristine.pdf) which includes recommendations that are in line with information published in 2001 by ISMP Canada (http://www.ismp-canada.org/download/ISMPCSB2001-10Vincristine.pdf).

As stated in the alert, the WHO World Alliance for Patient Safety recommends:

> "1) The labelling of vincristine should include a clear warning label that reads: 'FOR INTRAVENOUS USE ONLY - FATAL IF GIVEN BY OTHER ROUTES'.
>
> 2) Syringes should not be used for vincristine administration.
>
> 3) Vincristine should where possible be prepared by dilution in small volume intravenous bags (the 'minibag' technique), rather than in a syringe, to protect against accidental administration via a spinal route."

The WHO further commented that research is needed to develop and promote a long-term solution that will separate intravenous and spinal delivery systems. "The gold standard is to create a unique 'lock and key' design of needles, syringes, catheters, tubing and bags so that medications intended for intravenous administration cannot be administered via the spinal route and vice versa."

ISMP Canada is a national voluntary medication incident and 'near miss' reporting program founded for the purpose of sharing the learning experiences from medication errors. Implementation of preventative strategies and system safeguards to decrease the risk for error-induced injury and thereby promote medication safety in healthcare is our collaborative goal.

Medication Incidents (including near misses) can be reported to ISMP Canada:

(i) through the website http://www.ismp-canada.org/err_report.htm or

(ii) by phone: 416-733-3131 or toll free: 1-866-544-7672.

ISMP Canada can also be contacted by e-mail: cmirps@ismp-canada.org. ISMP Canada guarantees confidentiality and security of information received, and respects the wishes of the reporter as to the level of detail to be included in publications.

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