



Clinical Pharmacology & Toxicology Pearl of the Week

~ Accidental Daily Methotrexate Exposure ~

Case:

- ✓ A 60 yo female is admitted to hospital for sore throat, general malaise, as well as an incidental finding of severe new pancytopenia (WBC 0.7, Neutrophils 0.1, Hgb 90, PLT 8).
- ✓ Hematology was consulted and identified that the patient had been recently started on Methotrexate (MTX) 2 weeks prior for an unknown indication. Instead of taking her dose weekly, the patient had accidentally begun taking it daily.
- ✓ Her MTX level is found to be <0.05 (undetectable). She was appropriately started on Leucovorin (Folinic Acid). A few days later Leucovorin was stopped by the inpatient team as it was identified that the patient had only been taking 2.5 mg tablets/day, instead of 15 mg/day (her weekly dose).
- ✓ The impression was that this was too low a dose (her weekly prescribed dose taken over 7 days instead of a single day) to cause severe pancytopenia; additional workup was thus ordered to investigate her profound pancytopenia.

Background:

- ✓ MTX is an immunosuppressive and antiinflammatory agent used in treatment for numerous malignant conditions, inflammatory diseases (e.g., rheumatoid arthritis), psoriasis, as well as for termination of pregnancy.
 - Commonly, MTX is dosed weekly 5-25 mg PO for treatment of autoimmune conditions such as rheumatoid arthritis.
 - IV high-dose therapy is seen in the context of chemotherapeutic regimens.
- ✓ Both therapeutic and toxic effects revolve around the ability to inhibit dihydrofolate reductase (DHFR) and thymidylate synthetase (TS).
 - DHFR Inhibition → Failure of production of reduced folates for purine nucleotides needed for DNA/RNA synthesis.
 - TS Inhibition → Failure of production of thymidyl, which is required for DNA synthesis.

Acute Oral Overdose vs. Accidental Daily Ingestion

- ✓ MTX bioavailability is roughly 60-90% for single oral doses <30 mg/m² – doses higher than this demonstrate significantly decreased absorption, due to a saturable active transport system.
 - As a result, acute methotrexate toxicity from large oral overdoses is rare unless accompanied by underlying renal failure preventing effective clearance (Chan 2017; LoVecchio 2008).

- ✓ Although MTX is often dosed weekly, a disturbing number of innocent mistakes are made, whereby dosing is taken daily inadvertently by patients.
 - Even in low doses, this daily exposure to MTX can lead to potential significant toxicity.
 - Hocaoglu et al. (2008) describes a case of severe pancytopenia and stomatitis after only 3 days exposure to MTX 2.5 mg PO BID.
- ✓ MTX toxicity is thought directly proportional to the duration of exposure and is less dependent on the MTX dose or serum concentrations obtained (Bleyer 1978).
 - With the above in mind, the same dose split over multiple days is considered more toxic than the same full dose given once.
 - EX: The bioavailability of a single weekly dose of MTX at 30 mg is 0.76 – when this same dose is taken as divided doses 8 hours apart, the bioavailability increases to 0.9 (Chan 2017; Comandone 2005).
- ✓ The treatment for any MTX related toxicity remains the same, primarily involving administration of Leucovorin (Folinic Acid)
 - Continue leucovorin until signs of bone marrow recovery are noted (elevated neutrophils, leukocytes, platelets, and improved anemia) despite undetectable serum MTX levels.

Case Resolution:

- ✓ The patient was restarted on Leucovorin given the ongoing possibility of MTX toxicity causing her pancytopenia.
- ✓ Bone marrow biopsy demonstrated no changes in keeping with hematological malignancy, and therefore the diagnosis of low-dose MTX toxicity was confirmed.
- ✓ The patient went on to demonstrate sustained bone marrow recovery with further Leucovorin therapy.

PEARL:

- ✓ Be cognizant of the patient on methotrexate who presents with new onset oral lesions (stomatitis), and especially in cases of new pancytopenia (Ahmadzadeh 2019).
- ✓ Low-dose daily exposure can lead to significant toxicity and is a common error in patient administration of this medication.

References / Resources

1. Chan BS et al. What can clinicians learn from therapeutic studies about the treatment of acute oral methotrexate poisoning? *Clin Toxicol.* 2017;55(2):88-96.
2. LoVecchio F et al. Four-year experience with methotrexate exposures. *J Med Toxicol.* 2008;4:149-50.
3. Bleyer WA. The clinical pharmacology of methotrexate: new applications of an old drug. *Cancer.* 1978;41:36-51.
4. Comandone A et al. High dose methotrexate in adult patients with osteosarcoma: clinical and pharmacokinetic results. *Acta Oncol.* 2005;44:406-11.

The Clinical Pharmacology (CP) physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA on the AHS Insite page. CP consultations are also available through Netcare e-referral and Specialist Link. You can also find us in the [Alberta Referral Directory](#) (ARD) by searching “Pharmacology” from the ARD home page. Click [HERE](#) for more details about the service.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK). Information about our outpatient Medical Toxicology Clinic can be found in [Alberta Referral Directory](#) (ARD) by searching “Toxicology” from the ARD home page.

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Created: November 2, 2023

Reviewed: November 4, 2025