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 newly started on Methotrexate (MTX) 2 weeks prior for an unknown indication; instead of taking her dose weekly, the patient had accidentally began taking it daily for now 2 weeks.

- ✓ Her MTX level is found to be <0.05 (undetectable). She was appropriately started on Leucovorin (Folinic Acid). A few days later Leucovorin is 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 antinflammatory agent used in treatment for numerous malignant conditions, inflammatory diseases (e.g., Rheumatoid), 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.
    - IV high-dose therapy is seen in the context of chemotherapeutic regimens.

- ✓ Both therapeutic and toxic effects revolve around its 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.

- ✓ The concept and presentation of MTX toxicity has been previously covered – *please refer to CPT pearl February 2019: Methotrexate* for review of signs and symptoms.

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 revolving around the administration of Leucovorin (Folinic Acid)
    - This is continued until signs of bone marrow recovery are noted (elevated neutrophils, leukocytes, platelets, and improved anemia) despite undetectable serum MTX levels.
    - *Please refer to CPT pearl February 2019: Methotrexate* for more in-depth review of management.

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 prescribed methotrexate who presents with new onset oral lesions (stomatitis), and especially in cases of new pancytopenia – oral lesions are seen in most cases (Ahmadzadeh 2019).

- ✓ Low-dose exposure daily 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.

More CPT Pearls of the Week can be found HERE.

Created: Nov 2, 2023

Reviewed: Feb 19, 2025