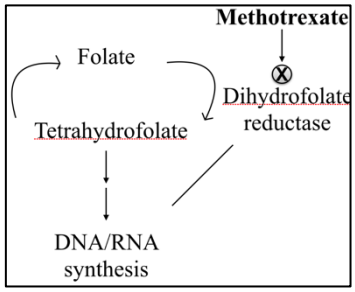
Clinical Pharmacology & Toxicology Pearl of the Week

~ Methotrexate ~



- ✓ Methotrexate (MTX) is a folate antagonist that causes disruption in DNA and RNA synthesis.
- ✓ It is used to treat blood and solid organ malignancies, dermatologic and rheumatologic diseases as well as some ectopic pregnancies.
- ✓ Mechanism of toxicity is different in acute overdose versus chronic toxicity.
- ✓ Once absorbed, methotrexate is rapidly distributed into cells - often within 2 hours of an ingested dose. Once intracellular, methotrexate and its active metabolites demonstrate a half-life of upwards of 1-4 weeks. Serum methotrexate is primarily eliminated renally and demonstrates a half-life of 2-3.4 hours.
- ✓ Oral regimens are typically administered in doses of 5 to 25 mg PO every week - this unusual dosing regimen often results in unintentional daily dosing/exposure. Even at low doses, daily exposure to oral methotrexate can lead to significant toxicity.
- ✓ Acute (within 2 to 4 hours) manifestations of toxicity include nausea and vomiting from folate inhibition. Renal, CNS, bone marrow and hematologic toxicity may also ensue.
- ✓ Clinical toxicity from oral methotrexate exposure most often presents with:
  - GI distress (nausea, vomiting, diarrhea)
  - Mucositis / stomatitis / oral ulcerations
    - Can develop over days to weeks after exposure
  - Pancytopenia / bone marrow suppression
    - Can develop over days to weeks after an exposure
- ✓ Hepatic and pulmonary toxicity are manifestations of chronic MTX toxicity and occur via different mechanisms (type IV hypersensitivity for pneumonitis, adenosine-mediated hepatic steatosis).

Management of Toxicity:

- ✓ Patients with acute, single ingestions should receive single dose activated charcoal 1 g/kg PO/NG as soon as possible, unless contraindicated (i.e., unable to protect airway, bowel obstruction, >2 hours post ingestion).
- ✓ Multi-dose activated charcoal (0.5 g/kg PO/NG q4h for 24 hours) may be considered to enhance MTX clearance.
- ✓ Adequate fluid hydration with 0.9% sodium chloride solution and consideration of urinary

alkalinization with IV sodium bicarbonate is important to prevent renal failure from precipitation of drug.

- ✓ Intravenous leucovorin (folinic acid) treatment serves as a cofactor necessary for synthesis of thymidylate and purine nucleotides that are essential for DNA synthesis. Do not wait for the serum MTX level to return prior to initiating therapy with leucovorin. Folic acid is ineffective because MTX inhibits dihydrofolate reductase, the enzyme required to convert folate to tetrahydrofolate and subsequently synthesize DNA and RNA.

- ✓ Leucovorin dosing is repeated every 6 hours and is based on calculation of Body Surface Area (BSA). Options for determining intravenous dosing:
  - Administer mg-to-mg dose of leucovorin to MTX ingested, up to 100 mg/m^2 of leucovorin every 6 hours.
  - If ingested dose of MTX is unknown, empirically give 100 mg/m^2 of leucovorin every 6 hours (should be effective in all but the most severe overdoses).

- ✓ Leucovorin can be discontinued when one of the following has occurred:
  - MTX level is less than 0.05 µmol/L
  - If evidence of marrow toxicity, continue leucovorin until recovery of bone marrow, even if the MTX level is undetectable
    - **Target endpoints for bone marrow recovery are variable; however, a safe endpoint includes:**
      - Platelet rise persistently greater than 100 x 10^9/L
        - This is often the earliest sign of bone marrow recovery and may be seen within the first few days of therapy.
      - Absolute neutrophil counts (ANC) persistently greater than 1.0 x 10^9/L
        - ANC may fluctuate and not demonstrate stabilization for weeks.
        - ANC greater than 1.0 x 10^9/L is desired given significant risk of febrile neutropenia with ANC below this target.
      - Stabilization and no further fall of other cell lines (red blood cells, hemoglobin).
  - If methotrexate concentrations are unavailable, leucovorin should be continued for a minimum of 3 days.

- ✓ Hemodialysis may be necessary in patients with renal failure, progressively diminishing renal clearance, or MTX concentrations> 100 µmol/L.

- ✓ G-CSF may also be considered in patients with pancytopenia, especially with coexisting renal failure and elevated MTX concentrations.

- ✓ Carboxypeptidase ($CPDG_2$, carboxypeptidase G_2, glucarpidase)
  - Inactivates MTX by hydrolyzing it to DAMPA and glutamate.
  - Carboxypeptidase should be considered for MTX levels greater than 100 µmol/L, persistently elevated MTX levels, and patients with severe toxicity or renal failure.
  - Carboxypeptidase is dosed at 50 units/kg IV over 5 minutes.
  - Serum MTX concentrations are <u>falsely elevated</u> after administration of carboxypeptidase.

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.

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