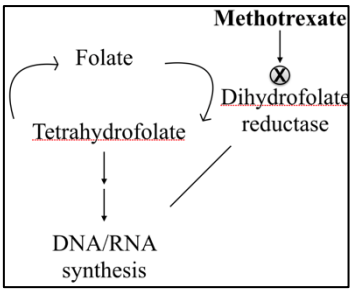
Clinical Pharmacology & Toxicology Pearl of the Week

~ 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.
- ✓ 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.
- ✓ Hepatic and pulmonary toxicity are manifestations of chronic MTX toxicity and occur via different mechanisms (type IV hypersensitivity for pneumonitis, adenosine-mediated hepatic steatosis).
- ✓ 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).

Management of Toxicity:

- ✓ 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
  - If MTX levels are not available, continue leucovorin for at least 12 doses (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 falsely elevated after administration of carboxypeptidase.

The Clinical Pharmacology physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA on the AHS Insite page. Clinical Pharmacology consultations are also available through the Netcare e-referral process and through Specialist Link. Our service is also listed in the Alberta Referral Directory. 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 HERE.

More CPT Pearls of the Week can be found HERE.