Methotrexate Poisoning

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A 10-year-old boy with osteosarcoma received an appropriate four-hour infusion of high dose-methotrexate (12.8 grams/m^2). A post-infusion methotrexate concentration was uninterpretable, but this result was not appreciated by the treating clinicians. The child developed blurry vision, painful mucositis, stomatitis, and facial blistering. A serum methotrexate concentration was 287 µmol/L 31 hours post-infusion and 171 µmol/L 48 hours post infusion. His creatinine rose from 0.57 mg/dL pre-infusion to 2.76 mg/dL 42 hours post infusion.

What is the mechanism of action of methotrexate?

Folate (vitamin B9) must be activated prior to utilization in the one-carbon metabolic pathway necessary for DNA synthesis. It is reduced first by *dihydrofolate reductase* to dihydrofolate (FH_2), and then again by *dihydrofolate reductase* to "active" tetrahydrofolate (FH_4). FH_4 obtains a carbon from serine to form 5,10-methylene-FH_4. *Thymidylate synthase* then utilizes 5,10-methylene-FH_4 to make thymidine from uracil; 5,10-methylene-FH_4 is converted back to FH_2 in the process.

Methotrexate competitively inhibits *dihydrofolate reductase* such that neither FH_2 nor active FH_4 can be generated from folate, nor can existing FH_2 be recycled. Methotrexate metabolites additionally inhibit *thymidylate synthase*, further inhibiting thymidine synthesis. Rapidly proliferating cells (e.g. malignancies and those in the gastrointestinal tract, bone marrow or skin)

which rely heavily on *de novo* nucleotide creation for DNA replication and RNA synthesis are most affected by methotrexate. Because of its ability to impair cellular replication, methotrexate has uses in addition to conventional chemotherapy regimens (e.g. breast carcinoma, choriocarcinoma, lymphoma, and osteosarcoma). These include the treatment of rheumatoid arthritis and psoriasis, and as an ablative therapy for ectopic pregnancy. Methotrexate may be administered via oral, intravenously, or intrathecal routes.

How does methotrexate poisoning with therapeutic dosing occur?

Methotrexate's primary route of elimination is renal. Patients with existing or the potential for impaired renal function (e.g. those taking nephrotoxic drugs) are at increased risk of developing methotrexate poisoning. In addition, precipitation of methotrexate or its relatively insoluble metabolites in the renal tubules can cause acute renal failure and tubular necrosis, further impairing excretion. Persistently elevated serum concentrations lead to hematological abnormalities, such as myelosupression, and nonhematological effects, which commonly include stomatitis/mucositis and diarrhea, dermatitis, and hepatotoxicity. Pulmonary toxicity and neurotoxicity (after either high-dose intravenous therapy or intrathecal use) are less common.

How is a patient with suspected methotrexate toxicity evaluated and treated?

Any of the above symptoms should prompt the clinician to obtain a serum methotrexate concentration, as well as assess renal, hematological, and hepatic function.

Intravenous fluids should be administered to reverse any volume depletion and to maintain brisk diuresis (>60 mL/hour) and are critical to maximizing methotrexate elimination. Since

methotrexate's urinary precipitation is enhanced by aciduria, intravenous sodium bicarbonate is routinely given along with aggressive hydration to maximize urinary solubility. At pH 7.5 methotrexate is ten times more soluble than at pH 5.5.

Folate is an ineffective antidote because methotrexate blocks the enzymes responsible for its activation (although folate will inhibit renal resorption of methotrexate). Leucovorin (5-formyl-FH_4; folinic acid; citrovorum factor) is effective, bypassing the blocked pathways and maintaining the folate cycle. The 10 mg/m^2 intravenous dose of leucovorin for chemotherapeutic "rescue" therapy must be increased significantly in patients with elevated methotrexate concentrations. Leucovorin intravenous doses of 100 mg/m^2, 1000 mg/m^2, or even higher every six hours (at a rate not to exceed 160 mg/min in adults) may be required. In the absence of a methotrexate concentration, empiric leucovorin (molecular weight 511) should be given to obtain a plasma concentration equal to or greater than that of the estimated methotrexate (MW 455) concentration. In patients not being treated with methotrexate for malignancy, leucovorin is continued until the serum methotrexate concentration is less than 10 nmol/L, or less than 50-100 nmol/L in patients receiving methotrexate therapeutically. Leucovorin loses its efficacy at methotrexate concentrations above 100 µmol/L. Leucovorin must not be administered intrathecally.

High flux hemodialysis or charcoal hemoperfusion is indicated for patients at risk for developing methotrexate toxicity despite leucovorin treatment, particularly those with worsening renal function. Clinically significant quantities of methotrexate can be removed, although there is often

a rebound in methotrexate concentration secondary to redistribution. Peritoneal dialysis is ineffective. Carboxypeptidase (see below) is largely replacing the need for dialysis.

Thymidine rescue ("thymidylate salvage") provides this essential nucleoside downstream from the sites of inhibition. However, thymidine is rapidly cleared and must be given by continuous infusion. The investigational dose for thymidine is 8 grams/m^2 per day IV. It is available from the National Cancer Institute (NCI: 888-624-1937 or 301-496-5725). Carboxypeptidase (see below) is replacing the need for thymidine rescue.

Glutamate carboxypeptidase ($CPDG_2$, glucarpidase), a bacterial derived, zinc-dependent metallo-enzyme, directly cleaves methotrexate into inactive 4-amino-4-deoxy-10-methylpteroic acid (DAMPA) and glutamate. The typical dose for an adult is 50 units per kilogram intravenously over five minutes. Administration of $CPDG_2$ produces rapid reduction of serum methotrexate concentrations (by 95-99%). DAMPA is known to cross-react with most commercial methotrexate immunoassays, such that persistently elevated concentrations of methotrexate may be reported if an immunological-based assay is subsequently used. High performance liquid chromatography must be used to determine actual serum methotrexate concentrations. $CPDG_2$ has at least a ten-fold higher affinity for methotrexate than it does for leucovorin. Despite this, many protocols recommend that leucovorin not be administered for 2 hours before, and for up to 2 hours after $CPDG_2$ is provided. A second dose of $CPDG_2$ may be administered at 48 hours because $CPDG_2$ acts only on extracellular methotrexate and slow redistribution of methotrexate from the intracellular compartment may occur. This necessitates continued leucovorin therapy (many protocols suggest 250 mg/m^2 for 48 hours after the second dose of carboxypeptidase).

Then, leucovorin is continued based on methotrexate concentration until it is less then 50 nmol/L.

$CPDG_2$ is available in the US on a compassionate-use basis from the NCI and under an open-label treatment protocol. Emergency inquiries and supply details may also be directed to AAIPharma: 866-918-1731 (intravenous emergencies) or Protherics Inc: 888-327-1027 (intrathecal emergencies). Specialty cancer centers which may have access to this antidote might also serve as a source. Common adverse effects include feeling of warmth, tingling fingers, flushing, shaking, burning of the face and extremities, and pruritus.

How did the patient do?

The patient received saline hydration, urinary alkalinization with sodium bicarbonate, and leucovorin (1500 mg/m^2). $CPDG_2$ (50 U/kg) was given at 68 hours post-infusion followed by a second identical dose 48 hours later. The methotrexate concentration by immunoassay dropped by approximately 90%. The patient's creatinine peaked at 2.95 mg/dL; aminotransferases (AST and ALT) rose to 815 U/L and 1574 U/L with a bilirubin of 3.5 mg/dL. Within 24 hours of $CPDG_2$ administration, renal and hepatic dysfunction stabilized and began trending downward. He did develop abdominal pain which required parenteral opioids for several days. Visual symptoms rapidly resolved. Ultimately he was discharged and was able to undergo his next chemotherapy cycle.

Suggested Reading

Bleyer WA. Methotrexate: clinical pharmacology, current status, and therapeutic guidelines. Cancer Treat Rev. 1977;4:87-101.

Buchen S, et al. Carboxypeptidase G2 rescue in patients with methotrexate intoxication and renal failure. Br J Cancer. 2005;92:480-7.

Goto E, et al. Methotrexate poisoning with acute hepatorenal dysfunction. J Toxicol Clin Toxicol. 2001;39:101-4.

Widemann BC, et al. High-dose methotrexate-induced nephrotoxicity in patients with osteosarcoma. Cancer. 2004;100:1111-32.