

Methotrexate Toxicity

Methotrexate (MTX) is a chemotherapeutic drug that is structurally similar to folic acid. MTX inhibits dihydrofolate reductase, an enzyme that reduces folic acid to tetrahydrofolic acid. This inhibition interferes with DNA synthesis and cell reproduction. MTX is used in the treatment of a variety of illnesses including cancer, rheumatoid arthritis, systemic lupus erythematosus, and psoriasis. It is given intravenously, intramuscularly, orally and intrathecally.

Methotrexate toxicity develops due to increased patient susceptibility during treatment, excessive parenteral or intrathecal administration, therapeutic errors by patients (e.g. taking MTX orally daily instead of weekly), self-administration to induce abortion, or intentional oral overdoses. Clinical manifestations of toxicity include nausea, vomiting, diarrhea, mucositis, stomatitis, esophagitis, elevated hepatic enzymes, renal failure, rash, myelosuppression (leukopenia, pancytopenia, thrombocytopenia), acute lung injury, tachycardia, hypotension, and neurologic dysfunction (depression, headache, seizures, motor dysfunction, stroke-like symptoms, encephalopathy, coma). Toxic effects may occur hours to days to weeks after MTX administration or overdose.

Treatment of MTX toxicity includes the administration of activated charcoal in the event of a recent, oral overdose. Renal failure may be prevented by adequate hydration and urinary alkalinization with sodium bicarbonate. There are three antidotes that have been used for MTX toxicity: leucovorin, thymidine and glucarpidase. Leucovorin (folinic acid) is the reduced and active form of folic acid. It selectively "rescues" normal cells from the toxic effects caused by MTX's inhibition of the production of reduced folates. The recommended dosage in most cases is 100 mg/m² intravenously every 3 to 6 hours until the plasma MTX level is less than 0.01 mcmol/L or for 3 days or longer if levels are not available. Thymidine rescues cells from the cytotoxic effects of MTX. Its use is investigational and is only given along with other therapies. Glucarpidase (carboxypeptidase) is an antidote that has been used recently for MTX toxicity in combination with leucovorin. It converts MTX to an inactive form and rapidly lowers MTX blood levels. It is given as a single bolus of 50 units/kg intravenously over 5 minutes. Leucovorin should be continued for 48 hours after glucarpidase administration. Hemodialysis and hemoperfusion have been used to lower MTX levels. Intrathecal overdoses require special measures including cerebrospinal fluid drainage and exchange, steroids, and antidotes.

DID YOU KNOW THAT... glucarpidase (carboxypeptidase), an antidote for methotrexate toxicity, is available for compassionate use only?

Glucarpidase is not stocked in hospitals. It is only available under an Open-Label Treatment Protocol for compassionate use in patients with high serum methotrexate levels or in patients with intrathecal methotrexate overdoses. Call the Specialists at the Maryland Poison Center for assistance in obtaining glucarpidase for methotrexate toxicity.

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