Canterbury District Health Board
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Clinical Pharmacology Bulletin

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Drug interactions with methotrexate

Methotrexate (MTX) is an antimetabolite cytotoxic drug with immunosuppressant properties. It is used in high doses (>1g/m^2 of body surface area) to treat malignant neoplasms, and in low doses (<25mg) in the treatment of psoriasis and rheumatoid arthritis. This bulletin aims to provide an overview of some clinically significant drug interactions of MTX.

Toxicity

The common dose-related toxic effects of MTX are on the bone marrow and gastrointestinal tract. Bone-marrow depression (e.g. leucopaenia, thrombocytopaenia and anaemia) can occur abruptly, and gastrointestinal toxicity can be serious (e.g. haemorrhagic enteritis and intestinal perforation). High dose MTX is also associated with neurotoxicity, acute hepatic damage, acute renal failure, interstitial lung disease and severe skin reactions. Patients with pre-existing hepatic or renal impairment are at greater risk of MTX toxicity. Folinic acid (as leucovorin calcium) neutralises the anti-folate effects of MTX, and can be used with high dose regimens or in the event of overdose or toxicity. Oral folic acid is sometimes used with low dose MTX.

Monitoring

Regular monitoring of haematological, renal and hepatic function and gastrointestinal toxicity is advisable with MTX. Gastrointestinal symptoms such as stomatitis and diarrhoea are early signs of toxicity and indicate that MTX therapy may need to be interrupted. For high dose regimens, plasma concentrations of MTX can be monitored.

Drug interactions

Like most drugs, both pharmacokinetic and pharmacodynamic drug interactions can occur with MTX. Some clinically significant interactions are presented in the table below.

- Pharmacokinetic drug interactions: MTX is mainly cleared unchanged by the kidneys via passive diffusion and active secretion. Appropriate dose reduction should occur in renal impairment. A reduction in renal excretion of MTX increases plasma concentrations and the risk of toxicity. Any drug that impairs kidney function, e.g. drug-induced decline in renal perfusion, direct drug-induced nephrotoxicity or competition with MTX for active elimination, can result in toxicity.
- Pharmacodynamic drug interactions: Concomitant use of MTX with drugs which have a similar pharmacology can increase the incidence and severity of adverse effects. For example, there is a greater risk of myelosuppression if MTX is used with other cytotoxic agents, or an increased risk of nephrotoxicity with non-steroidal anti-inflammatory drugs (NSAIDs). MTX and trimethoprim both have anti-folate activity, so concurrent use can lead to severe folate depletion and myelosuppression.

Table: Some clinically significant drug interactions with MTX

Drug/Drug class	Mechanism	Importance	Management
Anti-folate antibiotics e.g. trimethoprim or sulphamethoxazole + trimethoprim	Additive folate depletion.	Strong evidence: well documented interaction. Fatal pancytopaenia and megaloblastic anaemia have occurred.	Consider alternative antibacterial. Monitor for MTX toxicity.
Cisplatin	Renal toxicity can impair MTX excretion and lead to increased MTX concentrations.	Limited evidence: small numbers of case reports, but severe MTX toxicity and fatalities have occurred.	High dose MTX: use cisplatin with caution. Risk with previous or concurrent use of cisplatin. Monitor for MTX toxicity.
NSAIDs e.g. ibuprofen, diclofenac, naproxen	Renal toxicity can impair MTX excretion leading to increased MTX concentrations. Additive effects with renal toxicity of high dose MTX.	Strong evidence: well documented interaction. Toxicity may occur quickly and be severe. Risk greatest with high dose MTX, or in renal impairment.	Consider alternative anti-inflammatory/analgesic therapy. Monitor for MTX toxicity.
Salicylates e.g. aspirin (low dose, 100 mg, likely safe)	Competition for active renal tubular secretion of MTX can increase MTX concentrations. Additive effects with renal toxicity of high dose MTX.	Strong evidence: well documented interaction. Toxicity may occur quickly and be severe. Risk greatest with high dose MTX, or in renal impairment.	Consider alternative anti-inflammatory/analgesic therapy. Monitor for MTX toxicity.
Penicillins e.g. amoxicillin, benzylpenicillin, piperacillin	Competition for active renal tubular secretion of MTX can increase MTX concentrations.	Limited and conflicting evidence: case reports of acute toxicity with various penicillins and low or high dose MTX. Risk may increase with larger doses of penicillins.	Low dose MTX: use with caution. High dose MTX: consider alternative antibacterial. Monitor for MTX toxicity.
Probenecid	Competition for active renal tubular secretion of MTX can increase MTX concentrations.	Strong evidence: well documented interaction. Probenecid markedly increases MTX concentrations.	Consider alternative therapy. Monitor for MTX toxicity. MTX dose reduction may be necessary.
Proton pump inhibitors (PPI) e.g. omeprazole, lansoprazole	Inhibition of renal MTX transporter proteins can impair excretion and increase MTX concentrations.	Limited evidence. Risk greatest with high dose MTX, or renal impairment.	Consider alternative therapy. High dose MTX: use a PPI with caution. Monitor for MTX toxicity.

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