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DRUGS THAT INTERACT WITH METHOTREXATE

Salicylates	Decreased renal excretion; displacement from plasma proteins
NSAIDS	Decreased renal excretion; displacement from plasma proteins
Sulfonamides	Decreased renal function; displacement from plasma proteins
Dipyridamole	Increased intracellular accumulation of methotrexate
Probenecid	Increased intracellular accumulation of methotrexate; decreased renal tubular function
Chloramphenicol	Displacement from plasma proteins
Phenothiazines	Displacement from plasma proteins
Phenytoin	Displacement from plasma proteins
Tetracyclines	Displacement from plasma proteins

DRUGS THAT SIMULTANEOUSLY INHIBIT FOLATE METABOLIC PATHWAY—INCREASE HEMATOLOGIC TOXICITY

Trimethoprim*	Inhibition of dihydrofolate reductase
Sulfonamides*	Inhibition of dihydropteroate synthetase
Dapsone	Inhibition of dihydropteroate synthetase

DRUGS THAT MAY SYNERGISTICALLY INCREASE HEPATOTOXICITY—COMMON TARGET ORGAN

Systemic retinoids	Common target organ for toxicity—liver
Alcohol	Common target organ for toxicity—liver

NSAIDS, Nonsteroidal anti-inflammatory drugs.
*Trimethoprim and sulfamethoxazole in combination (Bactrim, Septra) markedly increase the risk of hematologic toxicity when used with methotrexate due to more complete inhibition of two-step folate metabolic pathway.

METHOTREXATE MONITORING GUIDELINES

BASELINE

Examination
- Careful history and physical examination
- Identification of patients at increased risk for toxicity
- Recording concomitant medications that may interact with methotrexate

Laboratory
- CBC and platelet count*
- Liver function tests (especially transaminases)*
- Serologic tests for hepatitis A, B, C antibodies
- Renal function tests: BUN, Creatinine
- HIV testing in patients at risk for AIDS

Liver Biopsy
- Delayed baseline after 3-6months in most patients—once it is certain that methotrexate is effective, is well tolerated, and will be necessary for long-term therapy
- Consider true baseline liver biopsy in higher risk patients (probably best to avoid methotrexate altogether in these higher risk patients)

FOLLOW-UP

Laboratory
- CBC, platelet count and LFTs*
  Weekly for 2-4 wks
  5-6 days after dose escalations
  gradually decrease frequency
  of tests to every 3-4 months long-term
- Renal function tests (once or twice yearly)

Liver Biopsy
- After every 1.5-2.0g total dose for low-risk patients
- After every 1.0g total dose for higher risk patients

- Every 6 months for patients with grade IIIA liver biopsy changes.

Note: More frequent surveillance is needed if laboratory values are abnormal or with high-risk patients.
*Most optimal timing for laboratory tests is 5-6 days after the preceding methotrexate dose.
Methotrexate is not nephrotoxic at standard dermatologic doses; the risk of other toxicities markedly increases with a reduction of renal function due to any etiology.