Pyrimethamine

Class:
Pyrimethamine is a diaminopyrimidine.

Antiparasitic Activity:
Pyrimethamine has therapeutic activity against *Plasmodia* (*P. falciparum* is probably more susceptible than *P. vivax, P. ovale* and *P. malariae*) and *Toxoplasma.*

Mechanism of Action:
Pyrimethamine acts by inhibition of dihydrofolate reductase.

Mechanism of Resistance:
Resistance occurs through multiple mutations in the gene coding for this enzyme

Pharmacokinetics:
Pyrimethamine is well absorbed after oral administration. The elimination half-time ($t_{1/2}$) in healthy adults is between 46.1 and 150 hours.

Dosage:
Pyrimethamine is always used in combination with either a sulfonamide or dapsone. A single treatment of the combination pyrimethamine-sulfadoxine is three tablets for an adult; equivalent to 1.25 mg/kg pyrimethamine and 25 mg/kg sulfadoxine. Regimens for toxoplasmosis vary but the drug is nearly always used in combination with a sulfonamide, a sulfone or clindamycin.

Disease state based dosing:
Pyrimethamine clearance is not reduced by kidney disease, but the manufacturer recommends caution in both kidney and liver disease.

Adverse Effects:
Maloprim® (pyrimethamine-dapsone) for prophylaxis can cause agranulocytosis in 1 per 2,000-5,000 and usually occurs when the maximum recommended dose is exceeded. Fansidar® (pyrimethamine-sulfadoxine) causes severe skin reactions (including severe erythema multiforme and toxic epidermal necrolysis) in about 1:20,000 people. Both of these adverse effects are presumed to be due to the sulfonamide/sulfone.

Drug Interactions:
Dihydrofolate reductase-inhibition by pyrimethamine may exacerbate reactions resulting from other drugs such as cotrimoxazole, trimethoprim and methotrexate. The association between antiepileptic drugs (mainly phenytoin and phenobarbitone) and reduced serum folate concentration is well recognized, although its etiology is uncertain: drug-induced folate deficiency is the basis for possible interaction with pyrimethamine. Zidovudine may antagonize the toxoplasmacidal effect of low concentrations of pyrimethamine, and the synergy of pyrimethamine-sulfadiazine against *T. gondii* may be reversed by zidovudine.

Pregnancy:
There are no adequate and well-controlled studies in pregnant women. Daraprim should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Concurrent administration of folinic acid is strongly recommended when used for the treatment of toxoplasmosis during pregnancy.

Monitoring Requirements:
Ideally, parasitemia should be measured at 6-12 hours over 48 hours to ensure response, although this rarely possible in a tropical setting.

Brand names/Manufacturer:
Pyrimethamine (Daraprim®; Glaxo-Wellcome) is available as white scored 25 mg tablets; no parenteral formulations are available. Pyrimethamine is also available in compound formulations:

- Fansidar® oral (sulfadoxine 500 mg plus pyrimethamine 25 mg per tablet; Roche; the same drug ratios are available in local generic formulations world-wide)
- Fansidar® parenteral (sulfadoxine 500 mg and pyrimethamine 25 mg in 2.5 ml, for deep intramuscular injection).
- Fansimef® (sulfadoxine 500 mg, pyrimethamine 25 mg and mefloquine 250 mg; Roche).
- Maloprim® (dapsone 100 mg, pyrimethamine 12.5 mg per tablet; Glaxo-Wellcome).
- Metakelfin® (sulfalene 500 mg plus pyrimethamine 25 mg per tablet; Farmitalia; a paediatric suspension is also available).