

**Use**

Pyrimethamine is used, with sulfadiazine (q.v.), to treat toxoplasmosis and, with sulfadoxine, to treat malaria (as an alternative to co-trimoxazole [q.v.]) in areas where resistance has not yet developed.

**Pharmacology**

Pyrimethamine is a di-aminopyrimidine that blocks nucleic acid synthesis in the malaria parasite. It also interferes with folate metabolism. It was developed in 1951 and is still widely used in the treatment of toxoplasmosis (the natural history of which is briefly summarised in the monograph on spiramycin) although the only proof of efficacy comes from trials in patients where toxoplasmosis was a complication of HIV infection. Prolonged administration can depress haemopoiesis. Other side effects are rare, but skin rashes may occur and high doses can cause atrophic glossitis and megaloblastic anaemia. Folinic acid (the 5-formyl derivative of folic acid) is used to prevent this during pregnancy because folinic acid does not interfere with the impact of pyrimethamine on malaria and toxoplasma parasites. Pyrimethamine is well absorbed by mouth and slowly excreted by the kidney, the average plasma half life being about 4 days. Tissue levels exceed plasma levels ( $V_D \sim 3$  l/kg). The efficacy of pyrimethamine in treating toxoplasmosis is increased eightfold by sulfadiazine. Other sulphonamides are not as effective. Efficacy in treating malaria is also improved by giving sulfadoxine. For this reason a sulphonamide should *always* be prescribed when pyrimethamine is used to treat a baby for malaria or toxoplasmosis unless there is significant neonatal jaundice, even though the manufacturer only endorses such use in children over five years old. Long term administration can sometimes cause problems (as outlined in the monograph on sulfadiazine). Lactation should not be discouraged during treatment, even though the baby receives about a third of the maternal dose on a weight for weight basis.

**Intermittent prophylactic use where malaria is endemic**

See the web commentary on use to control subclinical infection during pregnancy and in early infancy.

**Treatment of malaria**

**During pregnancy:** A single three-tablet dose of Fansidar<sup>®</sup> (a total of 75 mg of pyrimethamine and 1.5 g of sulfadoxine) and a 3 day course of amodiaquine (q.v.) effectively eliminates tissue parasites. Some think this unwise in the first trimester, but the teratogenicity seen in animals seems absent in man.

**In infancy:** Uncomplicated malaria was once commonly treated with one dose of a synergistic mixture of 1.25 mg/kg of pyrimethamine and 25 mg/kg of sulfadoxine (i.e. Fansidar), but resistance to these two drugs has now rendered this strategy ineffective in many parts of the world, and an artemether based approach (q.v.) has now been adopted in many countries. Quinine (q.v.) remains the best studied way of treating children with severe malaria, although an artemether based approach may be equally effective.

**Treatment of toxoplasma infection**

**During pregnancy:** Spiramycin (q.v.) is often used to try and prevent transplacental spread. If fetal infection is thought to have occurred, sustained maternal treatment with 50 mg of pyrimethamine once a day and 1g of sulfadiazine 3 times a day by mouth may possibly lessen disease severity.

**In infancy:** Give an oral loading dose of 1 mg/kg of pyrimethamine twice a day for 2 days followed by maintenance treatment with 1 mg/kg once a day for 8 weeks if there is evidence of congenital infection. Treatment with 50 mg/kg of oral sulfadiazine once every 12 hours should be started at the same time. Check weekly for possible thrombocytopenia, leukopenia and megaloblastic anaemia.

**Older children:** It is not known whether a year's sustained treatment improves the outcome. Dormant cysts, which often give rise to ocular disease in later life, can not be eradicated by such an approach. Some centres intersperse continued treatment as outlined above with 4–6 week courses of spiramycin.

**Ocular disease:** Clindamycin (q.v.) is sometimes given in babies with ocular disease. Consider photocoagulation for choroidal scars. Prednisolone (2 mg/kg once a day) remains of uncertain value.

**Prophylaxis with Calcium folinate = Leucovorin (USAN)**

Give 15 mg by mouth twice a week during pregnancy to prevent pyrimethamine causing bone marrow depression. Exactly the same dose is often given to infants on long term pyrimethamine treatment.

**Supply and administration**

**Pyrimethamine:** 25 mg tablets cost 7p, and 25mg tablets compounded with sulfadoxine as Fansidar (see above) cost 25p each. Suspensions can be provided on request, but dosage is not critical and it is often good enough to give small babies a quarter or half tablet.

**Calcium folinate:** 15 mg tablets and 15 mg (2 ml) ampoules cost £4.80 and £7.80 respectively.

**References**

Remington JS, McLeod R, Thulliez P. *et al.* Toxoplasmosis. In: Remington JS, Klein JO, eds. *Infectious diseases of the fetus and newborn infant*. 5th ed. Philadelphia: WB Saunders, 2001: 205–346.

Plowe CV, Kublin JG, Dzinjalama FK, *et al.* Sustained clinical efficacy of sulphadoxine-pyrimethamine for uncomplicated falciparum malaria in Malawi after 10 years of first line treatment: five year prospective study. *BMJ* 2004;**328**:545–8. (See also 534–5.)

Omari A, Garner P. Severe life threatening malaria in endemic areas. *BMJ* 2004;**328**:154. [SR] (See also 155.)

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