

## Use

Isoniazid is used, with pyrazinamide (q.v.), in the primary treatment and re-treatment of tuberculosis (TB) which remains a serious notifiable disease. Guidance on dosing in children varies widely (see web site commentary). Babies who come into contact with a case of active tuberculosis also merit prophylaxis.

## Pharmacology

Isoniazid (INH) was first isolated in 1912 and found to be bacteriostatic and, in high concentrations, bactericidal against *Mycobacterium tuberculosis* in 1952. It is active against both intracellular and extracellular bacilli, but because resistance develops when given on its own so, when *active* infection is suspected, at least one other drug is always given as well. A nine month course of isoniazid on its own has long been the standard approach for *latent* infection, but studies in adults and children now suggest that a three or four month course of isoniazid and rifampicin (q.v.) may be better tolerated, and better adhered to. There is no evidence that isoniazid is teratogenic, but treatment does increase the excretion of pyridoxine (vitamin B<sub>6</sub>) and, to counter the risk of peripheral neuropathy, women should take 10 mg of pyridoxine (q.v.) once a day if pregnant or breast feeding. Malnourished children also deserve prophylactic pyridoxine, especially in the first year of life. Treatment during lactation will result in the baby receiving up to a fifth of the maternal dose of the drug, and of the drug's main metabolite, on a weight for weight basis. However, toxicity has not been seen, and breast feeding should only be discouraged if the mother is still infectious (i.e. sputum positive).

Isoniazide is well absorbed by mouth and excreted in the urine after inactivation in the liver. The half life is long at birth, but is substantially shorter in early childhood than it is in adult life (2–5 hours). However inactivation is by acetylation, the speed of which is genetically determined (fast acetylators eliminating the drug twice as fast as slow acetylators). Liver toxicity is not common in children but appears related to high dose treatment, and to combined treatment with rifampicin (q.v.). It is probably commoner in slow acetylators, but this has yet to be established. Haemolytic anaemia and agranulocytosis are rare complications, while a lupus-like syndrome, liver damage and gynaecomastia have been reported in adults. Treatment should be stopped and reviewed if toxicity is suspected. Use is usually contra-indicated in patients with drug-induced liver disease and porphyria.

## Maternal tuberculosis

Mothers found to have TB during pregnancy need expert management: they usually get a 10 month course of isoniazid and rifampicin, along with 6 months of pyrazinamide. Some may need 2 months of ethambutol. Fetal infection is only likely if the mother has an extra-pulmonary infection, but the baby is vulnerable to infection after birth from any care-giver with open untreated pulmonary disease, and remains at risk of serious generalised ('miliary') infection. Patients are not likely to pass infection to others after they have been on effective treatment for at least 2 weeks, so babies born into such a household only need prophylactic isoniazid as indicated below. Where there is a real possibility that the baby has become infected give both isoniazid and 10 mg/kg of rifampicin (q.v.) once a day for at least 6 months. Pyrazinamide (q.v.) should also be given for the first two months under expert supervision (30 mg/kg once a day), especially if there is a possible non-pulmonary focus of infection. Possible meningeal involvement calls for at least a year's expert treatment using four drugs.

## Prophylaxis and treatment

**Neonatal prophylaxis:** Give babies exposed to infection 5 mg/kg once a day by mouth. Dose adjustment is not necessary for poor renal function. If the baby is tuberculin negative at 3 months, treatment can be stopped and BCG (q.v.) given. Treat for 6 months (as outlined above) if the tuberculin test is positive.

**Treating latent infection:** Give 10 mg/kg of isoniazid and 10 mg/kg of rifampicin once a day for 3 months.

**Treating overt infection:** Give babies over a month old 10 mg/kg once a day by mouth.

## Toxicity

Treat any encephalopathy due to an overdose by giving one mg of pyridoxine IV (or by mouth) for every mg of excess isoniazid ingested. Control seizures, acidosis and respiration as necessary.

## Drug interactions

Isoniazid can potentiate the effect of carbamazepine and phenytoin to the point where toxicity develops.

## Supply

An inexpensive sugar-free oral elixir of isoniazid containing 10 mg/ml is available, as are 2 ml ampoules containing 50 mg (costing £7.40 each) suitable for IM or IV injection.

## References

- Roy V, Tekur U, Chopra K. Pharmacokinetics of isoniazid in pulmonary tuberculosis – a comparative study at two dose levels. *Indian Pediatr* 1996;**33**:287–91.
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- Page KR, Sifakis F, de Oca, *et al.* Improved adherence and less toxicity with rifampin vs isoniazid for treatment of latent tuberculosis. *Arch Int Med* 2006;**166**:1863–70.
- Spyridis NP, Spyridis PG, Gelseme A, *et al.* The effectiveness of a 9-month regimen of isoniazid alone versus 3- and 4-month regimens of isoniazid plus rifampin for treatment of latent tuberculosis infection in children: results of an 11-year randomized study. *Clin Infect Dis* 2007;**45**:715–22. [RCT]