

ISONIAZID (Commentary)**Dose recommendations**

Isoniazid is more widely used than any other drug in the treatment of tuberculosis. It is cheap, well absorbed when given by mouth, and bactericidal. Standard doses are also considered relatively non toxic. Penetration into all body fluids is rapid and complete, and a dose of 5 mg/kg once a day produces curative tissue levels that are 60 – 100 times the minimum inhibitory concentration (Mazouni, 1988; Roy, et al., 1996). The product's main disadvantage is that resistance develops quite quickly when the drug is used on its own to treat overt disease. Luckily, this does not seem to happen when it is used to eradicate the organism in a patient who has become infected but has not yet developed overt signs or symptoms of infection (chemoprophylaxis).

Liver toxicity is the most frequently recognised problem associated with treatment. Problems are commoner with high dose treatment, and more likely if the patient is also taking rifampicin. Monitoring is particularly important if there is pre-existing liver disease. Peripheral neuropathy, which is also dose related, and caused by interference with vitamin B₆ metabolism compounded by increased B₆ loss, is perhaps a more worrying complication because its occurrence could easily go unrecognised in infancy.

A 5 mg/kg oral dose once a day is recommended by the International Union against Tuberculosis and Lung Diseases, by the World Health Organisation, and by the British Thoracic Society when treating children. It is also the dose recommended by the American Thoracic Society when treating adults. It should, however, be noted that North American texts have long and consistently recommended a dose two or even three times higher than this when treating children, even in the first few weeks of life. The guideline issued by the American Thoracic Society in 1994 suggested a dose of up to 20 mg/kg a day, which is not far below the 30 mg/kg dose that has occasionally been reported as causing an acute encephalopathy. It is perhaps not surprising that most reports of toxicity, and almost all the guidelines stressing the need for prophylactic treatment with pyridoxine, come from North America.

Little is known about how the body handles isoniazid in early infancy, but such evidence as there is suggests that clearance is much reduced in babies only a few days old (Holdiness, 1987) and for that reason this text continues to recommend that children should not receive more than 5 mg/kg in the first month of life. Indeed several studies have shown that most older children also do very well when given 5 mg/kg once a day (Roy *et al.*, 1996). However, recent research (Schaaf, *et al.*, 2005) has shown that drug elimination in young children is more rapid than is generally appreciated, and that it also varies widely, depending on whether the child has inherited a fast-acetylator genotype or not. There is, as a result, real concern that some children will be sub-optimally treated if they are only given 5 mg/kg a day once they are more than a few weeks old. Since it is not generally realistic to try and assess a child's acetylator status, 10 mg/kg a day is probably the most pragmatic dose regimen to choose. Further research is clearly needed to optimise treatment while minimising the risk of toxicity in young children.

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Prophylactic pyridoxine

High dose isoniazid treatment can sometimes cause a subtle peripheral neuropathy to develop – especially if the patient is already subclinically pyridoxine deficient. For this reason many texts recommend that all patients taking isoniazid during pregnancy should take additional pyridoxine.

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Acute encephalopathic toxicity

Pyridoxine is not only effective in preventing neurotoxicity (see above) – it is also extremely effective in stopping the seizures, reversing the coma, and correcting the metabolic acidosis triggered by any acute overdose of isoniazid. Treatment is best given as a relatively rapid IV infusion – the standard dose being one mg of pyridoxine for every mg of isoniazid the patient is thought to have taken. Crushed tablets can be given down a nasogastric tube if no IV preparation is readily available. Prompt treatment is called for because any dose in excess of 90 mg/kg is extremely likely to trigger recurrent seizure activity, and can be fatal. Pyridoxine seems to work by reversing the fall in the γ -aminobutyric acid (GABA) content of the brain.

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Breast feeding

The breast fed baby will not normally ingest more than 15% of the woman's weight-related dose of isoniazid, and there are no reports of such a dose ever proving hazardous. It is, however, probably prudent to watch for signs of hepatotoxicity or peripheral neuropathy. Many texts say that women on isoniazid should take pyridoxine during lactation (10 mg by mouth once a day), but the evidence to support such a recommendation is not strong.

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