

METRONIDAZOLE (Commentary)**Dosing regimens in the newborn**

Reference texts in North America have, for the last 15 years, recommended dosing at very infrequent intervals in early infancy (once every 48 hours in babies weighing less than 1.2 kg or less than 30 weeks gestation for the first 4 weeks of life), but UK and Australian texts generally suggest a dose regimen similar to the one recommended here. The manufacturers do not have a licence to market the drug for use in infants in North America, or for use in neonates in the UK.

Management in North America has obviously been influenced primarily by the report of the Australian study by Jager-Roman *et al.* in an American journal in 1982, and UK policy by the paper published in a UK paediatric journal by Hall *et al.* in 1983. The discrepancy between the two approaches seems to have gone generally unnoticed. The prolonged half life seen on the first day of life in the three babies of less than 32 weeks gestation studied by Jager-Roman *et al.* was not seen by Hall *et al.* when they measured clearance at 5 days and there was no evidence of dangerous drug accumulation. The assumption must be that clearance increases rapidly in the first few days of life. No other reports of the way the preterm baby handles metronidazole seem to have been published.

Babies more than 6 weeks old seem to handle metronidazole in much the same way as adults, but just how rapidly drug handling matures in the first two months of life is not entirely clear. Very high doses seem to have been used successfully without signs of toxicity in a few babies with bacteroides meningitis. Neither has toxicity been reported with the dose regimen recommended here, and a dose interval of more than 12 hours could well result in the blood level falling below the minimum inhibitory concentration of 6 µg/ml generally considered necessary for the effective treatment of some anaerobic bacteria.

There is general agreement that a therapeutic blood level will be achieved more quickly if an initial loading dose is given. However, for reasons that are not very clear, some UK texts (including the BNF for Children and the Guy's Hospital Formulary) continue to recommend waiting an inappropriately long time after this loading dose has been given before starting maintenance treatment.

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Lau AH, Lam NP, Piscitelli SC, *et al.* Clinical pharmacokinetics of metronidazole and other nitroimidazole anti-infectives. *Clin Pharmacokinet* 1992;**23**:328-64.

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Maternal use in early pregnancy

The use of metronidazole in pregnancy remains controversial because the drug is known to be mutagenic in bacteria and carcinogenic in rodents. Multiple studies have failed to show any sign that either topical or oral use is hazardous in early pregnancy, but it is, of course, difficult to prove a negative.

It will always be particularly difficult to prove that use during early pregnancy does not increase the risk of the child developing cancer in later life (Thapa *et al.*, 1998), but there is no evidence that the drug is a direct carcinogen in adults (Beard *et al.* 1979).

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Therapeutic use later in pregnancy

Treatment will nearly always clear vaginal infection, but there is no evidence as yet that this reduces the risk of preterm birth. Where infection is due to *Chlamydia trachomatis* both partners should be treated if possible.

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Metronidazole and lactation

Apart from one early anecdotal report of diarrhoea in a breast fed baby whose mother was given metronidazole (Clements, 1980), maternal treatment during lactation seems to have been uneventful. There seems to be a sustained reluctance to endorse the systemic use of metronidazole in mothers who are breast feeding in North America. This arose because *in vitro* studies generated theoretical concerns about the drug's carcinogenic and mutagenic potential. While the relevant FDA warnings have never been withdrawn, the legitimacy of any such extrapolation can be questioned, and widespread use has not yet brought any clinical problem to light.

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- Erikson SH, Oppenheim GL, Smith GH. Metronidazole and breast milk. *Obstet Gynecol* 1981;**57**:48–50.
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Management of necrotising enterocolitis

Mortality in this poorly understood condition still exceeds 20% despite antibiotic treatment once intestinal perforation has occurred. Prophylactic measures and preventive strategies have received remarkably little study given the frequency with which this problem is now encountered in the very preterm baby. Observational studies suggest that breast milk can be protective, and there is one trial using an IgA-rich immunoglobulin that lends credence to this view. Small trials have suggested that oral prophylaxis with a poorly absorbed antibiotic can also provide substantial protection. A further large trial linked to an audit of all other sepsis will, however, be necessary to answer lingering concern that such an approach could eventually cause a rise in the total number of unit deaths attributable to candida infection, or to multiply-resistant Gram-negative bacteria. Whether delayed enteral feeding also reduces the risk remains very unclear.

There is equal uncertainty as to the best surgical strategy to adopt. 'Staging' (even using Kliegman's modification of the Bell score) is a poor measure of disease severity. It is much more important to know whether there is focal, multifocal, or pan-intestinal gut involvement, or gangrene of the whole intestinal tract. An approach involving nothing more than peritoneal drainage until the baby can be stabilised has become steadily more popular during the last twenty years. It has even been thought that such an approach can sometimes make later laparotomy unnecessary. However a meta-analysis of the available observational reports suggests that survival may be not much better than that achieved by immediate laparotomy and resection with or without a defunctioning enterostomy (or a 'patch, drain and

wait' approach if there seems to be widespread pathology). As a result, two prospective, multicentre, randomised controlled trials (the NEC and the NECSTEPS trials) were set up to address these questions in 2003. For more details contact Mr Pierro (a.pierro@ich.ucl.ac.uk).

Metronidazole is widely used where necrotizing enterocolitis is suspected in the UK along with flucoxacillin and gentamicin, but a combination of ampicillin, gentamicin and clindamycin is the most widely favoured regimen in North America. Peritoneal swabs should be taken for aerobic and anaerobic culture wherever possible to guide a less empirical approach to treatment. One recent study (Coates *et al*, 2005) suggests that while enterobacteriaceae, with or without *Enterococci*, are very frequently isolated in cases of frank necrotizing enterocolitis, coagulase negative staphylococci and *Candida* species are the pathogens most frequently isolated in cases of focal intestinal perforation.

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