

Use

Metronidazole is used in the management of anaerobic bacterial infection (including meningitis), and in the treatment of a range of protozoal infections such as amoebiasis, giardiasis and trichomoniasis. It is also widely used in the UK after intestinal surgery, and in the management of necrotising enterocolitis.

Pharmacology

Metronidazole, a unique bactericidal antibiotic which first came into clinical use in 1960, is a 5-nitroimidazole derivative. It is particularly useful in the treatment of dental, surgical and gynaecological sepsis because of its activity against obligate anaerobes such as *Bacteroides* and *Clostridium* species, and facultative anaerobes such as *Gardnerella* and *Helicobacter*. It seems rare for bacterial resistance to develop. Both partners should be treated when trichomonal infection is suspected. Short prophylactic courses, with or without ampicillin, are frequently given during abdominal and pelvic surgery in Europe, but cefoxitin (q.v.) is more often used for this purpose in North America (where metronidazole is not recommended for use in children). A reversible sensory neuropathy has been reported in adults after prolonged high dose treatment. Mild gastrointestinal symptoms can occur.

Metronidazole can be given IV, but is very well absorbed by mouth. Rectal bioavailability is about 60%. The drug has a large volume of distribution ($V_D \sim 0.8$ l/kg), penetrates most body fluids (including CSF and ascitic fluid) well, and is excreted in the urine after partial breakdown to a product that also has some antimicrobial activity. The plasma half life is long, and inversely related to gestational age at birth, but soon approaches that seen in adults (7–10 hours). The dosage interval may need to be increased where there is hepatic failure, but does not usually require modification in renal failure although metabolites may accumulate with prolonged usage. See the web site commentary for the reasoning behind the dose regimen recommended in this monograph.

Use in pregnancy was long considered controversial because the drug crosses the placenta with ease, is mutagenic to bacteria, and seems to produce tumours in rodents. However, there is no evidence that the drug is a carcinogen in man. Nor is there any evidence to suggest it is a teratogen, although it can increase the fetotoxic and teratogenic effect of alcohol in mice. More recently it has been widely used with apparent safety to treat trichomonal and bacterial vaginitis both during pregnancy and during lactation. However, while the increased vaginal discharge and the characteristic odour (vaginosis) caused when anaerobic bacteria replace lactobacilli can certainly merit treatment, the PREMETS trial recently suggested that treatment with metronidazole might actually *increase* the risk of preterm birth. Oral or vaginal clindamycin (q.v.) seems to be a better alternative. Other strategies that can sometimes be of benefit are summarised in the monograph on erythromycin.

Levels in babies being breast fed by mothers on the dose usually used to treat urogenital trichomoniasis (400 mg twice a day for 7 days) are about a quarter of the normal therapeutic blood level. While no adverse effect has ever been recognised as a result of treatment during lactation, women with trichomonal infection who are concerned for the theoretical long-term risk may choose to suspend lactation for 24 hours and request the well recognised alternative of treatment with one single high (2 g) oral dose of metronidazole. The drug is said to affect the taste of milk, but this seems to have been noticed more often by mothers (who read what the books have to say) than by babies (who do not).

Drug interactions

Concurrent barbiturate use can decrease the half life in children, making a higher daily dose necessary. Steroids and rifampicin may have a similar but less marked effect.

Treatment

Give a 15 mg/kg IV loading dose. Then give 7.5 mg/kg, orally or IV, once every 12 hours in babies less than 4 weeks old, and every 8 hours in older babies. Higher doses have been used in meningitis. Slow IV administration is only necessary in older children and adults because of the volume of fluid involved.

Supply

20 ml ampoules containing 100 mg of metronidazole (5 mg/ml) for IV use cost £1.50 each. A 7.5 mg/kg dose contains 0.2 mmol/kg of sodium. Limited solubility precludes IM use – the volume involved would be too large. An oral suspension containing 40 mg/ml in sucrose is available (100 ml costs £7.70). A more dilute (10 mg/ml) oral suspension can be prepared with a 2 week shelf life.

References

See also the relevant Cochrane reviews ©

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Shennan A, Crawshaw S, Briley A, *et al.* A randomised controlled trial of metronidazole for the prevention of preterm birth in women positive for cervicovaginal fibronectin: the PREMETS study. *BJOG* 2006;**113**:65–74. (See also 976–7.) [RCT]

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