Intravenous metronidazole in the newborn

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SUMMARY Twenty four neonates at high risk of anaerobic sepsis were treated with intravenous metronidazole, 7·5 mg/kg, 8 hourly, for a mean period of 5 days. The highest observed concentration after the first dose (mean ± SD) 9·6 ± 4·0 mg/l (56·1 ± 23·4 μmol/l) was significantly lower (P<0·001) than the highest observed concentration after the final dose (mean ± SD) 19·3 ± 8·6 mg/l (112·7 ± 50·2 μmol/l). The overall metronidazole half life was (mean ± SD) 23·4 ± 13·1 hours. The half life after the first dose (mean ± SD) 21·9 ± 10·1 hours was not appreciably different from the half life after the final dose (mean ± SD) 21·6 ± 12·4 hours. The concentrations of the major metabolite of metronidazole (20396RP) also rose appreciably during treatment. No side effects of metronidazole were noted and its extended half life in neonates suggests that less frequent dosage would be appropriate.

Anaerobic bacteria are more common than aerobes in the genital tract of healthy women.1 There is a risk of fetal infection by ascending anaerobic organisms2 where there is prolonged rupture of fetal membranes before delivery, particularly with maternal pyrexia, and offensive or purulent discharge. Anaerobic infection is also a potential hazard to and possibly a cause of necrotic bowel conditions such as necrotizing enterocolitis.3 Where there is a risk of anaerobic sepsis in neonates the use of metronidazole has become commonplace (N McIntosh, unpublished data) but there is little information in the published reports on its use in the newborn period. Rom et al.4 and Berman et al.5 reported single cases, and more recently Jager-Roman et al.6 have described pharmacokinetics obtained from its use in 11 infants of varying gestational age. We studied 24 neonates who were treated with metronidazole in the neonatal intensive care unit of this hospital. All but 1 of the infants were both preterm and of low birthweight.

Patients and methods

Twenty four neonates either born in this hospital or transferred within 24 hours of birth were treated with intravenous metronidazole (Flagyl, May and Baker) at a dose of 7·5 mg/kg 8 hourly, as a 30 minute infusion. In 21 patients (group I) (median gestational age 29·5 weeks, range 25–40 weeks; median birthweight 1420 g, range 780 to 3480 g) metronidazole was given for prolonged rupture of fetal membranes (median duration 5 days, range 1 to 53 days) associated with either maternal pyrexia in labour (14 patients), or offensive or purulent liquor (5 patients), or both. Three patients were treated with intravenous metronidazole because of an overwhelming bowel infection.

After each of the first 2 and the final dose of metronidazole an attempt was made to obtain at least 3, 100–200 μl heparinized whole blood samples from each patient. The infants’ size and the severity of the clinical condition prevented more samples being taken and sampling was usually at the same time as blood gas or dextrostix measurements. In only 50% of patients were all 3 samples obtained. A single sample was measured after the third dose. The course of treatment with metronidazole ranged from 1·5 to 10 days, depending on the infants’ clinical response.

The whole blood samples were stored at −20°C until assayed. The concentrations of both metronidazole and its major human oxidative metabolite 20396RP (1–(2 hydroxyethyl) —2 hydroxymethyl-5 nitroimidazole), which also possesses some anti-anaerobic activity, were measured using a specific high pressure liquid chromatographic method.7

A 1 compartment open model has been used to represent the pharmacokinetics of metronidazole.8 When 3 points were available to calculate the elimination constant the method of least squares was used to find the linear regression.

Results

Two infants in group I died aged 1 day and 4 days
respectively, from respiratory distress complicated by air leaks and intraventricular haemorrhage. Their birthweights were 780 g and 790 g. One infant in group 2 died aged 21 days from Enterobacter septicaemia and peritonitis. Her birthweight was 790 g. No infants showed any side effects that might have been caused by metronidazole and no case of anaerobic sepsis was identified by culture during this study.

The highest mean concentration (peak) of metronidazole measured from 1–5 hours after the first dose was 9.6 mg/l (range 4.3–24.1 mg/l) (56.1 μmol/l (25.1–140.7 μmol/l)) and 10–15 hours after the final dose was 19.31 mg/l (range 8.8–28.9 mg/l) (112.7 μmol/l/l (51.4–168.8 μmol/l/l)). The peak median concentration of 20396RP after the first dose of metronidazole was 0.7 mg/l (range 0.1–5 mg/l) (3.7 μmol/l/l (0.5–26.7 μmol/l/l)) and after the final dose was 5.2 mg/l (range 2.2–7.0 mg/l) (27.8 μmol/l/l (11.7–37.4 μmol/l/l)). A total of 35 measurements of the blood elimination half life of metronidazole were made during this study—15 after the first dose, 7 after the second, 4 after intermediate doses, and 9 after the final dose. Since the final dose was between 96 and 208 hours after the first dose a 'steady state' had been achieved. The mean elimination half life of metronidazole for all the results was 23.3 hours while that after the first and last doses was 21.9 and 21.6 hours respectively (see Table). There was no important difference in the half lives following the first, second, or final doses.

It was impossible to calculate 20396RP elimination half lives after the first dose of metronidazole as the concentrations frequently did not differ significantly from zero. Nine measurements of the 'apparent' half life of 20396RP were measured after the final dose and the results are shown in the Table. We have called these the 'apparent' blood elimination half lives as oxidation from metronidazole to 20396RP will have continued during the period of measurement thus retarding artificially the true half life by an indeterminate amount.

We emphasise that the half life calculations were made on the basis of measurements of 3 blood concentrations in 18 instances, but 2 only in 17 instances.

**Discussion**

Although it is suggested that many anaerobic bacteraemic episodes are self limiting, anaerobic infection in the newborn may lead to severe and fatal infection. Metronidazole is effective against all anaerobes and its use in children and adults is not associated with any serious side effects other than reversible sensory neuropathy with prolonged use of high doses. We felt justified in using this antibacterial agent when there was sufficient risk of anaerobic infections. Prolonged rupture of fetal membranes with either associated maternal pyrexia or offensive liquor was seen predominantly in mothers in preterm labour where obstetricians had to balance the risk of ascending infection of the fetus against preterm delivery of a very immature infant. The other indication for metronidazole in our unit was overwhelming infection including necrotic bowel. Our unit is not unique in its use of metronidazole, and 11 of 13 neonatal units in London also use it for similar indications (N McIntosh, unpublished data).

Our chosen dose of 7.5 mg/kg, which although lower than that of Rom et al., is the manufacturers' recommended paediatric dose regimen, established in our patients a mean apparent concentration of 11.1 mg/l (64.8 μmol/l/l) immediately after the first dose. Since most anaerobes have a minimum inhibiting concentration of metronidazole of less than 8 mg/l (46.72 μmol/l/l) this dose proved adequate. Wide ranges of results were obtained, although the mean values of metronidazole after the first and final dose were sufficiently higher than 8 mg/l (46.7 μmol/l/l) to be effective.

Metronidazole is hydroxylated, conjugated, and excreted renally. Many of these processes are poor in the neonate and are likely to be even more so in the preterm infant. It is not surprising, therefore, that the mean elimination half life after the first dose

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**Table Pharmacokinetics of metronidazole (MET) and its major metabolite 20396RP (20396) in 24 neonates after an intravenous dosage regimen of 7.5 mg/kg 8 hourly**

| MET peak after first dose (mg/l) | 18 | 9.6±4.0
| MET peak after final dose (mg/l) | 12 | 9.3±8.6
| 20396 peak after first dose (mg/l) | 18 | 6.4±1.03
| 20396 peak after final dose (mg/l) | 12 | 5.2±2.5
| Overall MET elimination half life (hours) | 35 | 23.4±13.1
| MET elimination half life after first dose (hours) | 15 | 21.9±10.1
| MET elimination half life after intermediate doses (hours) | 11 | 26.7±17.4
| MET elimination half life after final dose (hours) | 9 | 21.6±12.4
| 20396 elimination half life after final dose (hours) | 9 | 36.4±31.0

*Non paired Student's t test. NS = not significant; 'peak' = highest observed value.
Conversion: traditional units to SI—metronidazole 1 mg/l = 5.84 μmol/l; 20396 RP 1 mg/l = 5.34 μmol/l.
is approximately 3 times the half life of the drug in adults. Jager-Roman et al. have recently reported the considerably extended half life of metronidazole in neonates, but their data showed that the half life shortened during the course of treatment leading them to suggest that metronidazole metabolism was induced during treatment with the drug. Our study showed, contrary to theirs, that the half lives after the first and last doses during a 5 day course of treatment did not differ appreciably from each other. We confirmed their finding that the half life was inversely related to gestational age (r = 0.56) and to birthweight (r = 0.56).

It is well recognised that anaerobes are difficult to culture and may be sensitive to even very brief exposures to air. We were unable to identify clinical specimens by chromatographic patterns, and even though in retrospect no anaerobic organisms were cultured from these patients, we still feel that the use of metronidazole was justified in the circumstances. Twenty one of the 24 infants survived. Of the 3 deaths 1 only was caused by infection—by an organism insensitive to metronidazole. No side effects caused by metronidazole were seen, but the maintenance of a peripheral drip for the course of treatment led to considerable extra handling of the babies.

In view of the extended half life, the dosage frequency could be reduced. To achieve and maintain the recommended minimum inhibiting concentration of 6–8 mg/l (35–0.46–7 μmol/l) one could give a loading dose initially and an appropriately reduced dose at 8 hourly intervals, or administer a uniform dose every 12 hours. With a suitable increase in the first dose, a 24 hour dose regimen could, however, be used and this would reduce considerably both the handling of this fragile group of babies and the work load of neonatal staff.

We thank J Sykes for encouragement: M G Sankey, and J E Holt for technical assistance; medical and nursing staff for clinical management of the babies; Mrs S Garrett and Mrs C Ryan for secretarial help.

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Received 8 March 1983
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Arch Dis Child 1983 58: 529-531
doi: 10.1136/adc.58.7.529

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