

CASE REPORT

Rifampicin pharmacokinetics in extreme prematurity to treat congenital tuberculosis

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kirstyledoare@gmail.com**SUMMARY**

Little evidence is available on the pharmacokinetics of antituberculous medication in premature infants. We report rifampicin (RMP) pharmacokinetics in an extremely premature, low-birthweight female infant born to a mother with known miliary tuberculosis. Intravenous RMP, isoniazid (INH), ciprofloxacin and amikacin were used, as the enteral route was not possible. Area under the curve calculations revealed low average RMP concentrations at doses of 5–10 mg/kg. We review the literature with regard to the dosing regimen and therapeutic drug levels of RMP and INH in premature infants and discuss issues of management. Evidence from this case suggests 10 mg/kg/day is the minimum dose required.

BACKGROUND

Within the UK, London is an area of high tuberculosis (TB) prevalence (44.3/100 000 population, 2008), comparable with some resource-poor settings.^{1 2} The incidence of women of child-bearing age presenting with TB in London is estimated at 252/100 000 deliveries (2006).³ Clinicians dealing with these mothers and their infants are faced with complex management dilemmas surrounding prophylaxis and treatment of infants exposed to TB, especially where these infants are premature. All pharmacological interventions balance efficacy and toxicity; there are few efficacious agents that do not have some toxicity risk. In the case of antituberculous agents, the major risk is hepatotoxicity and three agents identified by WHO as essential, isoniazid (INH) rifampicin (RMP) and pyrazinamide (PZA), carry such a risk. Recent recommendations suggest increased dosages of INH (5–15 mg/kg), RMP (10–20 mg/kg) and PZA (30–40 mg/kg) for children.⁴ In preterm infants where biliary elimination is immature, extra care is needed with dosing. Current recommendations are based on drug clearance studies in children and adults, and no studies have addressed the pharmacokinetics of these drugs in preterm neonates less than 29 weeks' gestation.

CASE PRESENTATION

A woman of Somali origin presented at 26+2 weeks' gestation with a 3-month history of cough, night sweats and weight loss. She had smear positive *Mycobacterium tuberculosis* sputum cultures and a classical chest radiograph appearance of miliary TB. Maternal serology for HIV antibody was negative. She was started on antituberculous medication (RMP, INH, ethambutol (EMB) and PZA) while awaiting

resistance patterns. At 26+4 weeks' gestation, she went into spontaneous preterm labour and gave birth to an 850 g female infant. The maternal placenta was culture positive for acid-fast bacilli (AFB) at 48 h post-delivery. The mother was found to have fully sensitive *M tuberculosis* on day 35 postpartum. She responded well to treatment and was sputum culture negative for AFB on day 53 postpartum. At birth, the infant had a raised respiratory rate, subcostal and intercostal recession. She demonstrated signs of respiratory distress requiring increasing ventilatory pressures.

INVESTIGATIONS

Her C-reactive protein (CRP) rose to 17.9 ml/l with a white cell count of 4.8 ml/l. A lumbar puncture at 48 h of age demonstrated no white cells, no red cells and no organisms on gram stain. Bacterial cultures on blood, urine and cerebrospinal fluid (CSF) were negative. Gastric aspirates, blood and CSF cultures and PCR were all negative for *M tuberculosis*. A chest radiograph was consistent with respiratory distress syndrome; there were no focal lesions.

Owing to the need to monitor and maintain therapeutic concentrations of the antituberculous medications, routine drug levels were taken at 1 h predose and 1 h postdose for INH and RMP. Further samples for RMP analysis were sent at 2, 4 and 7 h postdose, which is part of our routine drug monitoring to guide clinical care. Levels of RMP 5 mg/kg were available on day 20 of life. As these were subtherapeutic, the dose was increased to 10 mg/kg/day on day 21. Levels at 10 mg/kg per day on day 40 were in the therapeutic range (table 1). INH was increased to 10 mg/kg per day on day 20 of life as the infant's liver function tests remained normal. Levels of INH on 10 mg/kg were 0.4 mg/l 1 h predose and 4.3 mg/l 1 hour postdose. The area under the curve (AUC) over the period 0–7 h after dosing was calculated by the linear trapezoidal rule. AUC calculations revealed low average RMP concentrations at both doses of 5–10 mg/kg/day with variability in peak levels over time (mean AUC (0–7) 15.8 mg/ml/h after 6 weeks at a dose of 10 mg/kg).

DIFFERENTIAL DIAGNOSIS

In view of the extent of placental *M tuberculosis* and the signs of sepsis and respiratory distress, our working diagnosis was congenital TB.

TREATMENT

In view of the high mortality associated with congenital infection in premature infants and the extent of AFB on the maternal placenta, the infant was started on daily intravenous RMP (5 mg/kg),

To cite: Le Doare K, Barber N, Doerholt K, et al. *BMJ Case Reports* Published online: [please include Day Month Year] doi:10.1136/bcr-2012-008207

Table 1 Neonatal drug levels for rifampicin and isoniazid

| | Mean gestational age (weeks) | Dosage (mg/kg) | Route of administration (intravenous—IV, oral—PO) | Peak (ml/l) | Range (ml/l) | Trough ml/l | Range |
|----------------------------|------------------------------|----------------|---------------------------------------------------|-------------|--------------|-------------|-------|
| <i>In previous studies</i> | | | | | | | |
| Tan <i>et al</i> | 35 | 5 (BD) | IV | 4.02 | ±1.02 | 1.11 | ±0.48 |
| Tan <i>et al</i> | 35 | 10 (OD) | PO | 1.86 | ±0.96 | 0.77 | ±0.03 |
| Pullen <i>et al</i> | 29.9 | 8.5 (OD) | IV | 4.66 | ±1.47 | 0.21 | ±0.2 |
| <i>In our case</i> | | | | | | | |
| Intravenous | 26+2 | 5 (OD) | IV | 2.4 | | <0.2 | |
| Oral | 28 | 10 (OD) | PO | 4.7 | | 0.3 | |

INH (5 mg/kg), ciprofloxacin (5 mg/kg) and amikacin (15 mg/kg) for congenital TB. Once the enteral route was tolerated, PZA (35 mg/kg) and ethambutol (EMB) (15 mg/kg) were started on day 10 and the ciprofloxacin discontinued. Her antituberculous medication was completely changed to oral on day 21 of life. PZA and EMB were continued until day 35 of life when the maternal cultures demonstrated full sensitivity.

OUTCOME AND FOLLOW-UP

Our infant received 6 months of antituberculous medication and is being followed up by the neonatal department until the age of 2 years due to her prematurity. She remains well with no permanent sequelae.

DISCUSSION

In the absence of pharmacokinetic data for children and, therefore, data that demonstrate the association between serum concentration and clinical outcome, optimal antituberculous medication should aim to produce the targeted serum drug concentrations that have been determined in adult pharmacokinetic and pharmacodynamic studies. RMP concentrations in adults after a dose of 600 mg are in the range of 8–24 µg/ml. Serum RMP levels below 8 µg/ml are considered low and levels below 4 µg/ml are considered very low.⁵ The PK of RMP for the treatment of TB in neonates is unknown and will change over time. The immaturity of hepatic esterases make this very difficult to predict as the infant matures, but it is likely that absorption and hepatic metabolism will improve over time. Our data suggest that adequate serum RMP concentrations are achieved in very low-birthweight infants at 10 mg/kg once daily. The WHO currently recommends once daily dosing, and available information from children and adults suggests that therapeutic levels are achieved at a once daily dose due to the long half-life of RMP.⁶

We undertook a literature review of MEDLINE, EMBASE and Web of Science using the key words: ‘congenital tuberculosis’, ‘pharmacokinetics’, ‘pharmacodynamics’, ‘neonates’ and ‘rifampicin’. Three studies reported the pharmacokinetics of RMP in a neonatal population. Thee *et al*⁶ (2010) reported peak RMP levels at a dose of 10 mg/kg and 15 mg/kg in children less than 2 years of age of 6.36/11.69 µg/ml and mean AUC (µg h/ml) of 17.78 and 36.95, respectively. The mean peak plasma concentration and AUC differed significantly between doses according to age, although none of the infants in this study were premature. Peak RMP levels in premature infants at 29 weeks’ gestation are described by Pullen *et al*⁷ at doses of 5–10 mg/kg once daily.⁷ A significant linear relationship between RMP dose and peak plasma concentrations was found ($r=0.556$, $p=0.009$), but interpatient variability was high. This study also demonstrated a reduction in peak concentrations

after 2 weeks of therapy, reflecting the altered drug metabolism in premature infants compared to children and adults. Tan *et al* 1993 report levels of RMP intravenously (5 mg/kg twice daily) and orally (10 mg/kg once daily) in premature infants with a mean gestational age of 35 weeks.⁸

While our data support an initial RMP dose of 10 mg/kg/day even in extremely premature infants, it is important to note the effect of RMP on liver enzyme induction and the subsequent need to consider increasing doses of other drugs commonly used in the neonatal period. All the evidence combined makes the need for more data on neonatal and very low-birthweight dosing essential in the development of future guidelines for the treatment of TB in this group.

Learning points

- ▶ Adequate peak serum rifampicin (RMP) concentrations in an extreme preterm low-birthweight neonate are achieved at 10 mg/kg.
- ▶ This evidence supports the implementation of higher dosing according to the WHO revised guidelines in premature infants.
- ▶ Caution should be used due to the enzyme induction effect of RMP and the consequential reduction in the concentrations of other medication with increasing doses of RMP.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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