Latamoxef and the newborn

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SUMMARY Thirty one preterm neonates who had clinical, radiological, or bacteriological evidence of infection and who would normally have received gentamicin and penicillin were treated with latamoxef (Moxalactam) 100 mg/kg/day. All were examined prospectively for clinical improvement and possible side effects. Biochemical and haematological values were monitored and pharmacokinetic variables determined. Thirty babies improved during treatment; latamoxef was effective in eradicating the infecting organisms in 7 of 9, including three babies infected with Lancefield group B streptococci. High serum concentrations of latamoxef were achieved after either intravenous or intramuscular administration and accumulation did not occur. Treatment had no effect on renal or hepatic function nor did it result in increased serum values of non-protein bound bilirubin. Clotting studies, where performed, were normal and no babies had bloody stools. Two disulfiram-like reactions were recorded. Latamoxef proved a safe and efficacious alternative to gentamicin with penicillin in the initial treatment of neonates with clinical evidence of infection.

Latamoxef (Moxalactam) is a new oxacephem antibiotic that should prove useful in neonatal treatment. Three characteristics commend it for use in this group of patients—excellent in vitro activity against most potential neonatal pathogens,¹ lack of serious toxicity, and good cerebrospinal fluid penetration.^{2,3}

The standard treatment for suspected or proved neonatal sepsis is an aminoglycoside (usually gentamicin) and penicillin or ampicillin. Although this combination has been successful, it has several inherent disadvantages: the narrow therapeutic margin and the unpredictability of blood concentrations, especially during the neonatal period, necessitates laboratory monitoring of serum aminoglycoside concentrations;⁴ problems associated with infection due to gentamicin resistant organisms are reported increasingly among neonates; and the poor penetration of gentamicin into cerebrospinal fluid limits its use in the treatment of neonatal meningitis.^{5,6} The early signs and symptoms of meningitis in the newborn are vague and non-specific and it usually arises as a complication of septicaemia, sometimes even where this has apparently been appropriately treated. It is desirable therefore that drugs used for the routine treatment of clinical sepsis should pass into the cerebrospinal fluid even when meninges are not inflamed.

The purpose of this study was to assess the safety

and usefulness of latamoxef for initial treatment of suspected sepsis in the newborn and to determine its pharmacokinetics in this age group.

Patients

Thirty one neonates with a birthweight of mean (SD) 2.0 (0.83) kg (range 0.68 to 3.97 kg) and a gestational age of 33 (4) weeks (range 27 to 40 weeks) who had clinical evidence suggesting serious infection and who would otherwise have received gentamicin and penicillin were treated with latamoxef (100 mg/kg/day in two divided doses). All except four began treatment during the first week of life and in 22 treatment started during the first three days. Signs and symptoms arousing suspicion of infection in the 31 babies included respiratory problems (26 babies), indicative radiological findings (18), prolonged rupture of membranes (10), need for ventilator support (14), maternal infection (6), maternal pyrexia (four), and general deterioration (three). Most babies had several indications of possible sepsis.

Organisation of the study

Only babies who were judged to require chemotherapy on clinical grounds were admitted to the study. Blood samples were collected before, during,

and after each course of treatment for determination of serum creatinine, urea, protein, albumin and alanine aminotransferase, and routine haematological values. Total, conjugated, and displaced (free) serum bilirubin concentrations were measured from samples taken before treatment and those collected on day three or four of treatment. Clotting studies were performed on blood from 8 patients during or immediately after treatment. Blood cultures, gastric aspirates, and surface swabs were collected routinely before treatment. Lumbar puncture was only performed if there was clinical suspicion of meningitis. With the approval of the hospital ethical committee timed series of blood samples (five to six samples) were collected by heelprick for assay of latamoxef after the first injection or on day three or four of treatment. Urine samples were collected for drug assay from 14 babies on 17 occasions. One sample of cerebrospinal fluid was collected during treatment. Clinical observations were made by one of us (JJ) and were recorded prospectively.

Materials and methods

Latamoxef was assayed microbiologically using DST agar (Oxoid) pH 7.4 and *Escherichia coli* NCTC 10418 as indicator organism. Pharmacokinetic variables were determined on those dose response curves which had a significant 'goodness of fit' with a computer model.⁷ First dose and steady state pharmacokinetics were compared as were the pharmacokinetics after intravenous and intramuscular administration. The effects of various patient characteristics on the pharmacokinetic variables were also evaluated. The results were analysed statistically using Student's *t* test, Pearson's correlation coefficients, and Duncan's one way analysis of variance.

Routine laboratory procedures were used for the biochemical, bacteriological, and haematological investigations. Measurement of bilirubin displacement was by the method of Jacobsen and Wennberg.⁸

Results

Nineteen babies received latamoxef for five days and two for 10 days. In 10 babies treatment was stopped after 48 hours because of clinical improvement and negative bacteriological results on specimens taken before treatment or a positive alternative diagnosis. Babies who received a five day course of latamoxef despite the absence of microbiological confirmation of sepsis did so because of continuing high risk status, continuing serious illness, or radiological evidence of infection. The final diagnoses based on clinical assessment, radiographs, and laboratory investigations on the 31 babies treated with latamoxef are shown in Table 1. Latamoxef was given for at least five days to babies in groups A to H (Table 1) and for only 48 hours to babies in groups I to O.

Pathogenic bacteria were isolated from bacteriological samples collected before treatment began and reported 48 hours later in 9 of the babies studied (Table 2). Overall clinical improvement occurred in

Table 1 Diagnoses on babies treated with latamoxef

Group	No
A Severe hyaline membrane disease (ventilated) (1 with <i>Haemophilus parainfluenzae</i>)	9
B Pneumonia (1 with bronchopulmonary dysplasia and <i>Staphylococcus aureus</i>)	2
C Septicaemia (group B streptococcus and <i>Staph aureus</i>)	2
D Meconium aspiration	2
E Aspiration	1
F Prolonged ventilation with purulent tracheal secretions (<i>Staph epidermidis</i>)	1
G Apnoea of prematurity*	2
H Asymptomatic babies, born after rupture of membranes > 48 hours and colonised with group B streptococcus	2
I Mild/moderate hyaline membrane disease	2
J Transient tachypnoea of newborn	1
K Respiratory distress associated with severe rhesus disease	1
L Heart failure	1
M Convulsions (central nervous system abnormality)*	1
N Polycythaemia with respiratory symptoms	1
O Asymptomatic babies born after rupture of membranes > 48 hours with negative bacteriology	3

*Two babies colonised with non-fermentative Gram negative rods and *Staph epidermidis*.

Table 2 Bacteria isolated from 9 of 31 babies treated with latamoxef

Bacteria isolated	Site	Latamoxef sensitivity*	Eradication after treatment
Group B streptococcus	Blood, surface swabs, gastric aspirate	+	+
Group B streptococcus	Surface swabs	+	+
Group B streptococcus	Surface swabs	+	+
<i>Staph aureus</i>	Blood and surface swabs	+	+
<i>Staph aureus</i>	Nasopharynx	+	+
<i>H parainfluenzae</i>	Surface swabs	+	+
<i>Staph epidermidis</i>	Nasopharynx	+/-	-/-
Inert Gram negative rod, <i>Staph epidermidis</i>	Surface swabs	-/+	-/-
Inert Gram negative rod, <i>Staph epidermidis</i>	Surface swabs	+/-	+/+

*Disc diffusion test: 30 mg/disc.

Figure Serum latamoxef concentrations/time curves after (a) single dose and (b) multiple doses.

all but one baby. The exception, a baby of 27 weeks' gestation weighing 0.68 kg with severe hyaline membrane disease, died aged 24 hours after a pulmonary haemorrhage. One other patient with pneumonia superimposed on bronchopulmonary dysplasia relapsed after treatment. Initial clinical and radiological response to a five day course of latamoxef was excellent but within 48 hours of stopping treatment the baby's condition had deteriorated and further chemotherapy was required. All surviving babies were discharged well from hospital. Ten babies became colonised with faecal streptococci during treatment but no infections were attributed to these organisms.

Biochemical investigations showed no alteration in renal or hepatic function attributable to latamoxef treatment. There was no increase in values of displaced bilirubin associated with latamoxef and clotting studies on 8 babies receiving antibiotic for five days were normal. There were no drug associated changes in haematological values. None of the babies studied had bloody stools during or within 48 hours of completing treatment. The only clinical side effects of latamoxef treatment were disulfiram-

like reactions in two babies receiving concomitant treatment with alcohol based phenobarbitone elixir. The reaction consisted of a florid urticarial-type rash over the whole body. No changes in vital signs were observed and vomiting did not occur. The rash faded after three to four hours.

Thirty of 31 data sets had a significant goodness of fit with the computer model. Pharmacokinetic variables after single and multiple injections are shown in Table 3. In babies of comparable gestational age, postnatal age, and birthweight peak concentrations were higher after multiple injections (Figure) but clearance was more rapid ($P < 0.02$) and half life shorter ($P < 0.03$) resulting in significantly lower trough concentrations ($P < 0.02$) after two to five days' treatment (Table 3). Serum half life decreased with increasing postnatal age ($r = -0.4118$, $n = 30$, $P < 0.02$).

Half life was also shorter ($r = -0.3944$, $n = 29$, $P < 0.05$) in babies who were pyrexial. The volume of distribution was significantly larger in babies with respiratory problems, ($t_{28} = 3.3$, $P < 0.005$), with low values of serum protein ($r = 0.4307$, $n = 24$, $P < 0.005$) and those receiving intravenous treatment

Table 3 Pharmacokinetics of latamoxef in the newborn (mean (SD)) after one dose and at steady state

	First dose (n = 9)	Steady state (n = 21)
Peak serum concentration (mg/l)	105 (18)	128 (27)
12 hour trough serum concentration mg/ml	37 (12)	31 (10)
B-phase half life (hours)	8.9 (3.3)	5.8 (1.1)
Volume of distribution (ml/kg)	478 (112)	515 (148)*
Total body clearance (ml/kg/min)	0.68 (0.23)	1.02 (0.33)
Time to peak concentration after intramuscular injection (hours)	1.6 (0.6)	0.9 (0.1)

*Derived after residual effect of previous dose had been deducted.

($t_{28} = 3.4$, $P < 0.005$). Apart from time to peak serum concentration there were no differences in pharmacokinetic variables between the intravenous and intramuscular routes of administration. No differences in pharmacokinetic variables were directly associated with gestational age.

Urinary concentrations of latamoxef were above 100 mg/l throughout treatment and reached maximum concentrations well above 1000 mg/l. The single sample of lumbar cerebrospinal fluid was collected five hours after injection. It contained 10 mg/l latamoxef but no excess of leucocytes.

Discussion

Latamoxef is a safe and efficacious alternative to gentamicin with penicillin or ampicillin in the initial treatment of neonates with clinical suspicion of infection. No unexpected clinical, biochemical, or haematological side effects were observed apart from the disulfiram-like reactions which may be explained by the chemical structure of the antibiotic. Care must be exercised so that no alcoholic elixirs are prescribed to patients receiving latamoxef. We could find no evidence that latamoxef treatment resulted in displacement of protein bound bilirubin, a finding recently confirmed by Stutman *et al.*,⁹ which is contrary to earlier reports by Cashore *et al.*¹⁰ Concern has been expressed that the new broad spectrum cephalosporins may affect gut flora sufficiently to upset vitamin K production and absorption and hence blood clotting mechanisms. We could find no evidence of this in the present study.

Latamoxef has a relatively low degree of activity against *Streptococcus agalactiae* (Lancefield group B streptococcus, MIC₉₀ = 4 mg/l). Nevertheless three babies in the study who were infected with this organism responded well and the organism was eradicated probably as a result of the high serum concentrations maintained throughout treatment (Table 3). In common with other third generation cephalosporins, latamoxef treatment is associated with a high degree of colonisation with faecal

streptococci (33% patients), organisms which are resistant to this group of antibiotics but sensitive to ampicillin and the ureido penicillins. In this study such colonisation was of no clinical importance.

The pharmacokinetic characteristics of latamoxef are similar to those of the other broad spectrum cephalosporins in neonates¹¹⁻¹³ showing high serum values in comparison with the minimal inhibitory concentrations for susceptible pathogens. Half life is longer and volume of distribution larger than in adults.¹⁴ In contrast to postnatal age, prematurity did not influence the pharmacokinetics of latamoxef in this age group. Apart from the first injection there is no need for intravenous administration of latamoxef to neonates since the pharmacokinetic characteristics are the same after intramuscular or intravenous administration. Latamoxef has been shown previously to penetrate into cerebrospinal fluid¹⁵⁻¹⁷ and has been used successfully to treat Gram negative bacillary meningitis in the neonate.¹⁸ Schaad *et al.*² have cautioned against its use in the treatment of group B streptococcal meningitis. The finding in this study that latamoxef achieved therapeutic concentrations in the cerebrospinal fluid in one patient, even when the meninges were not inflamed, has since been confirmed in other patients (unpublished information) and by other authors.^{16, 17} The treatment of clinical sepsis in the newborn with such antibiotics will we hope sterilise the cerebrospinal fluid before meningitis can develop.

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Maternal views on breast feeding, 1871

From a letter written to a father after the birth of a baby.

'I hope Mrs X is to have the happiness of nursing him herself. Tell her from me to let nothing and nobody dissuade her if possible from nourishing her baby with what nature provided. I hardly know a mother now who does so and have such strong views on the subject that I could write an essay to enforce them. There is often much to be contended against at first but the reward in health and happiness to both mother and child is far more than adequate. I am nursing this baby better than any of her predecessors having made up my mind to make everything secondary to it meantime and not to be thwarted as I have sometimes been by nurses and even doctors.'