Rectal aminophylline in the management of apnoea of prematurity

A J LYON AND N McINTOSH

Neonatal Unit, St George's Hospital, London

SUMMARY Rectal suppositories as an alternative to intravenous aminophylline in the management of recurrent apnoea were studied in 41 preterm infants of mean gestation 28.3 weeks and mean birthweight 1176 g. Therapeutic blood concentrations were obtained two hours after a rectal loading dose of 10 mg/kg, with steady concentrations and maximum reduction in apnoeic episodes (from a mean of 0.5 per hour to 0.09 per hour) within 24 hours on a maintenance dose of 10 mg/kg/day. There was good correlation between the rectal dose and the plasma theophylline concentration. Several infants showed a significant reduction in P_{CO_2} when treated with aminophylline. Side effects were related to the plasma theophylline concentration and were not seen at concentrations less than 14 mg/l.

Methylxanthines are effective in the management of apnoea of prematurity.^{1,2} Dosage schedules for intravenous aminophylline have been reported,^{3,4} but repeated venous access can be a problem in the preterm neonate if no intravenous line is in situ. Oral preparations are absorbed erratically and have possible gastrointestinal side effects.³

There have been reports of unpredictable blood concentrations and deaths in children and adults using aminophylline suppositories in the treatment of asthma.^{5,6} In the apnoeic neonate, however, aminophylline suppositories have been effective,^{1,7} but neither blood concentrations nor any assessment of toxic effects have been reported.

The policy at this hospital has been to use an intravenous loading dose of aminophylline followed by maintenance treatment with suppositories. The intravenous dose has often been omitted, however, if no intravenous line has been available.

This study aimed to evaluate clinical experience with aminophylline suppositories in the management of apnoea of prematurity and to obtain pharmacokinetic data for this preparation. In particular, suppositories were compared with intravenous aminophylline as an effective means of administering a loading dose of theophylline.

Patients and methods

To determine the optimum maintenance dose of rectal aminophylline the plasma theophylline concentrations achieved in 40 infants on varying doses

were obtained retrospectively from hospital notes; all concentrations were determined after the baby had been on aminophylline for at least 48 hours. The concentrations were plotted against dose and the regression line calculated by the method of least squares.

Forty one preterm infants (gestation, mean (SD) 28.3 (2.2) weeks; birthweight, mean (SD) 1176 (350 g)) with recurrent apnoea, defined as cessation of respiration for 20 seconds with associated bradycardia or cyanosis, were then studied prospectively.

Three groups of similar gestation, birthweight, and age at start of treatment were compared:

- (a) No loading dose (n=17).
- (b) Rectal loading dose 10 mg/kg (n=12).
- (c) Intravenous loading dose 6 mg/kg (n=12).

Starting four hours after the loading dose, maintenance treatment in all three groups was with aminophylline suppositories (Macarthy Ltd), 10 mg/kg/day in three or four divided doses. The suppositories were held in the rectum by a finger over the anus until dissolved, usually in one to two minutes.

Theophylline concentrations in plasma were determined using an enzyme multiplied immunoassay technique (EMIT, SYVA Chemicals). Blood (0.5 ml) for plasma theophylline determinations was taken at one, two, and three hours after the loading dose, before maintenance treatment had begun, and then at 24 hours and 48 hours after starting this. Plasma concentrations were checked further, as necessary, for therapeutic monitoring, the dose

being altered to keep the concentrations between 6 and 13 mg/l.

After treatment for at least 48 hours, the plasma concentrations in five infants were determined immediately before and at one and two hours after a suppository, to check for variability in concentrations at different times after a dose. In these same infants the half life of theophylline was calculated from concentrations 12 and 36 hours after stopping treatment.

Six infants had $Paco_2$ values recorded before and after treatment with aminophylline and three other babies had continuous transcutaneous CO_2 recordings, linked to a computer based monitoring system,⁸ over the period that treatment was started.

All side effects related to aminophylline were noted.

Results

The relation between plasma theophylline concentrations and dose for the retrospective analyses of the hospital notes of 40 infants is shown in Fig. 1. Concentrations while on different dosages were determined in six babies, and in each of these the correlation coefficient for plasma concentration and dose was between 0.76 and 0.95.

After the intravenous and rectal loading doses, maximum concentrations were achieved by two hours. The Table shows the mean plasma concentrations and numbers of apnoeic episodes, at two, 24, and 48 hours after starting treatment with aminophylline for each group.

In the groups (b) and (c), who received a loading dose, similar therapeutic concentrations were obtained by two hours, with steady concentrations and maximum effect achieved within 24 hours. In group (a) with no loading dose, the steady state and maximum therapeutic effect were still not obtained by 48 hours.

After treatment for at least 48 hours with a particular dose, there were no significant differences between the plasma concentrations taken at varying

Fig. 1 Relation between plasma concentration of theophylline (mg/l) and dose (mg/kg/d).

times after a dose. The half lives calculated from concentrations after treatment ranged from 23 to 37 hours.

Figure 2 shows the effect of aminophylline on $Paco_2$ values in four infants who responded to treatment and in two who showed no reduction in apnoeic episodes despite therapeutic blood concentrations. Continuous monitoring of transcutaneous Pco_2 showed similar changes in transcutaneous Pco_2 after treatment with theophylline.

Toxic effects were recorded in 14 infants. These were related to the plasma concentrations and were not found at concentrations less than 14 mg/l. Twelve developed a tachycardia (greater than 170/minute), six had glycosuria, and one infant became hyponatraemic. In two patients increased jitteriness and fits were recorded with plasma concentrations of 14.5 and 17 mg/l.

An increase in basal heart rate occurred in all treated infants, and the rise correlated significantly

Table Relation between plasma concentration of theophylline at 2, 24, and 48 hours after starting treatment, with and without loading doses, and the number of apnoeic episodes (values, mean (SD))

Loading dose Concentration (mg/l) Apnoeic episodes per hour	Time after loading dose								
	2 hours			24 hours			48 hours		
	None	pr	iv	None	pr	iv	None	pr	iv
Concentration (mg/l)	—	7.81 (1.84)	7.73 (2.26)	5.81 (1.44)	11.19 (2.46)	10.73 (2.09)	10.16 (1.38)	12.42 (2.08)	12.44 (1.56)
Apnoeic episodes per hour	0.51 (0.29)	0.49 (0.43)	0.51 (0.20)	0.31 (0.37)	0.09 (0.10)	0.15 (0.10)	0.15 (0.17)	0.06 (0.06)	0.10 (0.09)

pr=per rectum; iv=intravenously.

*pr and iv v none. $P<0.01$.

Fig. 2 Effect of aminophylline on P_{aCO_2} in 4 infants with apnoea who responded clinically (●—●) and 2 infants with no clinical response (○—○).

Conversion—SI to traditional units: 1 kPa $\approx$ 7.52 mmHg.

Fig. 3 The rise in heart rate with plasma theophylline concentration at 'therapeutic' and 'toxic' blood values.

with the concentration of theophylline ($r=0.65$, $P<0.05$). A rise of greater than 20 beats/minute was seen in 12 of 14 infants with concentrations greater than 14 mg/l, but in only one of 20 with a concentration less than 14 mg/l (Fig. 3).

No local side effects of the suppositories were noticed.

Discussion

Aminophylline suppositories proved an effective and safe means of administering theophylline to

preterm neonates. The absorption was rapid, with therapeutic concentrations achieved within two hours of a loading dose of 10 mg/kg. The correlation of plasma concentrations and dose was much better than that found in older children and adults, and possibly reflects a more controlled method of administration.

One of the major problems with suppositories is the difficulty in tailoring the dose to the needs of the individual. In most infants, therapeutic concentrations were maintained using 10 mg/kg/day and this dose was achieved with a combination of 3 and 5 mg suppositories given three or four times a day. The long half life of theophylline in preterm infants means that even if given eight hourly, there will be very little change in concentration between doses. Good concentrations and response were achieved by a twice daily suppository in two infants. The manufacturers will supply suppositories of any required strength.

Theophylline improves respiratory drive, probably by increasing the sensitivity of the respiratory centre to CO_2 .⁹ This increase in respiratory drive is shown by the reduction in P_{CO_2} after treatment.

All preterm infants being treated with aminophylline should have the plasma concentration determined regularly for therapeutic monitoring. Even in the best centres, however, there can be a substantial delay in obtaining results from the laboratory. An increase in basal heart rate greater than 20 beats/minute is an indication that the plasma concentration may be in the toxic range.

Aminophylline suppositories used in the management of apnoea of prematurity are as effective as, and a safe and convenient alternative to, the intravenous preparation.

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Correspondence to Dr N McIntosh, Neonatal Unit, St George's Hospital, London SW17 0QT.