Plasma xanthine levels in low birthweight infants treated or not treated with theophylline

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SUMMARY The use of theophylline in the management of apnoea in the newborn was studied in 33 preterm infants. Infants received a dose of 3 mg/kg, 13 of them every six hours, the remaining 20 every eight hours. All the infants had significantly fewer apnoeic episodes. In a pharmacokinetic study, the half life of theophylline was 30.3 ± 7.2 hours and the clearance rate was 23.9 ± 5.06 ml/kg per hour (means and SD). The plasma theophylline level remained constant at between 13 and 15 mg/l from the 5th day of treatment but, at the same time, the plasma levels of caffeine rose to a mean level of 4.4 mg/l. Caffeine was detectable in plasma at birth, and in preterm infants not receiving theophylline; plasma levels of caffeine tended to be similar to the levels in their mothers' milk. These observations have led to clear conclusions on the optimum timing and dosage of theophylline, and on the need to monitor plasma levels of both theophylline and caffeine in newborn infants treated with theophylline.

About one-quarter of newborn babies <2500 g have an apnoeic episode during the first 10 days of life (Daily *et al.*, 1969); repeated episodes can lead to brain damage because of hypoxia and acidosis (Bacola *et al.*, 1966; Alden *et al.*, 1972). We do not yet know the pathogenesis of apnoea: several factors seem to operate, especially an alteration in the sensitivity of central nervous receptors to hypoxia and (or) hypercapnia due to cerebral immaturity (Parmelee *et al.*, 1972; Rigatto and Brady, 1972; Kattwinkel, 1977). Kuzemko and Paala (1973) were the first to treat apnoea in premature infants with xanthines, and this treatment has been shown to be successful (Shannon *et al.*, 1975; Uauy *et al.*, 1975; Aranda *et al.*, 1976; Bednarek and Roloff, 1976; Giacoia *et al.*, 1976; Demarquez *et al.*, 1977).

The aim of this study is to present our results on the use of theophylline in the treatment of premature apnoea with particular reference to the pharmaco-

kinetic study of theophylline and caffeine. It is well known that caffeine, like theophylline, prevents apnoea but is equally dangerous; however, this study shows that caffeine is always present in the plasma of premature infants treated only with theophylline.

Material and methods

In the 7 months from 1 March to 31 October 1977, we treated 33 infants for recurrent apnoea, using theophylline (1–3 dimethylxanthine). Recurrent apnoea was defined as cessation of breathing for more than 25 seconds with bradycardia, with or without cyanosis, occurring at least 3 times a day.

The mean birthweight was 1450 ± 281.5 g (SD) (900–2100) and mean gestational age, assessed by the Dubowitz score system (Dubowitz *et al.*, 1970), 33.6 ± 2.3 weeks (27–37). The mean age when theophylline was first given was 2.9 ± 2 days and the duration of this treatment was between 5 and 35 days (mean 15.2). In addition to the recurrent apnoeic spells, concomitant diseases were respiratory distress syndrome (2), and *Klebsiella septicaemia* (treated with gentamicin) (2). Clinical and laboratory evidence of metabolic abnormalities (e.g. hypoglycaemia or hypocalcaemia) or other correctable causes of apnoea was absent at the time of starting treatment. None of the infants was treated

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with continuous distending airway pressure (positive pressure or negative pressure respirator).

The baby was placed in an incubator with servo controlled temperature; apnoea was observed visually or by the use of an apnoea monitor (Infants Sentry Stolting, USA) adjusted to signal after 9 seconds of apnoea. The heart rate was monitored by cardiograph, and an alarm signalled when the rate fell below 80. The respiratory rate was recorded hourly by inspection during the critical phase (1 to 3 days) and thereafter every three hours. Arterial blood-gases and pH were checked regularly every 3 to 6 hours during the first day of life by means of an arterial catheter; thereafter arterialised blood for measuring pH and PCO_2 was obtained daily by heel pricks, or more often if clinically indicated.

Theophylline dissolved in 10% alcohol in a concentration of 5 mg/ml was administered by nasogastric tube. Initially, 13 newborn babies received a dose of 3 mg/kg every 6 hours, but when we found that xanthine bases tended to accumulate in the plasma the dose was changed and 20 infants received the same dose every 8 hours. (No infant received caffeine.) A single IM injection of phenobarbitone (10 mg/kg) was given to each baby immediately after birth to diminish neonatal jaundice (Salle *et al.*, 1977).

Plasma levels of theophylline and caffeine were measured on the mornings of the 1st, 2nd, 3rd, 5th, and 11th days of theophylline treatment, and then every 3 or 4 days. The blood was taken by heel prick 2 hours after administration of the drug. In 10 infants the levels of theophylline and caffeine were measured at periods of one hour, and then 5, 6, 7, and 8 hours immediately after the oral administration of 3 mg/kg theophylline on the 2nd day of treatment to estimate the clearance rate of theophylline and caffeine. In 20 infants, the clearance and half life of plasma theophylline were measured.

In 55 preterm and term newborn babies, the plasma level of caffeine was measured at birth and before any drug treatment; mean birthweight was 1757 ± 494.6 g (SD) and mean gestational age was 35 ± 3.3 weeks.

The level of caffeine was also measured in the plasma of 6 breast-fed babies not treated by theophylline and in their mothers' milk for 6 days. Mean birthweight was 1906 ± 118 and mean gestational age 34.8 ± 1.8 weeks.

Plasma theophylline and caffeine levels were measured in 20 μ l plasma by gas liquid chromatography (GLC) using nitrogen-specific detection (Ribon *et al.*, 1979). The method allows the simultaneous measurement of theophylline, caffeine, and phenobarbitone (Fig. 1). The three drugs are extracted

Fig. 1 Chromatogram of plasma from a preterm infant.

from plasma or whole blood with a mixture of chloroform and isopropanol (95.5 v/v) in a buffered medium at pH 5.2. The pentyl derivatives of the extracted molecules are separated by GLC on a column coated with 3% OV17 on chromosorb W A W D M C S. The quantitative minimum sensitivity is $<0.5 \mu\text{l/ml}$ for the three drugs.

The bio-availability of the solution of theophylline (in ethanol/water 10% v/v) is about 100%. The drug is administered by doses of 3 mg/kg every 8 hours, the pharmacokinetic parameters may be calculated from the following equation.

$$P_{ss} = \frac{D_o}{K_e V_f T} \quad (1), \text{ where}$$

P_{ss} = plasma level at steady state, D_o = administered dose, K_e = elimination rate constant, V_f = volume of distribution, T = time interval between two doses.

The total clearance is given by the relation

$$Cl = K_e V_f \quad (2),$$

and combining equations (1) and (2),

$$Cl = K_e V_f = \frac{D_o}{P_{ss} T} \quad (3)$$

Clearance may be calculated from the plasma level at steady state after 5 days' treatment with theophylline. For each baby the dose (D_0) and time interval (T) are known, allowing the clearance value to be calculated from equation (3). During the first reaction, the constant elimination rate is related to half life ($t_{1/2}$) by the equation,

$$K_e = \frac{0.693}{t_{1/2}} \quad (4)$$

The half life was calculated by the fall in plasma level of theophylline after oral administration. The volume of distribution (V_f), is then given by,

$$V_f = \frac{Cl \times t_{1/2}}{0.693} \quad (5)$$

Results

Out of 33 treated infants 18 had no further apnoea. Of the 15 remaining infants in this group, none required to be ventilated for apnoeic spells. Fig. 2 shows the course of apnoeic spells after birth in these 15 infants. The treatment was stopped in one baby because of tachycardia and at that time the plasma level of theophylline was 24 mg/l.

Pharmacokinetic study. In 20 infants, the mean clearance was 23.96 ± 5.06 ml/kg (SD) per hour. The half life was 30.3 hour ± 7.2 , the distribution of the volume of theophylline was 1.03 ± 0.2 l/kg. The absorption of theophylline was rapid because the half life is long and plasma levels remained fairly constant between each oral adminis-

Fig. 2 Number of infants (out of 33) who had apnoeic spells after the 1st day of treatment.

tration (Fig. 3); plasma levels were measured at various times after oral administration so that the absorption of the drug could be studied.

With the dose used, the mean plasma level of theophylline rose rapidly to plateau between 13 and 15 mg/l from the 5th day of treatment. The plasma level was maintained within these two limits with a

Fig. 3 Course of plasma theophylline levels in 10 infants after an oral dose of 3 mg/kg (mean and SD). Theophylline was given every 8 hours.

Fig. 4 Course of xanthine base levels (theophylline, blank column; caffeine, hatched column) in 33 infants (mean and SD).

dose of 3 mg/kg 8-hourly. At the same time, the plasma level of caffeine rose to a mean level of 4.4 mg/l by the 11th day of treatment. The total mean level of xanthines (caffeine + theophylline) was between 15.7 and 18 mg/l (Fig. 4).

The plasma levels of caffeine and theophylline correlated (104 measurements, r 0.56, $P < 0.01$) (Fig. 5).

Plasma levels of caffeine at birth

Caffeine readily crosses the placenta (Parsons *et al.*, 1976). The level of caffeine at birth (age 1–2 hours), is shown in the Table. 76% of infants studied had detectable caffeine in the plasma (Table).

Table Plasma levels of caffeine at birth (55 infants studied)

Plasma levels of caffeine (mg/l)		%
mg/l		
0		23.63
Between 0 and 1		20
1 and 2		29.09
2 and 3		16.36
3 and 4		3.63
4 and 5		3.63
5 and 6		3.63

Infant plasma and maternal milk levels of caffeine

There was a significant correlation between the two levels against time (Fig. 6). Low levels of caffeine

Fig. 5 Plasma theophylline levels related to caffeine levels. (r : 0.56; $P < 0.01$).

Fig. 6 Plasma caffeine levels in 6 babies related to level in the mothers' milk.

in maternal milk were associated with undetectable levels in the infants' plasma, while high levels in the maternal milk gave a raised level in the child. In this study, the infants were aged either 8–15 or 15–21 days. Results showed that diet alone could not have been responsible for the accumulation of caffeine in the plasma up to levels of 1.5 mg/l, although the half life of this substance is very long in the newborn (Aranda *et al.*, 1977a).

Discussion

Our study confirms results on the pharmacokinetics of theophylline in term infants; we found it had a long half life, the clearance rate being 23.96 ± 5.06 ml/kg per hour. Our results were slightly higher than some others: Aranda *et al.* (1976), measuring theophylline in total blood, found a clearance of 17.6 ml/kg per hour, Giacoia *et al.* (1976), a clearance of 30 ml/kg per hour. Our values were closer to those of Demarquez *et al.* (1977), 23.6 ± 9.41 ml/kg per hour.

In order to maintain a minimum level of theophylline of 8 mg/l and to avoid exceeding 15 mg/l (Aranda *et al.*, 1976; Demarquez *et al.*, 1977), we now give 3 mg/kg theophylline every 8 hours, the same dose recommended by Shannon *et al.* (1975) and Uauy *et al.* (1975). The plasma level of theophylline was kept low, so decreasing the possible side effects—such as sleep disturbance, diuresis, and failure to gain weight. Nevertheless, it is important to check the plasma level of theophylline every three days, because the clearance rate varies between different infants (from 15.5 to 34.5 ml/kg per hour). We had no complications in our babies except in one (see Results).

By observing the plasma level of theophylline we have developed a new method of treatment. In order to increase the plasma level of theophylline rapidly on the first day and then maintain a plateau below 15 mg/l, we give a high oral dose of 6 mg/kg initially.

It is known that the toxicity and pharmacological activity of caffeine are similar to those of theophylline. Some have advocated the use of caffeine in the prevention and treatment of apnoea in the preterm infant (Aranda *et al.*, 1977a, b). 76% of newborn babies had detectable levels of caffeine at birth; this fact could possibly explain why apnoeic spells often start after the 2nd day of life in preterm infants. In the theophylline-treated infants, the plasma level of caffeine rose to about 5 mg/l; thus it seems important to measure the levels of both theophylline and caffeine in order to know the total level of xanthine bases in infants receiving either theophylline or caffeine.

The presence of caffeine in the plasma of infants receiving only theophylline was surprising. It is possible that the baby had received caffeine from the mother: we have shown that in preterm infants *not* treated with theophylline, the plasma levels of caffeine were similar to those in their mothers' milk, although in no baby did the plasma level of caffeine exceed 1.5 mg/l. In the theophylline-treated preterm infants, the plasma levels of caffeine were higher and the mothers' milk alone could not have been responsible for the accumulation of caffeine.

Another possible explanation is biochemical. It is known that in adults, caffeine is metabolised by demethylation to give theophylline. The inverse process (i.e. methylation in N₇ of theophylline) might exist in the infant; we are testing this hypothesis by means of molecules labelled with stable isotopes. The fact that phenobarbitone was given at birth to these preterm infants and that a dose of phenobarbitone increases liver enzyme activity could be relevant.

Theophylline is useful for treating or preventing apnoeic spells in the preterm infant but, because of the varying clearance rate in individuals, it should be given in low doses and plasma levels should be checked regularly; as there is a parallel accumulation of caffeine in the plasma, the plasma level of caffeine should also be checked.

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