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# Apnoea of immaturity

## 1. A controlled trial of theophylline and face mask continuous positive airways pressure

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SUMMARY A randomised controlled trial of theophylline versus face-mask continuous positive airways pressure (CPAP) treatment for recurrent apnoea of immaturity was carried out in 32 infants of 25 to 32 weeks' gestation. Continuous recording of electrocardiogram and impedence pneumogram added objective assessment to the nurses' observations for 11 courses of treatment. The CPAP group had more adverse perinatal factors but the frequency of apnoeic attacks before treatment was comparable. Infants given theophylline had a greater reduction in the incidence of prolonged apnoeic attacks, and this difference persisted after allowing for the effect of perinatal complications. Continuous recordings showed a greater reduction in episodes of bradycardia of $\leqslant$80/minute with theophylline. Five of 18 infants given theophylline needed intermittent positive pressure ventilation for apnoea compared with 12 of 14 given CPAP. The poor response in 17 of 32 infants suggests a need for a more effective method of preventing or treating apnoea in very immature babies, in whom adverse perinatal factors often coexist.

Recurrent apnoea is a common problem in preterm infants,[1] with a high mortality and risk of long-term handicap.[2–4] Successful treatment with aminophylline was first reported in 1973[5] and there have been further reports of its benefit.[6–9] Continuous positive airways pressure (CPAP) has also been found effective.[10–12] No trials have directly compared these two treatments, both now in common use. A randomised controlled trial was therefore undertaken to determine which treatment was most effective and which produced least side effects.

### Method

**Patients.** Infants of 32 weeks' gestation or less at birth admitted between November 1977 and January 1980 were considered for the trial if they developed recurrent apnoea during the first 4 weeks of life. Infants were nursed routinely on mattress apnoea alarms and audible cardiorates. Recurrent apnoea was defined as cessation of breathing for $\geqslant$10 seconds with bradycardia $<$100/minute or cyanosis, occurring at least twice within any 6-hour period or three times within 24 hours.

Infants were investigated with blood count, blood cultures, surface swabs, lumbar puncture, serum electrolytes, and Dextrostix, and the majority with a chest *x*-ray film; they were excluded if a treatable cause for apnoea was found, such as sepsis, cardiac failure, deteriorating hyaline membrane disease, or convulsions. Infants with coexisting conditions—such as recovering hyaline membrane disease, patent ductus arteriosus murmur without clinical heart failure, and mild electrolyte disturbances—were included.

**Procedure.** Parental consent was obtained and the infants randomly assigned to theophylline or CPAP treatments. Aminophylline was given as an intravenous loading dose, followed by intravenous maintenance, adjusted by blood levels as previously recommended.[13] CPAP was administered by face-mask[14] at a pressure of 2-3 cm water increasing to 4–5 cm water if apnoea did not improve. If response to one treatment was poor (as defined below), the infant was changed to the other. Successful treatment was continued for 48 hours after the last episode of apnoea with bradycardia, and was restarted if the infant relapsed. The decision to start intermittent positive pressure ventilation (IPPV) was left with the clinical staff.

Nurses recorded episodes of apnoea ($\geqslant$10 seconds) bradycardia ($<$100/minute), and cyanosis, and the duration of the episode and any intervention required. Later in the study, continuous recordings of

electrocardiogram and impedence pneumogram were made on to cassette tapes before and during treatment and were analysed by me blindly. The infants' notes were reviewed for problems before the onset of apnoea. A perinatal complication score was computed allowing one point each for: intrauterine asphyxia (antepartum haemorrhage, type II dips, or cord prolapse), breech delivery, temperature <35°C, onset of respiration at 5 to 9 minutes after birth; and two points each for onset of respiration at ⩾10 minutes and IPPV (after initial resuscitation).

Complications arising during or after treatment were noted. Two-hourly observations of heart rate, respiratory rate, and body and incubator temperature were kept for the 24 hours before and after starting treatment. Time of establishing milk feeding was recorded. The development of surviving infants is reported separately.[15]

**Analysis.** Episodes of apnoea ⩾10 seconds were counted from the nurses' charts and hourly rates calculated for the 24 hours preceding treatment (less if treatment started during the first day of life), for the first 24 hours on treatment and for the whole course of treatment. Rates were calculated separately for episodes with and without associated bradycardia <100/minute or cyanosis, and for prolonged episodes ⩾60 seconds' duration. Response to treatment was considered good if apnoea was reduced ⩽25% of pretreatment rates, moderate if apnoea was reduced to 26–74%, and poor if apnoea remained ⩾75% of pretreatment rates or if attacks became more prolonged. From the continuous recordings, all episodes of apnoea ⩾10 seconds, and of bradycardia ⩽80/min and ⩽60/min, were counted and hourly rates calculated on and off treatment. The percentage of the recording time spent apnoeic or with heart rate ⩽80/min was also calculated. For each baby the differences were calculated between treatment and no treatment periods. The following statistical tests were used as appropriate: Student's *t* test, Wilcoxon's rank sum test, $\chi^2$ test with Yates's correction, Fisher's exact test, multiple covariance analysis, and Kendall's rank correlation coefficient. Differences were considered significant if $P<0.05$.

Table 1 *Infants excluded from controlled trial*

| | |
|---|---|
| Treatment started before transfer from another hospital | 8 |
| Too severe (18 infants required urgent IPPV, one considered not viable at 24 weeks) | 19 |
| Too mild (paediatrician felt treatment unnecessary, despite trial criteria being fulfilled) | 30 |
| Randomisation not possible (two on CPAP for recovering hyaline membrane disease, one severe facial bruising precluded mask CPAP, one given theophylline when all CPAP circuits were in use) | 4 |
| Randomisation omitted (treatment started before trial considered, generally because of staff changes) | 8 |
| Parental consent refused | 1 |
| Incorrect dose of theophylline given (see text) | 1 |

*One hundred and three infants had recurrent apnoea, of whom 32 entered the trial.

## Results

Three hundred and sixty-two infants of 32 or less weeks' gestation were admitted during the study period and 103 developed recurrent apnoea for which no cause apart from immaturity could be found. Exclusions from the trial are shown in Table 1. Despite strict criteria for entry, 31 eligible infants were not treated as the nursing or resident medical staff thought the signs too mild and did not report them immediately. Of those entering the trial 29 had had more than the required number of episodes. The possible effects of delay in treatment, and the outcome for those not entered into the trial are reported separately.[15] In each case the randomisation was made only after the decision to start treatment. Thirty-three infants entered the trial but in one on theophylline the loading dose was omitted, therapeutic levels being reached 23 hours later. Of the

Table 2 *Characteristics of infants before treatment with theophylline or CPAP*

| | *Theophylline (n = 18)* | *CPAP (n = 14)* | *P value* |
|---|---|---|---|
| Birthweight (g) mean ± SD | 1107 ± 332 | 1121 ± 238 | NS |
| Gestation (weeks) mean ± SD | 28·0 ± 1·7 | 27·4 ± 1·2 | NS |
| Boys (number) | 13 | 10 | NS |
| Breech delivery (number) | 3 | 7 | NS |
| Birth asphyxia (number) (onset of respiration ⩾ 5 minutes) | 6 | 10 | NS |
| IPPV (after initial resuscitation) | 2 | 8 | <0·02 |
| Perinatal complication score*, median | 1·5 | 3·5 | <0·01 |
| Range | (0–5) | (0–6) | |
| Total number of apnoeic attacks before treatment, median | 11 | 6 | NS |
| Range | (2–38) | (2–25) | |
| Apnoeic attacks per hour in 24 hours before treatment, median | 0·40 | 0·38 | NS |
| Range | (0·17–3·82) | (0·17–1·71) | |

*See method.

remaining 32 infants, 18 received theophylline and 14 CPAP, and their characteristics are shown in Table 2.

**Effect of treatment as judged by nurses' records.** Fourteen of 18 infants receiving theophylline had a good or moderate response, compared with 5 of 14 receiving CPAP ($\chi^2$ 4·16 $P<0·05$). Table 3 shows the reduction in apnoeic attacks per hour compared with pretreatment rates for the two treatments. Prolonged episodes $\geqslant$60 seconds responded significantly better to theophylline than to CPAP, whereas shorter episodes showed less difference between the two treatments. Table 4 shows the actual hourly rates of apnoea before and during both treatments. Using each infant as his own control the difference in attack rate before and during treatment has been calculated. On theophylline all 18 infants had a reduction in attack rate, and of 11 having prolonged attacks, 10 had fewer while on theophylline, highly significant differences; for infants receiving CPAP, there was no significant difference in attack rates before and during treatment. Respiratory rate rose by 5 breaths/minute after starting theophylline and fell by 3 breaths/minute with CPAP (Wilcoxon's rank sum test $P<0·01$).

**Effect of treatment as judged by continuous recordings.** Continuous recordings were available for only 11 courses of treatment (7 theophylline and 4 CPAP), the duration of recording ranging from 9 to 49 hours. From the 7 recordings with and without theophylline, episodes of bradycardia of $\leqslant$80/minute were reduced during treatment (Wilcoxon's signed rank sum test $P<0·05$). There was no significant change in episodes of apnoea $\geqslant$10 seconds, but the percentage of apnoeic attacks with bradycardia decreased significantly from 47% to 28% ($P<0·01$). Comparing the effect of theophylline with that of CPAP, episodes of bradycardia $\leqslant$80/minute and $\leqslant$60/minute, both showed significantly greater reduction with theophylline ($P<0·05$ and $P = 0·01$ respectively), as did the percentage of recording time spent with heart rate $\leqslant$80/minute ($P = 0·01$).

**Factors influencing effect of treatment.** There was no change in incubator or body temperature before or during either treatment. There was no significant correlation between birthweight or gestation and response to treatment. A multiple covariance analysis was carried out using the rate of apnoea on treatment as the dependent variable and the pretreatment rate, perinatal complication score, and type of treatment as independent variables. The pretreat-

Table 3 *Apnoeic attack rates during treatment, expressed as a percentage of pretreatment rates*

| | *Theophylline median (range)* | *CPAP median (range)* | *P value*** |
|---|---|---|---|
| 1st day of treatment, all attacks $\geqslant$ 10 seconds (n = 18 and 14) | 15% (0–83) | 43% (0–698) | $0·05<P<0·1$ |
| Whole course of treatment, all attacks $\geqslant$ 10 seconds (n = 18 and 14) | 14% (0–72) | 45% (0–698) | $P = 0·05$ |
| 1st day of treatment, all attacks with bradycardia or cyanosis (n = 18 and 14) | 18% (0–83) | 44% (0–408) | $0·05<P<0·1$ |
| Whole course of treatment, all attacks with bradycardia or cyanosis (n = 18 and 14) | 13% (0–64) | 50% (0–408) | $0·05<P<0·1$ |
| 1st day of treatment, prolonged attacks $\geqslant$ 60 seconds (n = 10 and 10)* | 0% (0–64) | 57% (0–408) | $<0·01$ |
| Whole course of treatment, prolonged attacks $\geqslant$ 60 seconds (n = 11 and 10)* | 0% (0–>100)† | 52% (0–408) | $<0·05$ |

*Infants omitted who had no attacks $\geqslant$60 seconds before or during treatment. ** Wilcoxon's rank sum test. †One infant had no prolonged apnoea before treatment, thus a percentage increase could not be calculated. For calculating Wilcoxon's test, he was given the largest rank, thus minimising the difference between theophylline and CPAP.

Table 4 *Hourly rates of apnoea before and during treatment*

| | *Attacks per hour* | | *Difference (rate during −rate before)* | *Attacks per hour* | | *Difference (rate during −rate before)* |
|---|---|---|---|---|---|---|
| | *Before theophylline* | *During theophylline* | | *Before CPAP* | *During CPAP* | |
| All attacks $\geqslant$ 10 seconds, median | 0·46 | 0·07 | −0·45*** | 0·37 | 0·26 | −018 |
| Range | (0·17–3·82) | 0–0·93) | (−2·06– −0·10) | (0·08–2·93) | (0–1·45) | (−1·61–+1·25) |
| All attacks $\geqslant$ 10 seconds with bradycardia, median | 0·40 | 0·07 | −0·34*** | 0·38 | 0·26 | −0·17 |
| Range | (0·17–3·82) | (0–0·93) | (−2·89– −0·09) | (0·08–1·71) | (0–1·45) | (−0·47–+0·65) |
| Prolonged attacks* $\geqslant$ 60 seconds, median | 0·24 | 0 | −0·22** | 0·19 | 0·08 | −0·07 |
| Range | (0–1·27) | (0–0·58) | (−0·69–+0·02) | (0–1·14) | (0·01–0·86) | (−0·59–+0·65) |

*Infants omitted who had no attacks $\geqslant$60 seconds before or during treatment, **$P<0·01$, ***$P<0·001$ } Wilcoxon's signed rank test,

ment rate of apnoea (that is severity) had a highly significant effect on the outcome, but after the effect of this and the perinatal complication score had been allowed for, there was still a significant effect of treatment, theophylline being associated with lower rates of prolonged apnoea ($\geqslant$60 seconds) than CPAP during the first 24 hours and the whole course of treatment ($P<0.05$). The rate for all apnoeic episodes ($\geqslant$10 seconds) with bradycardia during the first 24 hours of either treatment was similar, but during the whole course of treatment was lower on theophylline ($P<0.01$).

**Subsequent progress.** Of the 13 infants who failed to respond to treatment, 7 needed immediate IPPV. Four infants were changed from CPAP to theophylline, 3 responding; 2 infants changed from theophylline to CPAP continued with severe apnoea, requiring IPPV. Six of these infants were at some time given theophylline and CPAP together; in none was this more effective than theophylline alone. Of the 19 who responded initially, 11 relapsed when treatment was stopped. Six of 7 infants given a second course of theophylline responded again, but only one of 3 given further CPAP did so. Ultimately 17 infants required ventilation for apnoea, 5 of 18 given theophylline and 12 of 14 given CPAP ($\chi^2$ 8·42 $P<0.01$). Four of the theophylline group and 8 of the CPAP group died ($P>0.1$). A clinical diagnosis of intraventricular haemorrhage was made in 5 infants who died (4 in the CPAP group) all of whom deteriorated neurologically after starting treatment. Necropsy consent was refused in 2, but in the other 3 intraventricular haemorrhage was confirmed.

**Side effects.** Most infants had several courses of treatment, and altogether 44 courses of theophylline and 54 courses of CPAP were examined for possible side effects. Six infants on 7 occasions had a tachycardia >180/minute, all during theophylline treatment ($P<0.05$). In 2 infants this was associated with cardiac failure, one had a transient tachycardia of 230/minute during the initial bolus injection, and the other 3 had serum levels above 67 μmol/l (12 mg/l) at the time. Hyponatraemia (plasma sodium <130 mmol/l) occurred during 9 of 31 courses of theophylline, but none of 14 courses of CPAP in which sodium was measured ($P<0.05$). Five infants developed cardiac failure attributed to patent ductus arteriosus, one after theophylline alone, one after CPAP alone, and 3 after both treatments. Three infants developed necrotising enterocolitis, 2 after theophylline alone and one after both treatments. Feeding difficulties were encountered during 14 of 41 courses of theophylline and 21 of 37 courses of CPAP ($0.05 <P<0.1$). The most common reason for failure to establish feeding was difficulty in passing a transpyloric tube. Gastric distension precluded gastric feeding during face-mask CPAP and in babies requiring frequent bag-and-mask resuscitation.

## Discussion

In this study, theophylline was more effective than CPAP in the treatment of apnoea of immaturity, even after allowing for perinatal complications and severity of apnoea. The greatest effect was seen on prolonged episodes $\geqslant$60 seconds, the majority of which were associated with bradycardia. The continuous recordings confirmed a fall in the proportion of apnoeic attacks with bradycardia during theophylline therapy. The significant reduction in need for ventilation in the theophylline group supports a genuine advantage. The poor response to CPAP in 9 of 14 infants contrasts with previous reports.[10–12] In these three studies, a total of 31 infants was treated, of whom the condition of all but 4 improved. In the first 2 studies[10 11] CPAP was given by nasal prongs but in the third,[12] as in the present one, a face mask was used. The high incidence of perinatal complications present in 13 of our 14 infants might have contributed to the poor results. Immediate side effects from either treatment were few. Hyponatraemia may occur with theophylline, which increases urinary sodium excretion.[16] Tachycardia is also a well-known complication.[6] During face-mask CPAP there may be difficulty in passing a transpyloric tube and establishing milk feeds, but this problem would not necessarily occur if using nasal catheters.

Although theophylline appeared more effective than face-mask CPAP in treating apnoea, the response to both treatments was disappointing: 17 out of 32 infants required mechanical ventilation and 12 died. There is clearly a need for further studies into more effective treatment or, preferably, prevention of apnoea in the very immature.

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