Methylxanthine treatment for apnea in preterm infants (Review)

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[Intervention Review]

Methylxanthine treatment for apnea in preterm infants

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ABSTRACT

Background

Recurrent apnea is common in preterm infants, particularly at very early gestational ages. These episodes of loss of effective breathing can lead to hypoxemia and bradycardia that may be severe enough to require resuscitation including use of positive pressure ventilation. Methylxanthines (such as caffeine or theophylline) have been used to stimulate breathing and prevent apnea and its consequences.

Objectives

To determine the effects of methylxanthine treatment on the incidence of apnea and the use of intermittent positive pressure ventilation (IPPV), and other clinically important effects in preterm infants with recurrent apnea.

Search strategy

Searches were made of the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 4, 2007), the Oxford Database of Perinatal Trials, MEDLINE (1966 to January 2008), EMBASE (1982 - January 2008), previous reviews including cross references, abstracts, conferences and symposia proceedings, expert informants, journal hand searching mainly in the English language.

Selection criteria

All trials utilizing random or quasi-random patient allocation in which methylxanthine (theophylline or caffeine) was compared with placebo or no treatment for apnea in preterm infants were included.

Data collection and analysis

Methodological quality was assessed independently by the two review authors. Data were extracted independently by the two review authors. Treatment effects were expressed as relative risk (RR) and risk difference (RD) and their 95% confidence intervals, using a fixed effect model. For significant results, the inverse of the risk difference (1/RD) was used to calculate the number needed to treat (NNT).

Main results

The results of five trials that enrolled a total of 192 preterm infants with apnea indicate that methylxanthine therapy leads to a reduction in apnea and use of IPPV in the first two to seven days. There are insufficient data to adequately evaluate side effects and no data to examine effects within different gestational age groups. There are no data in the included studies that examine long-term effects.

Authors' conclusions

Methylxanthines are effective in reducing the number of apneic attacks and the use of mechanical ventilation in the two to seven days after starting treatment. In view of its lower toxicity, caffeine would be the preferred drug. The effects of methylxanthines on long-term outcomes will be addressed in data from the trial awaiting assessment (CAP Trial 2006).

PLAIN LANGUAGE SUMMARY

Methylxanthine treatment for apnea in preterm infants

There is some evidence that methylxanthines are effective in the short-term for reducing apnea in premature babies. Apnea is a pause in breathing of greater than 20 seconds. It may occur repeatedly in preterm babies (born before 34 weeks gestation). Methylxanthines (such as theophylline and caffeine) are drugs that are believed to stimulate breathing efforts and have been used to reduce apnea. Adverse effects of feeding intolerance and a rapid heart rate have been found with theophylline. The review of trials found methylxanthines help reduce the number of apnea attacks in the short term. The trials included in this review now have not published longer term outcomes, although the general use for a number of indications has been evaluated and outcomes are better in the methylxanthine group. This trial is awaiting assessment.

BACKGROUND

Infant apnea has been defined as a pause in breathing of greater than 20 seconds or one of less than 20 seconds and associated with cyanosis, marked pallor, hypotonia or bradycardia (AAP 2003). Recurrent episodes of apnea are common in preterm infants and the incidence and severity increases at lower gestational ages (reviewed by Henderson-Smart 2004). Although recurrent apnea can occur spontaneously and be attributed to prematurity alone, it can also be provoked or made more severe if there is some additional insult such as infection, hypoxemia or intracranial pathology.

If prolonged, apnea can lead to hypoxemia and reflex bradycardia which may require active resuscitative efforts to reverse. There are clinical concerns that these episodes might be harmful to the developing brain or cause dysfunction of the gut or other organs. Frequent episodes may be accompanied by respiratory failure of sufficient severity to lead to intubation and the use of intermittent positive pressure ventilation (IPPV).

Methylxanthines are thought to stimulate breathing efforts and have been used in clinical practice to reduce apnea since the 1970's (reviewed by Samuels 1992; Henderson-Smart 2004; Comer 2001). Theophylline and caffeine are two forms that have been used. The mechanism of their action is not certain. Possibilities include increased chemoreceptor responsiveness (based on a lower threshold for breathing responses to CO_2), enhanced respiratory muscle performance and generalized central nervous system excitation.

Adverse effects such as feed intolerance and tachycardia have been reported in observational studies, particularly with theophylline therapy. There are potential adverse effects of increased central nervous system stimulation on long term development of the nervous system, although this has not been suggested from cohort studies. The increased metabolic rate induced by methylxanthines could increase the rate of blood oxygen desaturation during apnea, even if the rate of events were reduced. A metabolic load, if sustained, could affect growth. Issues of neonatal morbidity have been reviewed (Blanchard 1992; Martin 1998; Schmidt 1999).

This review updates the existing review of 'Methylxanthine for apnea in preterm infants' which was published in the Cochrane Library, Issue 4, 2004 (Henderson-Smart 2004a).

OBJECTIVES

To determine the effects of methylxanthine treatment on the incidence of apnea and the use of intermittent positive pressure ventilation (IPPV) and other clinically important effects in preterm infants with recurrent apnea.

Prespecified subgroup analyses:

1. Effects of different methylxanthines (theophylline, caffeine)
2. Effects of different doses of methylxanthine
3. Effects at different gestational ages or birth weights

METHODS

Criteria for considering studies for this review

Types of studies

All trials utilizing random or quasi-random patient allocation were included.

Types of participants

Preterm infants with recurrent apnea. There must have been an effort to exclude specific causes of apnea.

Types of interventions

Any methylxanthine (aminophylline, theophylline, caffeine) compared with placebo or no treatment for recurrent apnea.

Types of outcome measures

Measures of the severity of apnea as well as the response to treatment must have been consistent with an evaluation of 'clinical apnea', as defined by the American Academy of Pediatrics (AAP 2003, see Background).

Primary

1. Failed treatment (less than 50% reduction in apnea, or use of IPPV, or death during study)
2. Use of IPPV
3. Death before hospital discharge

Secondary

1. Acute drug side effects (tachycardia or feed intolerance leading to omission of treatment)
2. Neonatal morbidity such as - patent ductus arteriosus requiring treatment, intracranial hemorrhage, necrotizing enterocolitis
3. Duration of IPPV
4. Duration of oxygen therapy
5. Chronic lung disease indicated by respiratory support (oxygen &/or positive airway pressure) still given at 36 weeks postmenstrual age
6. Longer term outcomes, such as growth and neurodevelopmental outcome

Search methods for identification of studies

Searches were made of the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 4, 2007), the Oxford Database of Perinatal Trials, MEDLINE (1966 to January 2008), EMBASE (1982 to January 2008), previous reviews including cross references, abstracts, conferences and symposia proceedings, expert informants, journal hand searching mainly in the English language. Expert informant's search in the Japanese language was made by Pr of. Y. Ogawa in 1996. Searches used the text terms 'apnea or apnea', 'theophylline', 'aminophylline' or 'caffeine'; and Mesh term 'infant;premature'. All titles and abstracts were reviewed to select random or quasi randomised trials. The full papers were reviewed when only the title and the abstract did not make eligibility clear.

Data collection and analysis

Trials were assessed for method of randomizations, blinding of intervention, blinding of outcome assessment and completeness of follow up. The methodological quality of each trial was reviewed by the second author blinded to trial authors and institution(s). Each author extracted data separately. Then data were compared and differences resolved. Additional information was provided by Gupta (Gupta 1981) on the use of IPPV.

Results were meta-analyzed using a fixed effect model and treatment effects were expressed as relative risk (RR) and risk difference (RD) and their 95% confidence intervals. For significant results, we used the inverse of the risk difference (1/RD) to calculate the number needed to treat (NNT). If there was significant heterogeneity based on I^2 statistic that is unresolved by subgroup analyses, the random effects RR was also reported.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

The five included trials (Sims 1985; Murat 1981; Peliowski 1990; Gupta 1981; Erenberg 2000) studied a total of 192 infants. Details of these studies are included in the table of included studies. No studies were excluded.

One trial reported on the use of oral theophylline (Gupta 1981) and two used the intravenous equivalent, aminophylline (Peliowski 1990) or theophylline (Sims 1985). Two trials examined the effects of caffeine (Murat 1981; Erenberg 2000).

All trials measured apnea/bradycardia consistent with clinical events as defined in Background (AAP 2003). These were recorded from clinical monitors in two trials (Gupta 1981; Erenberg 2000) and by chart records of apnea and heart rate in the remaining three. The timing of outcome assessments varied from 48 hrs to 10 days after initiation of treatment.

In the Erenberg 2000 trial, a large number of infants exited from double blind treatment during the 10 day study period and failure

was determined on the day of exit and "carried forward over the subsequent days" (the status on day seven when responses were stable was taken for the result presented here).
A new trial (CAP Trial 2006) comparing outcomes at discharge and infant follow-up of caffeine versus placebo is awaiting assessment. It cannot be included in this review yet, because despite one indication for inclusion of participants being appropriate (caffeine treatment of apnea of prematurity), two other indications for inclusion in the trial and published results were prophylactic methylxanthine for apnea of prematurity or prophylactic methylxanthines for extubation in preterm infants. The latter are potentially eligible for two other Cochrane reviews (Henderson-Smart 2006, Henderson-Smart 2006a).

Risk of bias in included studies

Details of each study appear in the table of included studies. There was variation in trial design. Peliowski 1990 clearly concealed randomization and used placebo controls; Erenberg 2000 used an unclear method of randomization and placebo controls; Gupta 1981 used a quasi-random method with placebo controls; Sims 1985 and Murat 1981 used an unspecified method of randomization without placebo blinding.

Effects of interventions

Compared with control (placebo or no drug therapy), methylxanthine administration to infants with recurrent apnea of prematurity is followed by less treatment failure [summary RR 0.43 (0.31, 0.60), RD -0.40 (-0.53, -0.28), NNT 3 (2, 4)] and less use of IPPV [RR 0.34 (0.12, 0.97), RD -0.08 (-0.16, -0.01), NNT 13 (6, 100)]. These effect sizes are large although the sample sizes are low.
These effects were analysed in the short-term only, with two of the studies (Gupta 1981; Peliowski 1990) evaluating effects 48 hours after randomizations, another study at five days (Murat 1981), and the other two studies (Sims 1985; Erenberg 2000) at one week. Although Sims 1985 claimed that there were no benefits by seven days, the mean number of apneic events was analysed only in the subgroup that did not require mechanical ventilation.

The results were similar across trials. Analysis of the three trials in which theophylline was used also showed significantly less treatment failure [summary RR 0.41 (0.27, 0.62), RD -0.50 (-0.67, -0.33), NNT 2 (1, 3)] and a reduction in use of IPPV that nearly reaches statistical significance. The two trials (Murat 1981; Erenberg 2000) evaluating caffeine, found significantly less treatment failure [summary RR 0.46 (0.27, 0.78), RD -0.31 (-0.49, -0.12), NNT 3 (2, 8)].
The difference in the low rate of death before discharge (methylxanthine 3/81 versus control 6/73) reported in three trials (Gupta 1981, Sims 1985, Erenberg 2000) is not significant.

Side effects were reported in three trials. Two reported that there were none (Peliowski 1990; Sims 1985) and one trial (Gupta 1981) reported that two infants in the theophylline group developed tachycardia. Erenberg 2000 provided the additional information that no infants had side effects such as tachycardia or feed intolerance leading to omission of treatment.
Long-term effects on growth and neurodevelopment were not assessed in any included trials.

DISCUSSION

Although avoiding the use of IPPV seems an appropriate clinical goal, it is not clear whether merely reducing the number of apneic episodes alters the long term outcome. Older small cohort studies have not been able to detect any independent adverse effect of apnea on later neurological development (reviewed by Henderson-Smart 2004; Comer 2001). A recent large cohort study (Davis 2000) raises concerns that there could be increased rates of cerebral palsy associated with caffeine use even after adjustment for confounders. This study also suggests that infants treated with caffeine, again after adjusting for confounders, might have a higher full scale and verbal intelligence quotients as measured by the Wechsler Intelligence Scale (WISC III) for children.

Data here and in another systematic review comparing caffeine and theophylline (Steer 2004) suggest that the short-term benefits of caffeine are similar to those of theophylline. Side effects appear to be less common with caffeine (reviewed by Blanchard 1992; Steer 2004; Comer 2001).

Although methylxanthines lead to a reduction of apnea in preterm infants who have this clinical problem, they are not effective when given as prophylaxis to spontaneously breathing preterm infants at risk of developing apnea/bradycardia because of their low gestational age (Henderson-Smart 2006a). Another review indicates that methylxanthines may be effective in facilitating extubation from IPPV in some infants and that this is partly due to a reduction in postextubation apnea (Henderson-Smart 2006).

The incidence as well as the severity of the clinical apnea is greatest in infants born at earlier gestational ages. It might be expected that infants born at the lowest gestation would benefit most from treatment. No study evaluated this as part of the initial stated aim so this prespecified subgroup analysis could not be done. In one study (Sims 1985), post-hoc analysis showed that 8 of the 11 control infants who required mechanical ventilation were born at less than 31 weeks gestation.

A major concern is the small numbers in each study which, while adequate to show the large effect on apnea, would not be able to detect less common adverse effects. Of particularly concern is the lack of trial data on long-term growth and development. The CAP Trial (CAP Trial 2006) has published outcomes at discharge and growth and development at 18 to 21 months. These results include a large number of very low birthweight infants (Caffeine group 1006, placebo group 1000) with any one of the three indications for trial entry (prophylaxis prevention of apnea in 22%, treatment of apnea in 40% or prophylaxis for extubation in 38%). At present the results cannot be specifically applied to this review on treatment for apnea, although they do provide a generalised effect of caffeine indicating that there is improved outcome at discharge and in neurodevelopment at follow-up. The CAP trial authors have been requested to evaluate outcomes for each indication which will make the trial eligible for inclusion in this review and also the other two Cochrane reviews dealing with the other two indications (Henderson-Smart 2006a; Henderson-Smart 2006) and allow for a more precise understanding of the effects in these related but different populations.

AUTHORS' CONCLUSIONS

Implications for practice

Methylxanthines are effective in reducing the number of apneic attacks in the short-term and in reducing the use of mechanical ventilation. In view of its lower toxicity, caffeine would be the preferred drug. In included studies, the safety of methylxanthine therapy is uncertain, especially in terms of lack of long-term growth and neurodevelopment outcomes.

Implications for research

In order to indicate which infants are likely to benefit from treatment, there is a need for stratification by gestation and/or other risk factors in future studies. In any future studies the longer term effects of treatment on growth and development should be evaluated. Data on neonatal and longer term outcome might be available for infants given caffeine treatment for recurrent apnea in the trial of general caffeine use, awaiting assessment (CAP Trial 2006).

ACKNOWLEDGEMENTS

Emeritus A/Pr of. Jugdish Gupta (Gupta 1981), and Richard Leff (Erenberg 2000) kindly provided addition data from their trials.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Erenberg 2000

Methods	Blinding of randomization - unclear; blinding of intervention - yes; complete follow up - 5 (6%) infants withdrawn after randomization (1 caffeine infant and 2 placebo infants did not meet apnea inclusion criteria during baseline measurement, 2 placebo infants never received drug); blinding of outcome assessment - yes
Participants	Multicentre (9); 87 preterm infants 28 - 32 weeks postmenstrual age and less than 24 hrs of age with six or more apnea episodes (> 20 secs duration) in 24 hrs. Exclusions: secondary apnea (CNS, lung disease, anemia, infection, shock)
Interventions	Caffeine citrate (10 mg/kg base) IV and 2.5 mg/kg daily vs placebo (citric acid/sodium citrate)
Outcomes	Failure = < 50% reduction in apnea (> 20 secs); use of IPPV (provided by author); death by 30 days
Notes	Clinical observations of monitors used to assess outcome. Use of open label caffeine allowed at discretion of staff (14 caffeine and 16 placebo), also 10 caffeine and 9 placebo infants withdrawn from double blind treatment (adverse event 2 vs 1, apnea recurrence 5 vs 6, investigator discretion 2 vs 2, transferred 1 vs 0. 21 caffeine and 12 placebo infants completed full 10 days of double blind treatment. Author provided information that no infant received IPPV or had side effects such as tachycardia leading to withholding treatment

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Gupta 1981

Methods	Blinding of randomization - unclear (pharmacy made up 4 mixtures labelled a,b,c,d,e,f; letter drawn from a 'hat'); blinding of treatment - yes; completeness of follow-up - no (3 subjects excluded after randomisation) ; blinding of outcome assessment - yes
Participants	29 preterm infants born at 26 to 34 weeks gestation who had clinical apnea; >3 events per 12 hours of apnea >15 sec with heart rate < 100 or cyanosis; infants in treatment and placebo groups were of similar mean gestational age (28.6 vs 29.1 weeks) and mean birth weight (1101 vs 1171 gms); commenced on treatment at median of 7 (range 2-19) days and placebo at median of 8.5 (range 1-29) days
Interventions	Oral theophylline (4 mg/kg 6 hourly, increased to 6 mg/kg if no response to first dose) vs placebo
Outcomes	Apnea (no decrease in first 6-12 hours or need for nursing interventions for events in the next 48 hours) ; use of mechanical ventilation (personal communication); death before hospital discharge; tachycardia leading to an adjustment of dose

Gupta 1981 (*Continued*)

Notes	Dose of theophylline high but no loading dose given. Clinical observations of monitors used to detect apnea/bradycardia. No power calculation given; trial terminated early

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Murat 1981

Methods	Blinding of randomization - unclear; blinding of intervention - no; complete followup - yes; blinding of outcome measurement - no
Participants	18 preterm infants with apnea (>2 apneas with heart rate <100 per day); treatment and untreated controls of similar mean gestational age (30.1 vs 29.8 weeks) , birth weight (1247 vs 1411 gms) , postnatal age at study entry (13.2 vs 16.1 days) and frequency of apnea in the day before study entry (1.17 vs 0.65 /100 mins)
Interventions	Caffeine sodium citrate (20 mg/kg load im, then 5 mg/kg/day oral) vs no treatment
Outcomes	Failure on day 1 and day 5 (continued apnea or use of mechanical ventilation); use of mechanical ventilation
Notes	Four infants in the untreated group crossed over during the study and were classified as 'failed treatment'. Chart recording of apnea/bradycardia used

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

Peliowski 1990

Methods	Blinding of randomisation - yes; blinding of intervention - yes; complete followup - 3 withdrawals after randomization (parental request, suspected sepsis, possible seizures) , groups not specified; blinding of outcome measurement - yes
Participants	20 preterm infants (<35 weeks gestation) with apnea (apnea > 20 sec with > 25% fall in heart rate and 10% fall in oxygen saturation or 5 torr or more fall in transcutaneous oxygen tension; 0.33 or more events per hr) ; other causes of apnea excluded; similar mean gestational age (30.7 vs 31.3 weeks), birth weight (1441 vs 1598 g), postnatal age at study entry (4.0 vs 2.9) and baseline apnea rate (0.72 vs 0.70/hr)
Interventions	Theophylline (8 mg/kg load iv then continuous iv infusion of 0.5 mg/kg/hr) vs placebo. Cross over design (after 48 hrs) and comparison with doxapram - not evaluated here

Peliowski 1990 (*Continued*)

Outcomes	Failure [apnea rate not below 0.33/hr (baseline rate 0.70/hr in treatment group and 0.72/hr in controls) or use of mechanical ventilation by 48 hrs]; use of mechanical ventilation
Notes	Three infants withdrawn after randomisation (parental request, suspected sepsis, possible seizures) and use of continuous positive airways pressure was permitted at the discretion of the clinician (no data given) - seeking author clarification. Chart recording of apnea/bradycardia used

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Sims 1985

Methods	Blinding of randomisation unclear; blinding of intervention - no; complete follow-up - yes; blinding of outcome measurement - no
Participants	43 preterm (<37 weeks gestation) infants; infants in treatment and no treated groups were of similar mean gestational age (31.4 vs 30.8 weeks) , mean birth weight (1345 vs 1306 gms) and postnatal age at study entry (2.5 vs 2.0 days)
Interventions	Theophylline (6.8 mg/kg load iv, then 1.4 mg/kg 8 hourly) vs no treatment
Outcomes	Failure (no 'resolution' of apnea or use of mechanical ventilation by 7 days); use of mechanical ventilation; death before hospital discharge
Notes	Used continuous print out on chart recorder to detect apnea and bradycardia

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Hochwald 2002	This trial compared two loading doses of aminophylline without a control group

DATA AND ANALYSES

Comparison 1. Any methylxanthine vs control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failed treatment after 2 - 7 days	5	192	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.32, 0.60]
2 Use of mechanical ventilation	5	192	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.12, 0.97]
3 Side effects	4	149	Risk Ratio (M-H, Fixed, 95% CI)	4.69 [0.24, 89.88]
4 Death before discharge	3	154	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.14, 1.78]

Comparison 2. Theophylline vs control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failed treatment after 2 - 7 days	3	92	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.28, 0.63]
2 Use of mechanical ventilation	3	92	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.13, 1.16]
3 Side effects	2	49	Risk Ratio (M-H, Fixed, 95% CI)	4.69 [0.24, 89.88]
4 Death before discharge	2	72	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.05, 1.52]

Comparison 3. Caffeine vs control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failed treatment after 5 - 7 days	2	100	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.27, 0.78]
2 Use of mechanical ventilation	2	100	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.01, 3.66]
3 Side effects	2	100	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4 Death before discharge	1	82	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [0.16, 17.43]

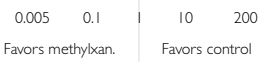
Analysis 1.1. Comparison 1 Any methylxanthine vs control, Outcome 1 Failed treatment after 2 - 7 days.

Review: Methylxanthine treatment for apnea in preterm infants

Comparison: 1 Any methylxanthine vs control

Outcome: 1 Failed treatment after 2 - 7 days

Study or subgroup	Methylxanthine n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Erenberg 2000	14/45	20/37		32.3 %	0.58 [0.34, 0.97]
Gupta 1981	5/15	14/14		22.0 %	0.36 [0.18, 0.70]
Murat 1981	0/9	6/9		9.6 %	0.08 [0.00, 1.19]
Peliowski 1990	2/10	8/10		11.8 %	0.25 [0.07, 0.90]
Sims 1985	9/21	17/22		24.4 %	0.55 [0.32, 0.95]
Total (95% CI)	**100**	**92**		**100.0 %**	**0.44 [0.32, 0.60]**
Total events: 30 (Methylxanthine), 65 (Control)					
Heterogeneity: Chi^2 = 4.43, df = 4 (P = 0.35); I^2 =10%					
Test for overall effect: Z = 5.04 (P < 0.00001)					



Analysis 1.2. Comparison 1 Any methylxanthine vs control, Outcome 2 Use of mechanical ventilation.

Review: Methylxanthine treatment for apnea in preterm infants

Comparison: 1 Any methylxanthine vs control

Outcome: 2 Use of mechanical ventilation

Study or subgroup	Methylxanthine n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Erenberg 2000	0/45	0/37			Not estimable
Gupta 1981	0/15	0/14			Not estimable
Murat 1981	0/9	2/9		21.2 %	0.20 [0.01, 3.66]
Peliowski 1990	0/10	1/10		12.7 %	0.33 [0.02, 7.32]
Sims 1985	3/21	8/22		66.1 %	0.39 [0.12, 1.28]
Total (95% CI)	**100**	**92**		**100.0 %**	**0.34 [0.12, 0.97]**

Total events: 3 (Methylxanthine), 11 (Control)

Heterogeneity: $Chi^2 = 0.18$, df = 2 (P = 0.91); $I^2 = 0.0\%$

Test for overall effect: Z = 2.02 (P = 0.043)

Analysis 1.3. Comparison 1 Any methylxanthine vs control, Outcome 3 Side effects.

Review: Methylxanthine treatment for apnea in preterm infants

Comparison: 1 Any methylxanthine vs control

Outcome: 3 Side effects

Study or subgroup	Methylxanthine n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Erenberg 2000	0/45	0/37			Not estimable
Gupta 1981	2/15	0/14		100.0 %	4.69 [0.24, 89.88]
Murat 1981	0/9	0/9			Not estimable
Peliowski 1990	0/10	0/10			Not estimable
Total (95% CI)	**79**	**70**		**100.0 %**	**4.69 [0.24, 89.88]**

Total events: 2 (Methylxanthine), 0 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 1.03 (P = 0.31)

Analysis 1.4. Comparison 1 Any methylxanthine vs control, Outcome 4 Death before discharge.

Review: Methylxanthine treatment for apnea in preterm infants

Comparison: 1 Any methylxanthine vs control

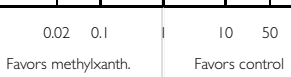
Outcome: 4 Death before discharge

Study or subgroup	Methylxanine n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Erenberg 2000	2/45	1/37		16.5 %	1.64 [0.16, 17.43]
Gupta 1981	1/15	3/14		46.7 %	0.31 [0.04, 2.65]
Sims 1985	0/21	2/22		36.8 %	0.21 [0.01, 4.11]
Total (95% CI)	**81**	**73**		**100.0 %**	**0.49 [0.14, 1.78]**

Total events: 3 (Methylxanine), 6 (Control)

Heterogeneity: Chi^2 = 1.50, df = 2 (P = 0.47); I^2 =0.0%

Test for overall effect: Z = 1.08 (P = 0.28)



Analysis 2.1. Comparison 2 Theophylline vs control, Outcome 1 Failed treatment after 2 - 7 days.

Review: Methylxanthine treatment for apnea in preterm infants

Comparison: 2 Theophylline vs control

Outcome: 1 Failed treatment after 2 - 7 days

Study or subgroup	Theophylline n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gupta 1981	5/15	14/14		37.8 %	0.36 [0.18, 0.70]
Peliowski 1990	2/10	8/10		20.2 %	0.25 [0.07, 0.90]
Sims 1985	9/21	17/22		42.0 %	0.55 [0.32, 0.95]
Total (95% CI)	**46**	**46**		**100.0 %**	**0.42 [0.28, 0.63]**

Total events: 16 (Theophylline), 39 (Control)

Heterogeneity: Chi^2 = 1.88, df = 2 (P = 0.39); I^2 =0.0%

Test for overall effect: Z = 4.20 (P = 0.000027)

Analysis 2.2. Comparison 2 Theophylline vs control, Outcome 2 Use of mechanical ventilation.

Review: Methylxanthine treatment for apnea in preterm infants

Comparison: 2 Theophylline vs control

Outcome: 2 Use of mechanical ventilation

Study or subgroup	Theophylline n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gupta 1981	0/15	0/14			Not estimable
Peliowski 1990	0/10	1/10		16.1 %	0.33 [0.02, 7.32]
Sims 1985	3/21	8/22		83.9 %	0.39 [0.12, 1.28]
Total (95% CI)	**46**	**46**		**100.0 %**	**0.38 [0.13, 1.16]**

Total events: 3 (Theophylline), 9 (Control)

Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.92); I^2 =0.0%

Test for overall effect: Z = 1.70 (P = 0.090)

Analysis 2.3. Comparison 2 Theophylline vs control, Outcome 3 Side effects.

Review: Methylxanthine treatment for apnea in preterm infants

Comparison: 2 Theophylline vs control

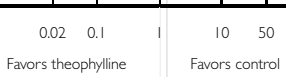
Outcome: 3 Side effects

Study or subgroup	Theophylline n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gupta 1981	2/15	0/14		100.0 %	4.69 [0.24, 89.88]
Peliowski 1990	0/10	0/10			Not estimable
Total (95% CI)	**25**	**24**		**100.0 %**	**4.69 [0.24, 89.88]**

Total events: 2 (Theophylline), 0 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 1.03 (P = 0.31)



Analysis 2.4. Comparison 2 Theophylline vs control, Outcome 4 Death before discharge.

Review: Methylxanthine treatment for apnea in preterm infants

Comparison: 2 Theophylline vs control

Outcome: 4 Death before discharge

Study or subgroup	Theophylline n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gupta 1981	1/15	3/14		55.9 %	0.31 [0.04, 2.65]
Sims 1985	0/21	2/22		44.1 %	0.21 [0.01, 4.11]
Total (95% CI)	**36**	**36**		**100.0 %**	**0.27 [0.05, 1.52]**

Total events: 1 (Theophylline), 5 (Control)

Heterogeneity: $Chi^2 = 0.05$, df = 1 (P = 0.83); $I^2 = 0.0\%$

Test for overall effect: Z = 1.49 (P = 0.14)

Analysis 3.1. Comparison 3 Caffeine vs control, Outcome 1 Failed treatment after 5 - 7 days.

Review: Methylxanthine treatment for apnea in preterm infants

Comparison: 3 Caffeine vs control

Outcome: 1 Failed treatment after 5 - 7 days

Study or subgroup	Caffeine n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Erenberg 2000	14/45	20/37		77.2 %	0.58 [0.34, 0.97]
Murat 1981	0/9	6/9		22.8 %	0.08 [0.00, 1.19]
Total (95% CI)	**54**	**46**		**100.0 %**	**0.46 [0.27, 0.78]**

Total events: 14 (Caffeine), 26 (Control)

Heterogeneity: $Chi^2 = 2.32$, df = 1 (P = 0.13); $I^2 = 57\%$

Test for overall effect: Z = 2.91 (P = 0.0036)

Analysis 3.2. Comparison 3 Caffeine vs control, Outcome 2 Use of mechanical ventilation.

Review: Methylxanthine treatment for apnea in preterm infants

Comparison: 3 Caffeine vs control

Outcome: 2 Use of mechanical ventilation

Study or subgroup	Caffeine n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Erenberg 2000	0/45	0/37			Not estimable
Murat 1981	0/9	2/9		100.0 %	0.20 [0.01, 3.66]
Total (95% CI)	**54**	**46**		**100.0 %**	**0.20 [0.01, 3.66]**
Total events: 0 (Caffeine), 2 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.09 (P = 0.28)					

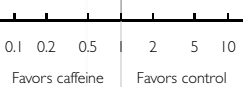
Analysis 3.3. Comparison 3 Caffeine vs control, Outcome 3 Side effects.

Review: Methylxanthine treatment for apnea in preterm infants

Comparison: 3 Caffeine vs control

Outcome: 3 Side effects

Study or subgroup	Caffeine n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Erenberg 2000	0/45	0/37			Not estimable
Murat 1981	0/9	0/9			Not estimable
Total (95% CI)	**54**	**46**			**Not estimable**
Total events: 0 (Caffeine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					

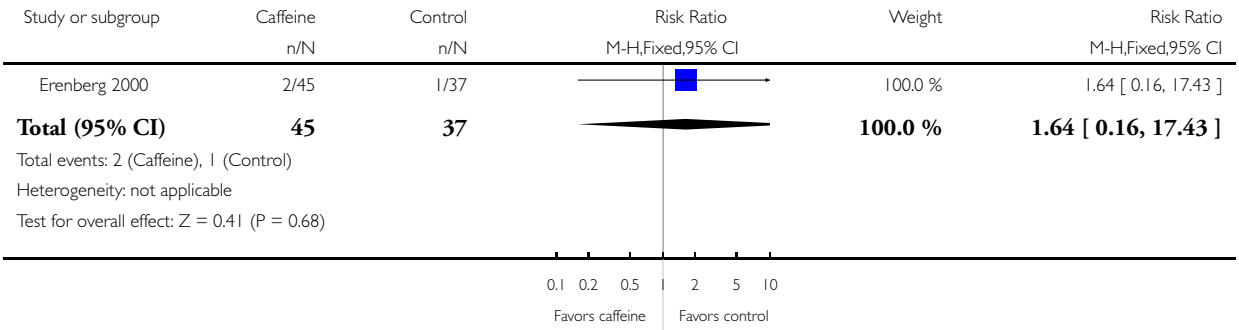


Analysis 3.4. Comparison 3 Caffeine vs control, Outcome 4 Death before discharge.

Review: Methylxanthine treatment for apnea in preterm infants

Comparison: 3 Caffeine vs control

Outcome: 4 Death before discharge



WHAT'S NEW

Last assessed as up-to-date: 5 February 2008.

Date	Event	Description
12 August 2009	Amended	Corrections made to citations in 'Studies awaiting classification'

HISTORY

Protocol first published: Issue 4, 1999

Review first published: Issue 4, 1999

Date	Event	Description
6 February 2008	Amended	Converted to new review format.
6 February 2008	New search has been performed	This review updates the existing review of 'Methylxanthine treatment for apnea in preterm infants' which was published in The Cochrane Library, Issue 4, 2004 (Henderson-Smart 2004). One new trial has been published, but requires further analysis of the data. This trial is referenced in 'Studies awaiting classification". The conclusions of

(*Continued*)

		this review are unchanged

CONTRIBUTIONS OF AUTHORS

Both review authors developed the protocol, evaluated trials and extracted data.

Henderson-Smart wrote the review and entered the data into RevMan.

Henderson-Smart has been responsible for searching for trials and updating the review with the approval of Steer.

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- NSW Centre for Perinatal Health Services Research, University of Sydney, Australia.
- Pediatrics, McMaster Childrens Hospital, Ontario, Canada.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Apnea [*prevention & control]; Caffeine [therapeutic use]; Central Nervous System Stimulants [*therapeutic use]; Infant, Newborn; Infant, Premature; Infant, Premature, Diseases [*prevention & control]; Theophylline [therapeutic use]; Vasodilator Agents [*therapeutic use]; Xanthines [*therapeutic use]

MeSH check words

Humans