Application for Inclusion of Caffeine in the WHO Model List of Essential Medicines

Submitted by

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To:
Expert Committee on the Selection and Use of Essential Medicines
Geneva 7- 11 March 2005

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1. Summary Statement Of The Proposal For Inclusion

Caffeine citrate is proposed for inclusion in the core/ complimentary WHO Model Essential Medicine list for the treatment of apnoea of prematurity in neonates. Methylxanthines including caffeine, aminophylline and theophylline have been used to treat apnea of prematurity for over 3 decades. Caffeine is the treatment of choice as it has a superior safety profile and does not require routine drug level monitoring.

2. Name Of The Focal Point In WHO Supporting The Application

Dr Martin Weber, Child and Adolescent Health and Development, Geneva Switzerland.

3. Name Of The Organizations Consulted And Supporting The Application

Child and Adolescent Health and Development department, WHO Department of Clinical Pharmacology, Royal Children’s Hospital, Melbourne Australia.
Centre for International Child Health, Department of Paediatrics, University of Melbourne, Australia.

4. International Nonproprietary Name Of The Medicine

Caffeine citrate

5. Whether Listing Is Requested As An Individual Medicine Or As An Example Of A Therapeutic Group

Listing is requested for Caffeine as an example of the therapeutic class of methylxanthines, with the alternatives being aminophylline and theophylline.

6. Information Supporting The Public Health Relevance

6.1 Definition of Idiopathic Apnea of Prematurity

Infant apnea is defined as a pause in breathing of greater than 20 seconds or one of less than 20 seconds and associated with bradycardia and/or cyanosis¹. Idiopathic apneas of premature infants may be considered as a developmental state that will resolve with maturity.² If prolonged, apnea can lead to hypoxemia and reflex bradycardia,³ ⁴ which may lead to the need for active resuscitation efforts⁵. Where
infants are not continuously monitored, as in most small hospitals in developing
countries, this will result in the death of most of these babies. Apneas are therefore
potentially harmful, due to their acute consequences for gas exchange, haemodynamic
disturbance, and altered cerebral blood flow. Frequent episodes may result in the
need for mechanical ventilation, which is not available in many health facilities in
developing countries.

6.2 Epidemiology
The frequency and severity of apneas of prematurity increases with decreasing
gestational age. More than 50% of infants under 31 weeks of gestational age have
apnea. The incidence decreases to about 7% for infants of 34-35 weeks gestation.

6.3 Methylxanthine treatment.
The methylxanthines, caffeine, aminophylline and theophylline, have been shown to
be effective treatments for apnea of prematurity. Caffeine is widely regarded as the
methylxanthine of choice as it has the best safety profile. In settings were
caffeine is not available aminophylline or theophylline would be acceptable
alternatives.

7. Treatment Details

7.1 Indications
Caffeine citrate is indicated to treat apnea of prematurity in premature infants up to 35
weeks postconception age and less than 2kg birth weight. Other causes such as
sepsis, hypothermia, hypoxaemia, hypoglycemia, anaemia and seizures should also be
sought and treated appropriately.

7.2 Dose
Caffeine citrate: Loading dose – 20mg/kg oral or IV over 20-30 min
Maintenance dose – 5mg/kg daily oral or IV

The maintenance dose should be commenced at least 24 hours after the loading dose
and is continued at 24 hourly intervals

(NB. 2mg of caffeine citrate = 1 mg of caffeine base)

7.3 Duration
Continue treatment for 4-5 days after the cessation of apneas and then wean the does.

7.4 Monitoring
Routine drug level monitoring is not required. It is recommended to check levels if
infant remains symptomatic or has adverse effects.
8. Summary Of Comparative Effectiveness In A Variety Of Clinical Settings

Methylxanthines have been used in the treatment of apnoea of prematurity since the early 1970’s, and remain a common treatment around the world. Caffeine and theophylline are the 2 most commonly used agents, with caffeine generally being the preferred agent due to it having a wider therapeutic index than theophylline. A search of peer-reviewed literature was performed via Medline using the search terms Caffeine and apnea; the search was limited to neonates. The Cochrane library was also searched. A summary of the literature is provided below.

The effectiveness of Methylxanthines to treat apnoea of prematurity has been the subject of a Cochrane review. This review found 5 studies which met the reviewers criteria and included at total of 192 patients. Studies using both caffeine and theophylline/aminophylline were included. All trials measured apnea and bradycardia consistent with clinical events as outlined in section 6.1. The timing of outcome measures varied from 48 hours to 10 days. One study clearly concealed randomization and used placebo controls, one study used unclear randomisation methods and placebo control, another study used a quasi-randomisation with placebo controls while the remaining 2 studies used unspecified methods of randomisation and did not placebo blind. The characteristics of each of these studies, adapted from the Cochrane review, are presented in Appendix 1.

In the Cochrane review, a fixed effect meta-analysis model was used, and treatment effects were expressed as relative risk (RR) and risk difference (RD) and their 95% confidence intervals. The review found that compared with control (placebo or no drug therapy), methylxanthine administration to infants with recurrent apnea of prematurity was followed by less treatment failure, and less use of mechanical ventilation (intermittent positive pressure ventilation or IPPV). For treatment failure, the RR was 0.43 with 95% confidence intervals of (0.31, 0.60), the risk difference was –0.40 (-0.53,-0.28 ) and the number needed to treat (NNT) was 3, (2,4). The results of IPPV use were RR 0.3 (0.12, 0.97), RD -0.08 (-0.16,-0.01), NNT 13, (6,100).

Studies of significance that were not included in the Cochrane review include an open label randomized controlled trial of 2 doses of caffeine which showed a reduction in the frequency of apneas for both treatment groups when compared to control. Similar results have been found in 2 other open label studies which used comparable doses of caffeine.

Caffeine is the preferred methylxanthine, due to its lower toxicity and wider therapeutic index. The question of which methylxanthine, caffeine or theophylline, is superior has also be the subject of a Cochrane review. This review included randomized and quasi-randomized trials comparing caffeine to theophylline for treatment of AOP. Nine studies were identified, 3 were excluded because of methodological concerns and a further 3 trial are awaiting assessment pending further information on clinical outcome data, thus leaving 3 studies, with a total of 66 patients, to be included in the meta-analysis. In 2 of these 3 randomized studies, treatment allocation was well concealed, while in the third study the method of
randomisation was not clearly reported. The analyses included both published and unpublished data for the 2 former studies, and published data only for the third study. Blinding of the intervention occurred in only one of the trials. All of the three trials analysis was on the basis of intention-to-treat. The characteristics of each of these studies, adapted from the Cochrane review, are presented in Appendix 2.

For the meta-analysis the weighted mean difference, WMD, (and 95% confidence intervals) were calculated for continuous variables while the relative risk and risk differences (and 95% confidence intervals) were calculated for categorical outcomes. A fixed effects model was used. The meta-analysis found no difference in the failure rate (<50% reduction in apnea/bradycardia) between treatment with caffeine or theophylline at 1-3 days (two studies) or 5-7 days (one study). Infants on caffeine showed a higher rate of apnea after 1-3 days of treatment than those on theophylline (WMD 0.40 episodes per 100 minutes (0.33,0.46)). However no difference was found after 5-7 days of treatment. The reviewers’ conclusion was that caffeine and theophylline and have similar short-term effect but that caffeine had a number of therapeutic advantages over theophylline, due to the greater safety of caffeine, which is outlined below.

9. Summary of Comparative Evidence on Safety

The methylxanthines including caffeine, aminophylline and theophylline have been used to treat AOP for over 30 years, and are now one of the most commonly used medications in the care of sick neonates. Caffeine is widely recommended as the methylxanthine of choice due to its lower acute toxicity. Due to its wider therapeutic index caffeine also has the advantage of not requiring routine therapeutic drug monitoring. Reported adverse reactions to methylxanthines generally represent an exaggeration of there pharmacological action, such as tachycardia, high arterial pressure increased gasto-oesophageal reflux and jitteriness. In a randomised dose-response trial, 127 infants were randomised to 3 different doses. As doses increased the probability of tachycardia increased (P=0.07), as did the risk of feed intolerance, but this was not significant (P=0.29). Only 2 babies were reported to have jitteriness. In the Cochrane review of caffeine compared to theophylline, caffeine had less acute adverse effects, including tachycardia and feed intolerance. (RR 0.17: 95% CI 0.04, 0.72; NNT 3.5 95%CI 2.1-9.6).

A recent multicentre, parallel, randomised, double blind, placebo controlled trial with open label rescue was conducted to evaluate the safety of caffeine for the treatment of apnoea of prematurity. This included 85 infants born at 28-32 weeks gestation: safety analyses were preformed in 85 infants, 46 receiving caffeine and 39 placebo. No clinically significant differences were seen in the frequency or proportion of adverse events between the two groups. There was no difference in the proportion of infants discontinued from double blind therapy because of adverse event. Four infants receiving caffeine and two receiving placebo developed necrotizing enterocolitis (NEC). The NEC was determined to be possibly related to caffeine in one case and not related in three. Toxicity following acute caffeine overdose may manifest as central nervous system irritability seizure activity and tachypnea.
As outlined above, the short-term effectiveness and safety of caffeine has been well established. The long-term safety of caffeine has not been as well established and is currently the subject of an international multicentre randomised placebo-controlled trial, launched in 2000. The Caffeine for Apnoea of Prematurity (CAP) trial will provide answers to questions about long term neuro-developmental, behavioural and growth effects of caffeine.¹¹

10. Summary of available data on comparative cost within the pharmacological class or therapeutic group.

As the International Drug Price Indicator Guide does not list prices of caffeine or theophylline syrup, comparative costs have been given in Australia for the 3 most commonly used methylxanthines. Costs are in Australian dollars; treatment doses are based on a 1.5kg neonate.

Table 1. Cost comparisons for Methylxanthines:

<table>
<thead>
<tr>
<th></th>
<th>Caffeine Oral</th>
<th>Caffeine IV</th>
<th>Theophylline Oral</th>
<th>Aminophylline IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost/mg</td>
<td>$0.60</td>
<td>$0.30</td>
<td>$0.001</td>
<td>$0.02</td>
</tr>
<tr>
<td>Cost/doses loading</td>
<td>$18.00</td>
<td>$9.00</td>
<td>$0.02</td>
<td>$0.20</td>
</tr>
<tr>
<td>maintenance/day</td>
<td>$4.50</td>
<td>$2.25</td>
<td>$0.01</td>
<td>$0.10</td>
</tr>
<tr>
<td>Cost for initial week of treatment</td>
<td>$49.50</td>
<td>$24.75</td>
<td>$0.09</td>
<td>$0.90</td>
</tr>
</tbody>
</table>

Cost for the alternative treatment of mechanical ventilation (IPPV) is not included as this varies greatly depending on the setting and is not a readily accessible treatment options in many resource poor settings.


Caffeine citrate is registered in the USA as a prescription only medication for apnoea of prematurity. Apnoea of prematurity is a FDA (Food and Drug Authority) approved indication for caffeine citrate.³²

12. Availability of Pharmacopoieal Standard

United States Pharmacopoeia - standard available.
13. Proposed Text for the WHO Model Formulary

**Caffeine citrate**
Caffeine citrate is a representative methylxanthine. Other methylxanthines may be substituted.

*Oral solution*, caffeine citrate 20mg/ml

*Injection*, (solution for injection) 20mg/ml

**Uses:**
Treatment of apnoea of prematurity, (where all other cause of apnoea have been excluded or are being treated) in a premature infant born less than 35 weeks gestational age and under 2kg.

**Contraindications:**
Hypersensitivity to caffeine products.

**Precautions:**
Necrotizing enterocolitis may occur in infants, infants with cardiovascular disorders, hepatic or renal impairment, infants with seizure disorders other causes of apnoea should be eliminated before use of caffeine citrate

**Dosage:**
Caffeine citrate:
- **Loading dose** – 20mg/kg oral or IV over 20-30 min
- **Maintenance dose** – 5mg/kg daily oral or IV

The maintenance dose should be commenced at least 24 hours after the loading dose and is continued at 24 hourly intervals

(NB. 2mg of caffeine citrate = 1 mg of caffeine base)

Continue treatment for 4-5 days after the cessation of apneas and then wean the does.

**Adverse effects:**
  - **Common**
    - Feeding intolerance, irritability
  - **Serious**
    - acidosis (rare), abnormal healing (rare), hyperglycemia, hypoglycemia cerebral hemorrhage (rare), excessive CNS stimulation, disseminated intravascular coagulation (rare), hemorrhage (rare), dyspnea (rare), lung edema (rare), gastritis (rare), gastrointestinal hemorrhage (rare), necrotizing enterocolitis (rare), kidney failure (rare), retinopathy of prematurity (rare) sepsis (rare)
14. References:

### Appendix 1

Characteristics of studies included in Cochrane Review of Methylxanthines in AOP.\(^\text{12}\)

<table>
<thead>
<tr>
<th>Study</th>
<th>Erenberg 2000</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>Multicentre (9); 87 preterm infants 28 - 32 weeks postmenstrual age and less than 24 hrs of age with six or more apnea episodes (&gt; 20 secs duration) in 24 hrs. Exclusions: secondary apnea (CNS, lung disease, anemia, infection, shock).</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Caffeine citrate (10 mg/kg base) IV and 2.5 mg/kg daily vs placebo (citric acid/sodium citrate).</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Failure = &lt; 50% reduction in apnea (&gt; 20 secs); use of IPPV (provided by author); death by 30 days.</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Allocation concealment</strong></td>
<td>B</td>
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</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Gupta 1981</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Blinding of randomization - unclear (pharmacy made up 4 mixtures labeled a,b,c,d,e,f; letter drawn from a 'hat'); blinding of treatment - yes; completeness of followup - no (3 subjects excluded after randomisation); blinding of outcome assessment - yes.</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>29 preterm infants born at 26 to 34 weeks gestation who had clinical apnea; &gt;3 events per 12 hours of apnea &gt;15 sec with heart rate &lt; 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.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Oral theophylline (4 mg/kg 6 hourly, increased to 6 mg/kg if no response to first dose) vs placebo.</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Allocation concealment</strong></td>
<td>B</td>
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<tr>
<td>Study</td>
<td>1981</td>
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<tr>
<td>---------------</td>
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</tr>
<tr>
<td>Methods</td>
<td>Blinding of randomization - unclear; blinding of intervention - no; complete followup - yes; blinding of outcome measurement - no</td>
</tr>
<tr>
<td>Participants</td>
<td>18 preterm infants with apnea (&gt;2 apneas with heart rate &lt;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).</td>
</tr>
<tr>
<td>Interventions</td>
<td>Caffeine sodium citrate (20 mg/kg load im, then 5 mg/kg/day oral) vs no treatment.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Failure on day 1 and day 5 (continued apnea or use of mechanical ventilation); use of mechanical ventilation.</td>
</tr>
<tr>
<td>Notes</td>
<td>Four infants in the untreated group crossed over during the study and were classified as 'failed treatment'. Chart recording of apnea/bradycardia used.</td>
</tr>
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<td>Allocation concealment</td>
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</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>1990</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>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.</td>
</tr>
<tr>
<td>Participants</td>
<td>20 preterm infants (&lt;35 weeks gestation) with apnea (apnea &gt; 20 sec with &gt; 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 gms), postnatal age at study entry (4.0 vs 2.9) and baseline apnea rate (0.72 vs 0.70/hr).</td>
</tr>
<tr>
<td>Interventions</td>
<td>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.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>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.</td>
</tr>
<tr>
<td>Notes</td>
<td>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.</td>
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<td>Allocation concealment</td>
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<table>
<thead>
<tr>
<th>Study</th>
<th>1985</th>
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<tbody>
<tr>
<td>Methods</td>
<td>Blinding of randomisation unclear; blinding of intervention - no; complete followup - yes; blinding of outcome measurement - no.</td>
</tr>
<tr>
<td>Participants</td>
<td>43 preterm (&lt;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).</td>
</tr>
<tr>
<td>Interventions</td>
<td>Theophylline (6.8 mg/kg load iv, then 1.4 mg/kg 8 hourly) vs no treatment.</td>
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<tr>
<td>Outcomes</td>
<td>Failure (no 'resolution' of apnea or use of mechanical ventilation by 7 days); use of mechanical ventilation; death before hospital discharge.</td>
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<tr>
<td>Notes</td>
<td>Used continuous print out on chart recorder to detect apnea and bradycardia.</td>
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<td>Allocation concealment</td>
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</table>

Appendix 2.

Characteristics of included studies included in Cochrane review of caffeine versus theophylline in AOP.⁵

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bairam 1987</td>
<td>Single centre. Blinding of randomization - yes*</td>
<td>20 preterm infants (mean gestational age 30 wks) included after 24 hour recording documented &gt;= 3 apneas</td>
<td>Exp: standard caffeine = loading dose 10 mg/kg, maintenance dose 1.25 mg/kg/12hrs</td>
<td>Frequency of apnea, systolic arterial pressure, tachycardia, weight gain, gastrointestinal intolerance, behavioural assessment (scaled-score of motor activity, reactivity and sucking)</td>
<td>Apnea defined as cessation of breathing &gt;15 seconds</td>
</tr>
<tr>
<td></td>
<td>Blinding of intervention - yes</td>
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<td>Control: theophylline = loading dose 6 mg/kg, mainenance dose 2 mg/kg/12hrs</td>
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<td></td>
<td>Complete followup - yes</td>
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<td></td>
<td>Blinding of outcome measure - yes</td>
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<td>*extra information provided by the author (personal correspondence)</td>
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<tr>
<td>Brouard 1985</td>
<td>Single centre. Blinding of randomization - can't tell</td>
<td>16 preterm infants (mean gestational age 30 weeks) enrolled infants where &gt;= 3 severe apneas noted per 24 hours</td>
<td>Exp: standard caffeine = loading dose 10 mg/kg, maintenance dose 2.5 mg/kg to target serum level of 8 - 16 mg/l)</td>
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<tr>
<td></td>
<td>Blinding of intervention - no</td>
<td></td>
<td>Control: theophylline = loading dose 5.5 mg/kg, maintenance dose adjusted to maintain plasma levels at 5 - 10 mg/kg</td>
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<td></td>
<td>Complete followup - yes</td>
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<td>Blinding of outcome measure - can't tell</td>
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<td></td>
<td>Blinding of intervention - no</td>
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<td></td>
<td>Complete followup - yes</td>
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<tr>
<td><strong>Participants</strong></td>
<td>Blinding of outcome measure - no</td>
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<tr>
<td>30 preterm infants &lt;= 30 week gestation with apnea (&gt;= 10 in 8 hours or 4 in 1 hour)</td>
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<tr>
<td><strong>Interventions</strong></td>
<td>Exp: standard caffeine = loading dose 12.5 mg/kg and maintenance 3 mg/kg/12 hours.</td>
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<tr>
<td></td>
<td>Control : theophylline = loading dose 7.5 mg/kg/8hrs (aiming for plasma levels of 13 - 20 mg/l)</td>
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</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Apnea frequency over 48 hours</td>
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<tr>
<td></td>
<td>number of infants with &gt; 50 % reduction in apnea frequency</td>
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<tr>
<td><strong>Notes</strong></td>
<td>Apnea defined as a decrease in heart rate of 40 beats per minute with cessation of breathing and requiring stimulation</td>
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<tr>
<td><strong>Allocation concealment</strong></td>
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