Application for Inclusion of Caffeine in the WHO Model List of Essential Medicines (Revised October 2006)

Submitted by

Royal Children's Hospital, Melbourne, Australia

To:
15th Expert Committee on the Selection and Use of Essential Medicines
Geneva

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Revised by Dr Sean Beggs; October 2006

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Introduction

This application was originally submitted to the 14th expert committee in 2005. At that meeting a decision on the inclusion of Caffeine citrate, as an example of the therapeutic class of methylxanthines for apnoea of prematurity, was deferred therefore the submission has been revised and is being resubmitted. No new long-term safety data is available since the original submission. The Caffeine for Apnoea of Prematurity (CAP) trial which was designed for this purpose is ongoing; it has reported short term outcomes and is due to report 18 month follow up results in May of 2007. Additional short term data is included in this reviewed application as are revised pricing figures, which show the cost of caffeine to be considerably reduced.

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 dose 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 cyanosis[1]. 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 bradicardia,[3, 4] which may lead to the need for active resuscitation efforts[5]. 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.[6] 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.[7]

6.3 Methylxanthine treatment.

The methylxanthines, caffeine, aminophylline and theophylline, have been shown to be effective treatments for apnea of prematurity.[8] Caffeine is widely regarded as the methylxanthine of choice as it has the best safety profile.[2, 5, 8-11] 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 of apnea such as sepsis, hypothermia, hypoxaemia, hypoglycemia, anaemia and seizures should also be sought and treated appropriately.

7.2 Dose[12, 13]

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.[2]

7.4 Monitoring

Routine drug level monitoring is not required. It is recommended to check levels if infant remains symptomatic or has adverse effects.[9]

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.[10] 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 preformed 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[8] 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[14], one study used unclear randomisation methods and placebo control,[15] another study used a quasi-randomisation with placebo controls[16] while the remaining 2 studies used unspecified methods of randomisation and did not placebo blind.[17, 18] 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.[8] 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).[8] 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 does of caffeine which showed a reduction in the frequency of apneas for both treatment groups when compared to control.[19] Similar results have been found in 2 other open label studies which used comparable doses of caffeine.[20, 21]

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.[5] 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 out come data, thus leaving 3 studies, with a total of 66 patients, to be included in the meta-analysis[5]. In 2 of these 3 randomized studies, treatment allocation was well concealed,[22, 23] while in the third study the method of randomisation was not clearly reported.[24]. 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.[22] 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,[5] 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.[25, 26] Caffeine is widely recommended as the methylxanthine of choice due to its lower acute toxicity.[2, 5, 8-11] Due to its wider therapeutic index caffeine also has the advantage of not requiring routine therapeutic drug monitoring.[9] Reported adverse reactions to methylxanthines generally represent

an exaggeration of there pharmalogical action, such as tachycardia, high arterial pressure increased gasto-oesophageal reflux and jitteriness.[2] 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.[5] 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).[5]

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.[15, 27] 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.[15] Toxicity following acute caffeine overdose may manifest as central nervous system irritability seizure activity and tachypnea. [28-30]

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] This group has recently published short term outcomes, of their multicenter, randomised, placebo-controlled trial of caffeine for apnoea of prematurity. They showed that fewer in the caffeine group required supplemental oxygen at 36 weeks postmenstrual age, ie 36.3% versus 46.9% for the placebo group (odds ratio of 0.63 95%CI 0.52 – 0.76; P< 0.001). There was no significant difference between the groups in terms of adverse outcomes, namely death before first discharge home, ultrasonographic sign of brain injury and necrotising enterocolitis.[31] The 18 to 21 month data is not scheduled to be published until May of 2007.

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 costs are based on its price in Vietnam and converted to US dollars. The cost for Theophylline and Aminophylline come form the International Drug Price Indicator Guide.
Costs are in US dollars; treatment doses are based on a 1.5kg neonate.

Table 1. Cost comparisons for Methylxanthines:

	Caffeine	Theophylline Oral	Aminophylline IV
Cost/mg	$0.0003	$0.002	$0.0006
Cost/does loading maintenance/day	 $0.006 $0.0015	 $0.016 $0.008	 $0.006 $0.0045
Cost for initial week of treatment	**$0.015**	**$0.064**	**$0.033**

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.

11. Summary of Regulatory Status of Medicine.

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

<u>Caffeine citrate</u>
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)

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Appendix 1

Characteristics of studies included in Cochrane Review of Methylxanthines in AOP.[12]

Study	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.
Allocation concealment	B
Study	Gupta 1981
Methods	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.
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.
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.
Allocation concealment	B

Study	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.
Allocation concealment	C
Study	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 gms), 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.
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.
Allocation concealment	A
Study	Sims 1985
Methods	Blinding of randomisation unclear; blinding of intervention - no; complete followup - 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.
Allocation concealment	C

Appendix 2.

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

Study	Bairam 1987
Methods	Single centre. Blinding of randomization - yes* Blinding of intervention - yes Complete followup - yes * Blinding of outcome measure - yes *extra information provided by the author (personal correspondence)
Participants	20 preterm infants (mean gestational age 30 wks) included after 24 hour recording documented >= 3 apneas
Interventions	Exp: standard caffeine = loading dose 10 mg/kg, maintenance dose 1.25 mg/kg/12hrs Control: theophylline = loading dose 6 mg/kg, mainenance dose 2 mg/kg/12hrs
Outcomes	Frequency of apnea, systolic arterial pressure, tachycardia, weight gain, gastrointestinal intolerance, behavioural assessment (scaled-score of motor activity, reactivity and sucking)
Notes	Apnea defined as cessation of breathing >15 seconds
Allocation concealment	A
Study	Brouard 1985
Methods	Single centre Blinding of randomization - can't tell Blinding of intervention - no Complete followup - yes Blinding of outcome measure - can't tell
Participants	16 preterm infants (mean gestational age 30 weeks) enrolled infants where >= 3 severe apneas noted per 24 hours
Interventions	Exp: standard caffeine = loading dose 10 mg/kg, maintenance dose 2.5 mg/kg to target serum level of 8 - 16 mg/l) Control: theophylline = loading dose 5.5 mg/kg, maintenance dose adjusted to maintain plasma levels at 5 - 10 mg/kg
Outcomes	Apnea frequency on day 0, 1, and 5 Tachycardia Weight
Notes	Severe apnea defined as cessation of breathing for 10 secs with heart rate < 80 for > 30 seconds or <60 for > 15 seconds
Allocation concealment	B
Study	Scanlon 1992
Methods	Single centre Blinding of randomization - yes Blinding of intervention - no Complete followup - yes

	Blinding of outcome measure - no
Participants	30 preterm infants <= 30 week gestation with apnea (>= 10 in 8 hours or 4 in 1 hour)
Interventions	Exp: standard caffeine = loading dose 12.5 mg/kg and maintenance 3 mg/kg/12 hours. Control : theophylline = loading dose 7.5 mg/kg/8hrs (aiming for plasma levels of 13 - 20 mg/l)
Outcomes	Apnea frequency over 48 hours number of infants with > 50 % reduction in apnea frequency
Notes	Apnea defined as a decrease in heart rate of 40 beats per minute with cessation of breathing and requiring stimulation
Allocation concealment	A