Caffeine citrate: a review of its use in apnoea of prematurity

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Authors' objectives
The focus of the review was stated to be on the efficacy and tolerability of caffeine citrate in the treatment of apnoea of prematurity.

Searching
MEDLINE and EMBASE were searched for literature published in any language since 1966. In addition, AdisBase (a proprietary database) was also searched. The search term used was 'caffeine citrate'. Searches were last updated on 14 December 2000. Additional studies were identified from the reference lists of published articles. Bibliographic information, including contributory unpublished data, was requested from the company developing the drug (the company was not named).

Study selection
Study designs of evaluations included in the review
There was no clear statement of inclusion criteria relating to study design. The report stated that large well-conducted trials with appropriate methodology were preferred. The included trials comprised randomised trials, uncontrolled observational studies, and one randomised dose comparison that used a historical no-treatment control.

Specific interventions included in the review
There were no specific inclusion criteria stated for the intervention. The included studies used either caffeine citrate or did not report the formulation of caffeine used. Caffeine was administered in various doses, either orally or intravenously. The comparator groups in the included studies were: placebo, no treatment, theophylline or aminophylline in studies of first-line treatment; and placebo, no treatment or aminophylline in studies of prophylaxis. The duration of treatment ranged from 1 to 14 days in first-line treatment studies, and from 2 to 21 days in prevention studies. The treatment duration was not specified in the included studies of second-line treatment.

Participants included in the review
There were no specific inclusion criteria stated for the participants. The included studies enrolled pre-term neonates with idiopathic apnoea, and excluded those who had obstructive apnoea or apnoea due to central nervous system, cardiovascular or metabolic abnormalities, infection, respiratory distress or anaemia. Some of the included studies excluded neonates who required mechanical ventilation prior to or during the study. The definition of apnoea of prematurity varied between trials.

Outcomes assessed in the review
Trials that assessed efficacy or tolerability were eligible for inclusion. The efficacy measures varied between the trials. The most common measure of efficacy was the number of apnoeic episodes within a given period; some studies assessed hypoxaemia.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The authors do not report the method used to assess quality, or how the quality assessment was performed.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.
Data were extracted from each study on the following: study design; the number of participants in each treatment group; the mean gestational age, mean birth weight and mean postnatal age; treatment dose, regimen, duration, and whether caffeine citrate or caffeine base; and results.

Methods of synthesis
How were the studies combined?
A narrative summary and synthesis of efficacy outcomes was presented. Tolerability data were presented separately. RCTs were given priority in the narrative.

How were differences between studies investigated?
The studies were grouped according to first-line treatment, second-line treatment, and prophylactic use. For the trials evaluating efficacy, the tables presented allowed some assessment of the differences and similarities between trial designs (double-blind or non-blinded), participants (gestational age, birth weight, postnatal age), treatments (caffeine or caffeine citrate dose, regimen and duration) and results. Any clinical differences and similarities between the included studies were also discussed in the text of the results section.

Results of the review
Six randomised trials of first-line treatment were included: 1 comparison with placebo (n=82), 1 comparison with no treatment (n=18), 2 comparisons with theophylline (n=64), and 2 comparisons with aminophylline (n=34). In addition, there were 2 small uncontrolled studies of second-line treatment (n=27), and 3 randomised controlled trials (RCTs) of prophylactic use (n=267, including 14 patients in an untreated historical control group in one dose comparison trial). Tolerability data from various randomised and non-randomised observational studies were also described, but the number of studies and participants was unclear.

First-line treatment.
In one double-blind placebo-controlled RCT (n=82), the frequency of apnoeic episodes was reduced by 50% or more from baseline for 7 to 10 days in 68.9% of neonates administered caffeine citrate, compared with 43.2% of those given the placebo; this effect was significant (P=0.02). Apnoea was eliminated for 7 to 10 days in 24.4% of those who received caffeine citrate, compared with 0% of those who received placebo (P=0.005). Similar numbers in each group were withdrawn because of the recurrence of apnoea, adverse events or investigator discretion. In one non-blinded RCT (n=18), levels of apnoea were statistically significantly lower on days 1 and 5 after treatment with caffeine citrate, compared with no treatment. Four small RCTs showed similar efficacy between caffeine and theophylline (n=64) or aminophylline (n=34).

No double-blind placebo controlled trials were identified. Two small (n=27) studies with no control groups showed a reduction in apnoeic episodes or apnoea density in 82 and 88% of the patients, respectively, in response to caffeine.

Prophylactic use.
One double-blind RCT (n=50) did not show any difference between caffeine citrate and placebo in hypoxaemic episodes over the 2 days of the study. One RCT (n=180) showed no difference between caffeine citrate and aminophylline in apnoeic or bradycardiac episodes over the 10 days of the trial. One RCT that compared a high and a low dose of caffeine citrate (n=23) with an untreated historical control group (n=14) concluded that caffeine citrate was significantly more effective than no treatment.

Tolerability.
Few adverse event data have been reported in clinical trials of caffeine citrate in premature neonates. The double-blind RCT evaluating the efficacy of first-line treatment, compared with placebo, reported no difference in the
discontinuation rate between caffeine citrate (4.4%) and placebo (2.7%). The authors reported that caffeine was associated with fewer adverse events than theophylline in RCTs, but it was unclear how many RCTs showed this and no data were reported. One non-blinded study suggested that treatment with caffeine citrate for an average (mean) of 6 days during the neonatal period did not affect long-term growth and neurological development later in life, but no date were provided. Another non-blind trial reported that caffeine citrate for up to 32 weeks did not adversely influence growth in 28 infants, but again, no data were provided.

**Authors' conclusions**
The authors concluded that in clinical trials, caffeine citrate decreased the incidence of apnoea of prematurity compared with placebo, and was generally well-tolerated by neonates. It has also demonstrated similar efficacy to theophylline, but is generally better tolerated.

**CRD commentary**
The review was a collation of pharmacodynamic and pharmacokinetic data, which also attempted to assess efficacy and tolerability. Perhaps as a consequence of this very broad scope, it lacked the rigorous methodology expected of a systematic review of the effectiveness of an intervention.

The inclusion criteria were not explicit for any component of the review question. The sources searched were adequate to identify published trials, although the use of only one search term as reported seemed unlikely. The search for unpublished trials of efficacy could have been more extensive, and publication bias was not explored. It was impossible to judge the extent of any potential bias in the review process, because no details of study selection, data extraction, or quality assessment were reported. Details of the individual included studies were presented in clear tables. Details of the studies of tolerability, and the associated data, were however, unclear.

A narrative synthesis was appropriate considering the clinical heterogeneity between the studies, and the authors attempted to highlight important differences and similarities in the text. The study quality was, however, not adequately taken into account; double-blinding is not the sole requirement of a good quality RCT.

The authors' conclusions on efficacy need to be interpreted with caution as all the data came from small heterogeneous trials, some of very short duration. Similar clinical trials were used to draw conclusions about tolerability, hence an even more cautious interpretation is recommended. Other authors have conducted a series of Cochrane systematic reviews in this area, which are available in the Cochrane Library (for example, see Other Publications of Related Interest).

**Implications of the review for practice and research**
Practice: The authors state that caffeine citrate should be considered the drug of choice when pharmacological treatment of apnoea of prematurity is required.

Research: The authors state that well-controlled, randomised, double-blind long-term studies of caffeine citrate treatment in neonates have yet to be completed. At least one large, long-term follow-up RCT in neonates is stated to be underway.

**Bibliographic details**

**PubMedID**
11220405

**Other publications of related interest**
**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Apnea /drug therapy /metabolism; Brain /drug effects /metabolism; Caffeine /chemistry /pharmacokinetics /therapeutic use; Central Nervous System Stimulants /pharmacokinetics /therapeutic use; Citrates /chemistry /pharmacokinetics /therapeutic use; Drug Combinations; Heart Rate /drug effects /physiology; Humans; Infant, Newborn; Infant, Premature /physiology; Randomized Controlled Trials as Topic /methods; Respiration /drug effects

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**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.