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REVIEW FOR THE SHEIKH HAMDAN BIN RASHID AL MAKTOUM AWARD FOR MEDICAL SCIENCES

Caffeine therapy for apnoea of prematurity in very low-birthweight infants

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Abstract

Caffeine and other methylxanthines have been used to treat apnoea of prematurity for over 30 years. However, until recently, experimental evidence of the potential harm and lack of rigorous evaluation of this drug therapy in controlled clinical trials resulted in substantial uncertainty about the safety of the routine use of methylxanthines in preterm infants. The international Caffeine for Apnoea of Prematurity (CAP) trial group was formed in 1998. This collaborative research team enrolled over 2000 very low-birthweight infants in North America, Australia and Europe, and followed the children to the end of their second year of life. The CAP trial investigators showed for the first time that neonatal caffeine therapy reduces the rates of important short- and long-term morbidities such as bronchopulmonary dysplasia, severe retinopathy of prematurity, cerebral palsy and cognitive delay. Of all the neonatal treatments that have been subjected to economic evaluations, caffeine therapy is the most certain to be both cost saving and beneficial. It is therefore imperative that responsible drug manufacturers make safe and affordable formulations of caffeine available worldwide.

Introduction

Caffeine is the most frequently used medication in preterm infants in the USA.[1] However, until recently, the benefits and possible risks of caffeine and of other methylxanthines remained uncertain in this high-risk population of children. The international Caffeine for Apnoea of Prematurity (CAP) trial group was formed in 1998 to investigate whether methylxanthine therapy in preterm infants is a sound practice or a potential therapeutic disaster.[2] This review will examine how this collaborative research is turning caffeine for apnoea of prematurity from a commonly used but insufficiently tested therapy into one of the most evidence-based treatments in neonatology.

What is apnoea of prematurity and why does it matter?

> *Apnoea of prematurity is the most common and frequently recurring problem in very low birth weight infants.*
>
> Finer *et al.*[3]

This developmental disorder of respiratory control is characterized by periodic breathing with pathological apnoea in a preterm infant. Pathological apnoea is the cessation of respiratory air flow for at least 20 seconds, or a respiratory pause of shorter duration which is associated with cyanosis (desaturation), marked pallor, hypotonia or bradycardia.[4] Apnoea of prematurity resolves spontaneously by 44 weeks post-menstrual age.[5]

Although it remains uncertain if apnoea of prematurity is an independent risk factor for adverse neurodevelopmental outcome, preterm infants who are bradycardic and hypoxic because of periodic

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breathing and apnoea nevertheless cannot be left untreated.[3,6,7] The two main treatment options are drug therapy with a methylxanthine and the application of positive airway pressure.[7]

What was known about methylxanthine therapy in very low-birthweight infants before the Caffeine for Apnoea of Prematurity trial?

In 1973, Kuzemko and Paala[8] reported the use of aminophylline to treat neonatal apnoea. Aranda *et al.*[9] described the use of caffeine therapy for apnoea in low-birthweight infants in 1977. Almost 30 years later, in March 2004, the US Food and Drug Administration and National Institutes of Health convened the Neonatal Drug Development Initiative Workshop during which the Apnoea-of-Prematurity Group concluded: 'The benefit of intervention, apart from a reduction in apnoea itself, remains largely unproven'.[3]

Before the CAP trial was designed in 1998, more than a dozen randomized trials had been published in which a methylxanthine – caffeine, aminophylline or theophylline – was compared with an alternative therapy such as no therapy, placebo or continuous positive airway pressure (CPAP). However, all of these trials were very small and fewer than 300 babies had received a methylxanthine across all of the published trials.[2] Unfortunately, neonatal trials in general tend to be fairly small.[10,11] Moreover, the study end points of past trials of methylxanthines were extremely short term: the median duration of follow-up was only 7 days.[2] Such a short period of follow-up is insufficient to evaluate the effects of methylxanthines on clinically important neonatal outcomes such as bronchopulmonary dysplasia or retinopathy of prematurity. Nothing could be learnt from past controlled trials about the effects of methylxanthines on long-term growth and neurological development.

What did we learn from these trials?

Table 1 summarizes the pertinent outcomes in Cochrane reviews that compared a methylxanthine with no or placebo therapy at the time the CAP trial was designed. Three systematic reviews and meta-analyses showed that methylxanthines reduce the frequency of apnoea of prematurity and the need for mechanical ventilation during the first 7 days of therapy, facilitate extubation and reduce post-operative apnoea/bradycardia and desaturation in infants born preterm.[12–14] Beyond these short-term outcomes, very little was known about the effects of methylxanthine therapy.

TABLE 1 Selected outcomes in meta-analyses of methylxanthines compared with controls in preterm infants reported in The Cochrane Library, Issue 3, 1998, the year in which the Caffeine for Apnoea of Prematurity trial was designed[12–14]

Outcome	Methylxanthine no./total no.	Control no./total no.	Relative risk (summary statistic)	95% confidence interval
Reduction of apnoea (four trials)	5/15	14/14		
	0/9	6/9	0.36	0.24 to 0.55
	2/10	8/10		
	9/21	17/22		
Use of mechanical ventilation (four trials)	0/15	0/14		
	0/9	2/9	0.34	0.12 to 0.97
	0/10	1/10		
	3/21	8/22		
Failed extubation (four trials)	3/10	2/10		
	5/23	15/28	0.44	0.27 to 0.72
	2/18	8/20		
	5/14	10/11		
Post-operative apnoea/bradycardia (three trials)	1/11	4/15		
	0/9	8/11	0.09	0.02 to 0.34
	0/16	13/16		
Post-operative desaturation (two trials)	1/11	5/15		
	0/16	8/16	0.13	0.03 to 0.63

Was there any evidence from experimental animals about the safety of methylxanthines?

A troubling series of experiments on young mice was published in 1978 in the journal *Science*.[15] In this study, weanling mice were exposed, as pairs of littermates, to an atmosphere of nitrogen; one member of each pair was pretreated with 7.5 mg/kg aminophylline. Ten of the 16 untreated controls survived this ordeal, but all 16 methylxanthine-treated mice died. At the time of these experiments, it was not yet known that methylxanthines are non-specific inhibitors of two of the four known adenosine receptors.[16,17] Adenosine is produced naturally in all human tissues, including the brain. Adenosine levels rise in the brain when energy demand outstrips supply and brain cells are at risk of dying. Situations that cause such an imbalance between ATP synthesis and ATP breakdown include hypoxia, ischaemia, seizures and hypoglycaemia. Adenosine reduces metabolic demand in order to conserve precious energy. Numerous animal experiments suggest that this is an important mechanism to protect the brain from permanent injury.[18] This experimental evidence of potential harm and the lack of rigorous evaluation of caffeine therapy in controlled clinical trials resulted in substantial uncertainty about the safety of the routine use of methylxanthines in preterm infants.

Why was the Caffeine for Apnoea of Prematurity trial needed and what did it add?

The CAP trial was designed to put an end to this long-standing uncertainty about the long-term efficacy and safety of methylxanthines in very preterm infants. Caffeine was chosen over aminophylline and theophylline for mostly pharmacokinetic reasons.[19] In addition, and in contrast with aminophylline and theophylline, caffeine can be used in a fixed-dose per kg body weight regimen, without the need for routine therapeutic drug monitoring.[20]

Tables 2 and 3 summarize the most important neonatal and 18-month outcomes of the CAP trial participants. To facilitate a direct comparison with the prior published evidence shown in Table 1, the CAP trial outcomes have been reanalysed for these tables with the software used by the Cochrane collaboration (RevMan, version 5.1; Nordic Cochrane Centre, Copenhagen, Denmark). Before the CAP study participants' first discharge home, caffeine reduced the risks of bronchopulmonary dysplasia,

TABLE 2 Neonatal outcomes in the Caffeine for Apnoea of Prematurity trial, analysed using Cochrane Software (RevMan version 5.1)

Outcome	Caffeine no./total no.	Placebo no./total no.	Relative risk	95% confidence interval
Death	52/1006	55/1000	0.94	0.65 to 1.36
Bronchopulmonary dysplasia	350/963	447/954	0.78	0.70 to 0.86
Severe retinopathy of prematurity	49/965	75/955	0.65	0.46 to 0.92
Brain injury	126/967	138/966	0.91	0.73 to 1.14
Necrotizing enterocolitis	63/1006	67/1000	0.93	0.67 to 1.30
Drug therapy for patent ductus arteriosus	293/1001	381/999	0.77	0.68 to 0.87
Surgical closure for patent ductus arteriosus	45/1001	126/999	0.36	0.26 to 0.50

TABLE 3 Outcomes at 18 months – corrected for prematurity – in the Caffeine for Apnoea of Prematurity trial, analysed using Cochrane Software (RevMan version 5.1)

Outcome	Caffeine no./total no.	Placebo no./total no.	Relative risk	95% confidence interval
Death or disability	377/937	431/932	0.87	0.78 to 0.97
Death before 18 months	62/974	63/970	0.98	0.70 to 1.38
Cerebral palsy	40/909	66/901	0.60	0.41 to 0.88
Cognitive delay	293/867	329/858	0.88	0.78 to 1.00
Severe hearing loss	17/909	22/905	0.77	0.41 to 1.44
Bilateral blindness	6/911	8/905	0.75	0.26 to 2.14

severe retinopathy of prematurity, and the use of medical and surgical therapy to close a patent ductus arteriosus.[21,22] However, information on short-term outcomes was insufficient to assess the overall benefits and risks of common neonatal interventions. Therefore, the main goal of the CAP trial was to determine how well the study participants survived and functioned at a corrected age of 18 to 21 months. At that age, caffeine improved the combined outcome of death or survival with neurodevelopmental disability. Among the components of this composite outcome, caffeine reduced the incidence of cerebral palsy from 7.3% in the placebo group to 4.4% in the caffeine group. Caffeine improved cognitive outcomes as measured by the Bayley Scales of Infant Development II.[22] The children in this trial continue to be followed worldwide to preschool[23] and school ages.

As a result of its many confirmed benefits on clinically important outcomes in the CAP trial, without any evidence so far of lasting harmful effects, caffeine has been called 'a silver bullet in neonatology'.[24]

Do the benefits of caffeine vary in subgroups?

The CAP trial had broad and pragmatic eligibility criteria. In a *post hoc* subgroup analysis, it was examined whether or not the benefits of caffeine varied according to (1) the clinical indication for starting study medication, (2) the level of respiratory support at randomization and (3) the age at starting treatment. We used regression models incorporating treatment or subgroup factor interactions to look at the consistency of treatment effects across the subgroups.[25] Outcomes assessed were those which showed an overall treatment effect in the original analyses.[21,22]

Mutually exclusive clinical indications for starting the study drug were documented at study entry to prevent apnoea, treat apnoea or facilitate the removal of an endotracheal tube. The treatment effect was consistent across these subgroups for all outcomes examined.[25]

The level of respiratory support at randomization was categorized as no support, non-invasive respiratory support or ventilation via an endotracheal tube. Evidence of heterogeneity of effect was found for the outcomes death or major disability and cognitive delay. It appears that infants receiving respiratory support derived greater neurological benefit from caffeine than those not receiving support. This result was consistent with our previous observation that earlier discontinuation of positive pressure ventilation was the most powerful of a number of mechanisms explored and explained 49% of the beneficial long-term effect of caffeine.[25]

The median age at starting treatment was 3 days. Evidence of heterogeneity of effect was found for the outcomes post-menstrual age at last intubation and at last positive pressure ventilation. Infants whose treatment commenced before 3 days of age appeared to derive greater respiratory benefit than those commencing treatment at 3 days of age or later. Although interesting, these observations should be interpreted with caution. Analyses were conducted *post hoc* and infants were not stratified according to clinical indication, time of study drug commencement or level of respiratory support.[25]

Is caffeine cost-effective?

A retrospective economic evaluation of the CAP trial showed that caffeine therapy compared with placebo was less expensive and more effective in improving survival without neurodevelopmental impairment.[26] Caffeine therapy is associated with a much higher degree of certainty that it is both cost saving and beneficial than any other neonatal treatments that have been subject to economic evaluations.[26]

Unfortunately, caffeine is currently unavailable in many resource-poor countries. Mueni *et al.*[27] have estimated that preterm birth is likely to result in more than 1 million deaths per year. These authors have called caffeine a 'neglected drug for a neglected condition in a neglected population'. Caffeine can be produced very cheaply. It is therefore imperative that responsible drug manufacturers make safe and affordable formulations of caffeine available worldwide.

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