

Caffeine for preterm infants: current indications and uncertainties

S. Nobile, V.P. Carnielli

Neonatology Unit, Salesi Children's Hospital, Ancona (Italy)

Summary. Caffeine is one of the most commonly used therapies in Neonatology, with different indications such as the treatment of apnea and the prevention of extubation failure and bronchopulmonary dysplasia. However, there are still uncertainties regarding effects on central nervous system development, time of discontinuation and dosing of the drug. (www.actabiomedica.it)

Key words: caffeine, preterm infant, apnea, bronchopulmonary dysplasia

Background

Caffeine is one of the most commonly used therapies in Neonatology, with different indications such as the prevention/treatment of apnea and the prevention of extubation failure.(1,2) Recent studies showed that caffeine is also effective in reducing bronchopulmonary dysplasia(BPD) rates (3-7).

Nearly all very low birth weight infants (VLBWi; <1,500 g) experience apnea due to brainstem and peripheral chemoreceptor immaturity; in addition, pathologic conditions such as sepsis, respiratory failure, intracranial hemorrhage, and seizures may increase the number and severity of apnea events (3).

BPD is another common complication of prematurity, which occurs in over 40% of VLBWi. Neonates with BPD are at high risk of long-term lung disease, adverse neurodevelopmental outcomes and hospitalization in the first year of life. Few safe and effective therapies are available to prevent the disease, including caffeine (4).

Methods

We performed a literature search on Pubmed and selected the most relevant studies about pharmacology and clinical use of caffeine among preterm infants.

Results

Pharmacology

Caffeine is a methylxanthine acting as a non-specific inhibitor of 2 (A1 and A2a) of the 4 known adenosine receptors A1, A2a, A2b and A3. Adenosine is a purine nucleoside produced in human tissues, including the brain, whose levels increase rapidly with inflammation (1). Adenosine preserves brain ATP levels and protects brain cells from energy failure and cell death during experimental hypoxia and ischemia in a variety of animal models.

Caffeine is thought to act by increasing central respiratory drive and by lowering the threshold of response to hypercarbia, as well as by stimulating diaphragmatic contractility and preventing diaphragmatic fatigue. Other suggested mechanisms include diuretic effect, increased cardiac output and blood pressure, improvement in overall pulmonary mechanics, resulting in a reduction of endotracheal ventilation and protection against associated lung injury (8).

Most studies reported intravenous administration of caffeine. The systemic absorption of caffeine from the gastrointestinal tract has been found to be complete in preterm infants (9). Therefore, caffeine administration can be simplified because dosing can

be switched between orogastric and intravenous routes as required. The mean absorption half-life is about 30 minutes.

Caffeine is very rapidly distributed, with a half-life of < 10 minutes. Caffeine clearance has been described as a function of body weight and postnatal age (which is in turn correlated with renal and hepatic development). Preterm infants tolerate caffeine very well, even at serum concentrations of 70 mg/L or above. Lee et al reported a very long caffeine half-life of 86 to 277 hours, much higher compared with 5 hours in adults (8). The large majority of the drug is cleared by the kidneys. Distribution reflects a partitioning of caffeine into the relatively larger extracellular fluid volume of the newborn, especially in skeletal muscle.

The binding to serum albumin is low (35%) for caffeine concentrations up to 20 mg/L. Indeed, it is likely that the protein binding of caffeine in premature neonates is linear to at least 70 mg/L, as pointed out by Lee and colleagues (8).

Natarajan et al. 2007 suggested that routine monitoring of plasma concentrations of caffeine is unnecessary, even in VLBWi with renal or hepatic dysfunction or after prolonged use, because the vast majority of patients achieve blood concentrations in the range of 5 to 20 mg/L (10). In the subgroup of infants who do not show a clinical response to standard doses of caffeine, higher plasma levels may be targeted, and monitoring of plasma levels may be prudent. Pharmacokinetic studies in premature neonates showed that the half-life of caffeine is prolonged to 102.9 ± 17.9 hours and remains prolonged for as long as 38 weeks' gestation. The transition to adult levels of elimination occurs at 3 to 4^{1/2} months. Other factors such as cholestasis and breastfeeding seem to further prolong the half-life of caffeine.

The recommended standard dosing for caffeine citrate is 20 to 40 mg/kg (loading dose) followed by 5 to 8 mg/kg per day as maintenance. Larger maintenance doses up to 20 mg/kg day in the periextubation period have shown higher rates of successful extubation, without adverse events in the first year of life (2).

Reported adverse events during caffeine therapy are tachycardia, central stimulation, and alimentary tract toxicity; however, caffeine is a relatively safe drug, and even at the maximum observed concentration of

approximately 80 mg/L, it has few significant acute adverse effects in preterm infants, and no apparent detrimental developmental outcomes up to at least 1 year of age after administration during the periextubation period (2).

There is uncertainty on the precise desired plasma concentration and its correlation with efficacy, as clinically effective plasma concentrations vary over a wide range of 5 to 50 mg/L. Although a decrease in apnea and increase in respiratory drive is known at plasma concentrations as low as 2.9 and 4 mg/L, optimal effect is at 10 mg/L. Higher doses and caffeine levels have been targeted with some benefit and no adverse effects. However, a recent study showed that administering intravenous loading dose 80 mg/kg compared to 20 mg/kg in the first 24 hours of life was associated with higher incidence of cerebellar injury with subsequent alterations in early motor performance (11).

Clinical studies

Caffeine has been increasingly used from the 70's to treat apnea, prevent extubation failure and BPD. Given the concerns for potential adverse events that emerged from in vitro studies (brain toxicity in hypoxia models), large trials have been conducted in order to evaluate short- and long-term safety and efficacy of caffeine (3,12,13).

The CAP trial, an international, multicenter, placebo-controlled randomized trial conducted on preterm infants (with birth weight below 1250 grams) showed that caffeine significantly reduced the frequency of BPD (36.3 vs 46.9% for placebo). The rates of death before the first discharge home, ultrasonographic signs of brain injury, and necrotizing enterocolitis did not differ significantly between the two groups (3).

Other studies confirmed the decreased neonatal morbidity (in terms of death, BPD, PDA, duration of endotracheal intubation) with early (before 3 days of life) versus late initiation of therapy (4-7).

In a later follow-up study from the CAP trial,(12) caffeine compared to placebo significantly improved the rate of survival without neurodevelopmental disability at a corrected age of 18 to 21

months (59.8% vs. 53.8%, odds ratio 0.77; 95% confidence interval 0.64 to 0.93; $P = 0.008$). There was no significant difference between the two groups in the rate of death before the age of 18 months. The rates of deafness and bilateral blindness were low and likewise not significantly different between the two groups. Treatment with caffeine as compared with placebo significantly reduced the incidence of cerebral palsy (4.4% vs. 7.3%; odds ratio 0.58; 95% CI 0.39 to 0.87; $P = 0.009$) and of cognitive delay (33.8% vs. 38.3%; odds ratio 0.81; 95% CI 0.66 to 0.99; $P = 0.04$). Nearly one-half of the neuroprotective effect of caffeine at 18 months could be explained by the earlier discontinuation of positive airway pressure in infants assigned to caffeine. Another possibility is that caffeine has antioxidant capacity, as suggested by a recent experimental study on mice reporting that caffeine exerts protection for neonatal neurons exposed to high oxygen (14).

In a subsequent follow-up study of the CAP trial in which infants were evaluated at 5 years of age, Schmidt et al. reported that there was no difference between children treated with caffeine and those who received placebo with regard to a combined outcome of death or survival with 1 or more of the following: motor impairment, cognitive impairment, behavioral problems, poor general health, severe hearing loss and bilateral blindness (13).

Regarding the optimal time of discontinuation of caffeine therapy, a recent study pointed out that extending caffeine treatment to 40 weeks' post-menstrual age decreases intermittent hypoxia events (SatO₂ <90%) compared to earlier discontinuation (34 to 37 weeks PMA); thus, prolonged administration might improve neurodevelopmental outcome among preterm infants (15).

Discussion

Caffeine appears to be a safe and effective therapy for apnea of prematurity, prevention of BPD and extubation failure in preterm infants (i.e. born <29 weeks' gestational age) who require ventilatory support or present apnea events. More clinical research is needed to confirm potential neuroprotective properties of the

drug and to clarify the optimal dosing and time to discontinuation of therapy.

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Correspondance:
Stefano Nobile, MD
Neonatology Unit
Salesi Children's Hospital
Ancona, Italy
E-mail: stefano.nobile@ospedaliriuniti.marche.it