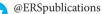# Caffeine in preterm infants: where are we in 2020?

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Correspondence: Charles Christoph Roehr, Dept of Paediatrics, Newborn Services, John Radcliffe Hospital, Oxford University Hospitals NHS, Headley Way, Headington, Oxford OX3 9DU, UK. E-mail: Charles.Roehr@ouh.nhs.uk

ABSTRACT   The incidence of preterm birth is increasing, leading to a growing population with potential long-term pulmonary complications. Apnoea of prematurity (AOP) is one of the major challenges when treating preterm infants; it can lead to respiratory failure and the need for mechanical ventilation. Ventilating preterm infants can be associated with severe negative pulmonary and extrapulmonary outcomes, such as bronchopulmonary dysplasia (BPD), severe neurological impairment and death. Therefore, international guidelines favour non-invasive respiratory support. Strategies to improve the success rate of non-invasive ventilation in preterm infants include pharmacological treatment of AOP. Among the different pharmacological options, caffeine citrate is the current drug of choice. Caffeine is effective in reducing AOP and mechanical ventilation and enhances extubation success; it decreases the risk of BPD; and is associated with improved cognitive outcome at 2 years of age, and pulmonary function up to 11 years of age. The commonly prescribed dose (20 mg·kg^{-1} loading dose, 5–10 mg·kg^{-1} per day maintenance dose) is considered safe and effective. However, to date there is no commonly agreed standardised protocol on the optimal dosing and timing of caffeine therapy. Furthermore, despite the wide pharmacological safety profile of caffeine, the role of therapeutic drug monitoring in caffeine-treated preterm infants is still debated. This state-of-the-art review summarises the current knowledge of caffeine therapy in preterm infants and highlights some of the unresolved questions of AOP. We speculate that with increased understanding of caffeine and its metabolism, a more refined respiratory management of preterm infants is feasible, leading to an overall improvement in patient outcome.

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Caffeine is the current drug of choice to prevent and treat apnoea of prematurity. There is no agreed protocol on the optimal timing and dosage of caffeine therapy for preterm babies. Data on caffeine metabolism may optimise individualised therapy. http://bit.ly/2LMuJPY

Background

Preterm birth represents a significant healthcare burden and is among the leading causes of infant mortality and long-term morbidity [1]. Therefore, the prevention of morbidities related to prematurity is considered a central health priority [2, 3]. As the number of children surviving extremely preterm birth is likely to continue to rise over the coming years, an increase in children with respiratory complications is expected [2, 4], especially those with chronic lung diseases such as bronchopulmonary dysplasia (BPD) [5–7]. To minimise lung injury and illnesses related to prematurity, neonatologists are focusing on non-invasive ventilation techniques from the very first minutes of life [8, 9]. However, non-invasive respiratory support is often ineffective, with a high failure rate of up to 50% in very low birthweight (VLBW) infants [10, 11], most commonly due to insufficient respiratory drive. Thus, apnoea is one of the major well-recognised challenges of prematurity, and remains one of the main indications for invasive ventilation [12–14]. Since the 1970s, methylxanthines have been routinely prescribed in preterm infants to prevent apnoea of prematurity (AOP) and reduce the need for invasive ventilatory support [13]. Of the methylxanthines, caffeine is the drug of choice because of its longer half-life, wider therapeutic range, cost-effectiveness and decreased need for drug-level monitoring compared to other methylxanthines, especially theophylline [15].

Caffeine is one of the top five most prescribed treatments in neonatology [16]. Its stimulating effect was originally recognised by the Ethiopians, but it was the Sufis who probably first used it expressly for its pharmacological effects, in the 15th century [17, 18]. Caffeine is a trimethylated xanthine with a similar molecular structure to adenosine. It acts as a nonspecific inhibitor of two of the four known adenosine receptors, in particular A1 and A2A, located at multiple sites in the brain [19]. The effects of caffeine on the brain, the lung and the cardiovascular system are summarised in figure 1 [12, 18–40]. The dosage used in the largest randomised controlled trial (RCT) conducted to date investigating caffeine in preterm infants, the Caffeine for Apnea of Prematurity (CAP) trial [33], is the most often quoted template for local caffeine therapy protocols. However, despite its frequent use in routine neonatal practice, there are currently no commonly agreed, standardised protocols on caffeine administration, and there is a particular dearth of knowledge regarding the optimal timing and dosage in the most immature preterm infants (<29

Increased respiratory neural output by reversing the adenosinergic inhibition on inspiratory neurons in the brainstem [18, 19]
Enhanced CO_2 responsiveness and decreased hypoxic depression of breathing by action on A_1 receptor and peripheral chemoreceptor (animal models) [20–22]
Neuroprotective anti-inflammatory effect against periventricular white matter injury and hypoxic insults by blocking adenosine action [23]
Increase in myelination, promotion of oligodendroglial maturation and process arborisation in hypoxia-exposed white matter [23]
Anti-apoptotic effect possibly by blocking TNF-α [24]

Enhanced cerebral cortical activity [25, 26]
Reduced incidence of death or clinical disability, cerebral palsy and cognitive delay at 18–21 months of corrected age compared to placebo [27]
No difference in death or severe impairment (motor impairment, behavioural problems, poor general health, deafness and blindness) at 5 years compared to placebo [28]
Improved motor function at 5 and 11 years [28, 29]
No difference in the combined rates of functional impairment, academic performance and behavioural problems at 11 years compared to placebo [29, 30]
Improved fine motor coordination, visuomotor integration, visual perception, visuospatial organisation at 11 years [29]

Improvement in diaphragmatic contractility and function 30 min after loading dose in ELBW infants [21]
Inhibition of pulmonary inflammation induced by hyperoxia by decreased proinflammatory cytokine expression (animal models) [18, 19]
Induction of surfactant protein B transcription through a cAMP-dependent pathway [18, 19]
Diuretic effect, probably by removal of excess fluids from the lungs and the facilitation of breathing [21, 31]

Reduction in ventilatory support and IPPV [32, 33]
Reduction in oxygen treatment at 36 weeks PMA [33]
Lower rates of BPD at 36 weeks PMA [32]
Improved minute ventilation and tidal volumes [12]
Reduced incidence of apnoea [15]
Reduced extubation failure [36]
Improved lung function at 11 years [37]

Increased left ventricular stroke volume with inotropic effect accompanied by pressor effect [38, 39]

Reduced need for PDA treatment [32, 33]
Reduced need for surgical closure of PDA [33, 36]
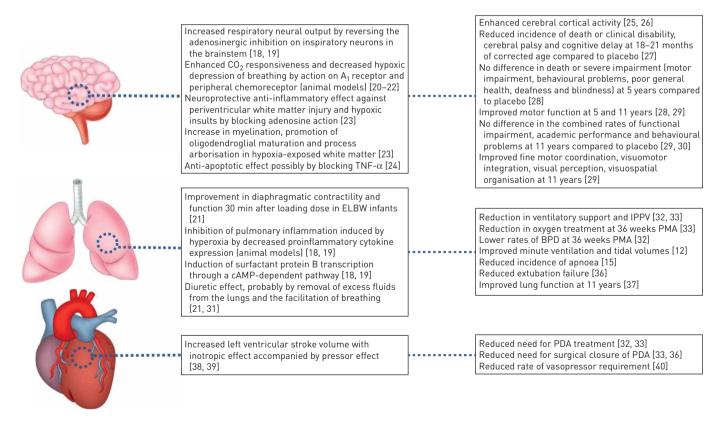Reduced rate of vasopressor requirement [40]

FIGURE 1 Schematic of the known effects of caffeine citrate during early development on the brain, the lung and the cardiovascular system derived from animal and infant studies. The first column indicates effects on a molecular level, while the second column describes demonstrated caffeine effects in the context of the specific system. CO_2: carbon dioxide; TNF: tumour necrosis factor; ELBW: extremely low birthweight; IPPV: intermittent positive pressure ventilation; PMA: post-menstrual age; BPD: bronchopulmonary dysplasia; PDA: patent ductus arteriosus.

gestational weeks (GW)). Additionally, concerns have been raised about potential safety issues and adverse effects, some of which may relate to high caffeine dosages [19, 32]. These data suggest that the optimal dose and timing of caffeine must still be investigated and be chosen with caution when treating preterm infants. The aim of this review is to present the state-of-the-art of current use of caffeine citrate in preterm infants, with a focus on the known short- and long-term effects of the drug, reported data on timing, dosage and monitoring in order to trigger future research on this hot topic.

The effects of caffeine in preterm infants

Neurological effects

A number of studies have suggested that caffeine intake in preterm infants may have a neuroprotective effect, although researches on animal models have shown contrasting results, probably impacted by the species examined, dose of caffeine used, neurodevelopmental stage at the time of administration and duration of exposure (figure 1) [23, 41–43].

In preterm infants, enhanced cerebral cortical activity, observed as increases in amplitude and periods of continuity on electroencephalography recordings, is seen within 2 h of administration of caffeine [25, 26], suggesting an effect on neurological function. Furthermore, at 36 weeks post-menstrual age (PMA) infants treated with caffeine therapy had a higher amplitude-integrated electroencephalography score compared to the control group (p<0.001), without an increase in seizure activity [26]. The most comprehensive study to date exploring the long-term effects of caffeine in preterm infants is the CAP trial, whose primary objective was to determine whether survival without neurodevelopmental disability at a corrected age of 18–21 months was altered if AOP was treated with caffeine [33]. 2006 infants (birthweight 500–1250 g) were enrolled and randomly assigned to receive either caffeine (20 mg·kg^{-1} intravenously as loading dose followed by a maintenance dose of 5 mg·kg^{-1} per day) or placebo. The caffeine group had a reduced likelihood of death or clinical disability (40.2% versus 46.2%; p=0.008), together with a reduced incidence of cerebral palsy (4.4% versus 7.3%; p=0.009) and of cognitive delay (33.8% versus 38.3%; p=0.04) [27]. The results of the subsequent follow-up at 5 years of age showed no significant difference between caffeine treatment and placebo in the composite outcome of death or disability (21.1% versus 24.8%; p=0.09) [28], but a significant improvement of gross motor function in the caffeine group (odds ratio adjusted for centre 0.64, p=0.006). The long-term follow-up at 11 years of age confirmed previous results of reduced risk of motor impairment (19.7% versus 27.5%; p=0.009), with no significant difference in the rates of functional impairment (31.7% versus 37.6%; p=0.07), academic performance and behavioural problems (10.9% versus 8.3%; p=0.22) [29, 30].

Prolonged treatment with caffeine reduces hypoxaemia events in premature infants [44], the severity and duration of which are probably associated with adverse neurodevelopmental outcomes [45, 46]. Overall neonatal caffeine therapy, at the doses used in the CAP trial, appears to be safe into middle-school age, with no adverse effects on general motor function, intelligence, attention and behaviour.

Caffeine for apnoea, ventilatory support and extubation

Methylxanthines have been used for >40 years in neonatal medicine to reduce the frequency of apnoea, but, apart from the CAP trial, studies and systematic reviews comparing caffeine versus placebo have mainly addressed short-term respiratory outcomes, such as apnoea prophylaxis (one review, two trials), apnoea treatment (one review, three trials), extubation success (one review, two trials) and ventilator support (intermittent positive pressure ventilation (IPPV) and/or mechanical ventilation) (five trials), with a consequent uncertainty of the long-term benefit/risk ratio of this therapy [15, 33, 47].

The Cochrane review published in 2010 [35], included, in addition to the CAP trial, two studies evaluating the effects of prophylactic caffeine on short-term outcomes. The review concluded against the support of the use of prophylactic caffeine for preterm infants at risk of apnoea, but only one study reported apnoea (as defined by duration >20 s with bradycardia <100 bpm or cyanosis) as an outcome in the results [48].

However, a single-centre RCT [49] on premature infants (birthweight <1200 g) demonstrated a reduction in apnoea episodes (as a breathing pause for ⩽20 s with bradycardia and/or cyanosis) in the caffeine-treated group compared to placebo (15.4% versus 61.5%, 95% CI 0.097–0.647; p=0.001), with the more immature infants having the greater benefit of prophylactic caffeine on the incidence and severity of apnoea. The limitations of this study, which was published after the 2010 Cochrane review, are the monocentric setting, the small sample size (26 infants in the treatment group versus 26 in the placebo group) and the unprecise detection of apnoea (daily neonatal intensive care unit reports and monitor downloads). In general, the definition of prophylactic caffeine in terms of hours of life at first administration can be debated, as it is supposed that apnoea events can occur from the first hour of life, and studies comparing caffeine in the delivery room versus placebo to reduce the incidence of apnoea are lacking.

Another Cochrane review published in 2010 [15] evaluated the effects of methylxanthine treatment on the incidence of apnoea (American Academy of Pediatrics 2003 definition [50]) and included three trials on caffeine. The analysis of the two trials [51, 52] on caffeine, without considering the CAP trial, found significantly less treatment failure (relative risk 0.46, 95% CI 0.27–0.78, number needed to treat 3) as defined by <50% reduction in apnoea, or use of IPPV, or death during the study period (by 5 and 10 days from starting treatment).

Finally, the last Cochrane review of the series summarised the effects of prophylactic methylxanthine treatment to improve the chances of successful extubation, with failed extubation defined within 1 week of commencing treatment, if unable to wean from IPPV and extubate, or reintubation for IPPV, or need for use of continuous positive airways pressure (CPAP) [36]. Overall analysis of the six included trials showed that methylxanthine treatment results in an absolute reduction of 27% in the incidence of failed extubation. However, although all trials had the aim of improving the chances of successful extubation, protocols differed considerably, and only two trials compared caffeine *versus* placebo [33, 53].

The large CAP trial was included in each of the three Cochrane reviews, but did not report on apnoea outcomes and extubation success, although recruited infants received caffeine for any one of the three indications (prophylaxis for apnoea (22%), treatment of apnoea (40%) or prophylaxis for extubation (38%)).

However, the CAP trial clearly demonstrated that caffeine treatment within the first 10 days of life determined a reduction in each of the three levels of respiratory support (need for endotracheal tube, any positive pressure ventilation (PPV), supplemental oxygen) of 1 week compared to placebo (p<0.001), with no difference according to the indication for starting treatment. Interestingly, the positive results on respiratory support, together with the significantly reduced rate of BPD, surgical closure of patent ductus arteriosus (PDA) and of use of postnatal steroids, explained 55% of caffeine effect on the primary neurological outcomes at 18–21 months of age (with the most important variable being earlier discontinuation of PPV), suggesting a direct neuroprotective effect of the drug [33].

As a result of these findings, caffeine is the drug of choice to reduce apnoea rates, need for IPPV, ventilatory support, extubation failure and PDA ligation in preterm infants. However, the role of caffeine on longer term clinical outcomes, such as apnoea incidence till 34 corrected gestational weeks, infant respiratory morbidity within the first year of age, need for oxygen treatment after discharge and lung function up until adult age needs to be further investigated in appropriately designed RCTs.

BPD and long-term pulmonary outcomes

Caffeine is one of the few known drugs proven to reduce the risk of BPD at 36 weeks PMA. However, most of the studies evaluating this outcome have been limited in number, have used different definitions of BPD and have not reported longer-term pulmonary outcomes. The main data stem from the results of the CAP trial. Other studies have compared different timing of caffeine treatment or different doses of the drug, and have been conducted mainly retrospectively.

In the Cochrane review on methylxanthines for extubation [36] two trials, the first comparing caffeine *versus* placebo [53] and the second comparing caffeine, theophylline and placebo, reported rates of BPD defined as oxygen supplementation at 28 days of life in the first, but undefined in the second. Therefore, conclusions on this outcome could not be performed.

In the CAP trial [33], caffeine use led to a 36% decrease in BPD at 36 weeks PMA as defined by SHENNAN *et al.* [54], although the definition of BPD is continuously put into question and debate [55, 56]. Interestingly, the *post hoc* subgroup analysis of the CAP data showed an influence of postnatal age at onset of caffeine treatment on BPD reduction [34], and these findings were confirmed by subsequent cohort studies (further details in section on Benefits of early caffeine administration) [32, 57]. Encouragingly, the effect of caffeine therapy on BPD in the neonatal period seems to have positive repercussions on later lung function as well, as demonstrated by the results of the follow-up at 11 years in Australian former CAP study participants. In this study, expiratory flows were improved by 0.5 SD in children randomised to caffeine (forced expiratory volume at 1 s mean z-score −1.00 *versus* −1.53, 95% CI 0.14–0.94; p=0.008), with 11% *versus* 28% with forced vital capacity values below the fifth centile [37]. However, when the respiratory outcomes were adjusted for the higher incidence of BPD in the placebo group, the independent effect of caffeine was lost. As suggested in a comment by JOBE [58] after the publishing of these results, caffeine is extremely useful in minimising apnoea of prematurity with associated improved lung and motor function at 11 years of age. Nevertheless, it is not a lung drug *per se*, as it minimises interventions for respiratory control abnormalities in the very preterm infant that result in lung injury persisting into childhood.

Overall, studies have demonstrated that caffeine is effective in reducing BPD rates, especially when administered in the first 3 days of life (see later). A follow-up of the CAP trial has shown a positive

long-term effect of caffeine on lung function. However, further trials are needed in order to draw more conclusions on the long-term benefits of caffeine in terms of respiratory outcomes, and to target the appropriate population for early treatment.

Caffeine timing: early *versus* late

Benefits of early caffeine administration

A *post hoc* subgroup analysis of results from the CAP trial suggested an influence of postnatal age at onset of caffeine treatment on BPD reduction, with a decrease in the rate of BPD by 52% in those with early treatment (1–3 days of life) in contrast with a reduction of only 23% if started after day 3 [34]. Since the publication of the results of the CAP trial caffeine has been administered closer and closer to birth, sometimes even in the delivery room [12]. The 2019 European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants and the recently published National Institute for Health and Care Excellence recommendations on preterm infants emphasise the role of the timing of caffeine initiation, suggesting that earlier treatment is associated with increased benefit [59, 60]. Nonetheless, no formal guidance specifying the exact timing of therapy commencement has been provided so far.

A retrospective cohort study on 140 infants (birthweight <1250 g) by PATEL *et al.* [61] in 2013 demonstrated that early caffeine initiation (<3 days of life) was associated with a reduced rate of death or BPD, decreased requirement of PDA treatment and shorter duration of mechanical ventilation compared to later caffeine initiation (⩾3 days of life). Infants with birthweight <750 g, considered to be at the highest risk for BPD or death, showed the strongest association between early caffeine initiation and decreased incidence of this combined outcome. These results were confirmed by two retrospective studies conducted in 2014. The first study included 29 070 VLBW infants [32], half of whom received early caffeine treatment and were matched on baseline demographics to infants in the late caffeine group. Infants in the early caffeine group had a reduced rate of the composite outcome of death or BPD, less PDA requiring treatment and fewer days of mechanical ventilation. Although infants born at <24 GW treated with early caffeine showed increased odds of death, this result was attributed to survival bias (need to survive to receive later caffeine), as many very preterm infants die in the first 48 h [32]. The second study by LODHA *et al.* [57] from the Canadian Neonatal Network also showed decreased odds of death or BPD in the group treated with early caffeine (<2 days of life), with most of this effect stemming from the reduction of BPD. In addition, they found a reduced incidence of PDA and duration of mechanical ventilations. Importantly, follow-up of 2108 infants in this study at 18–24 months corrected age demonstrated lower odds of neurodevelopmental impairment in the early caffeine group [62].

Three prospective studies have also suggested benefits of early caffeine administration. A small pilot double-blinded, randomised, placebo-controlled trial conducted in 2015 on 21 infants (<29 GW) randomised to early prophylactic use of caffeine (<2 h of age) or to later caffeine initiation (at 12 h of age), reported improved blood pressure and systemic blood flow (significantly higher superior vena cava flow and right ventricular output) in the early group, and a trend towards reduced rates of intubation by 12 h of age (27% *versus* 70%; p=0.08), but no reduction in the number of days of mechanical ventilation [40]. More recently, a prospective cohort study on 986 infants (⩽32 GW) with respiratory distress syndrome demonstrated that early caffeine treatment (<24 h after birth) compared to later treatment (⩾2 days) was associated with a significantly reduced need for invasive ventilation, total duration of mechanical ventilations and significantly lower odds of intraventricular haemorrhage (IVH) and PDA, but no difference in the incidence of BPD and mortality rates [63]. Finally, in a small cohort randomised study, DEKKER *et al.* [12] demonstrated benefits of caffeine administered in the delivery room on minute volumes and tidal volumes at 7–9 min after birth compared to caffeine given after arrival in the neonatal intensive care unit.

Three systematic reviews and meta-analyses have summarised the results of all the studies published so far comparing early *versus* late caffeine administration. The first, conducted by PARK *et al.* [64] in 2015 included VLBW infants (birthweight <1500 g) treated with early use of caffeine (0–2 days of life) *versus* late use (⩾3 days of life). This meta-analysis of five studies [32, 34, 61, 65, 66] concluded that early caffeine use was associated with a decreased incidence of death, BPD and the composite measure of the two, while the duration of mechanical ventilation was not significantly reduced. The second review and meta-analysis by KUA and LEE [67], published in 2017, selected 14 studies in which early caffeine (<3 days of life) was compared with late caffeine, placebo or theophylline. The meta-analysis of the five cohort studies [34, 57, 61, 65, 68] comparing early *versus* late caffeine showed reduced rates of BPD, PDA, PDA requiring surgical intervention, brain injury and duration of mechanical ventilation in the early caffeine group, but an increased rate of death, which was not confirmed by the pooled analysis of two randomised control trials [34, 69]. A more recent systematic review and meta-analysis by PAKVASA *et al.* [70] has explored the effect of both timing of caffeine initiation and dose of caffeine therapy on clinical outcomes

(primary: BPD as defined by each specific study or by the need for oxygen at 36 weeks PMA; secondary: death, BPD or death, PDA, necrotising enterocolitis, retinopathy of prematurity, duration of mechanical ventilation and neurodevelopmental impairment). The analysis of the five included observational studies [32, 57, 61, 66, 71] demonstrated a decreased risk of BPD with earlier initiation of caffeine (<3 days of life), while only one RCT comparing early *versus* routine use of caffeine was identified, and therefore meta-analysis could not be performed [34].

The clinical benefits of beginning caffeine treatment before 3 days of age has been summarised recently by DOBSON and HUNT [72], showing the reduced incidence of BPD (with moderate quality of evidence according to the Grading of Recommendations Assessment, Development and Evaluation system), death or BPD, IVH, necrotising enterocolitis, need for treatment of PDA, retinopathy of prematurity and use of postnatal steroids (all of which with low quality of evidence) with the early treatment.

Contrasting results on early caffeine administration

A retrospective analysis conducted by PATEL *et al.* [73] on VLBW infants (birthweight <1500 g) receiving initial CPAP (on day of life 0) compared the effect of early caffeine (day of life 0) *versus* routine caffeine (day of life 1–6). The results demonstrated no difference in CPAP failure defined as invasive mechanical ventilation or surfactant therapy on day of life 1–6 (22% *versus* 21%, adjusted odds ratio (aOR) 1.05), in exposure to a maximal inspiratory oxygen fraction >0.3 in the first week of life (27% *versus* 32%, aOR 1.05) and in the total duration of CPAP therapy (median 3 *versus* 2 days, aOR 1.02). The authors hypothesised that mechanisms influencing CPAP failure might be different from those influencing the risk of BPD or duration of respiratory support.

In a recent single-centre double-blinded placebo-controlled trial [74], preterm infants (23–30 GW) requiring mechanical ventilations in the first five postnatal days were randomised to receive an early caffeine loading dose of 20 mg·kg^{-1} followed by 5 mg·kg^{-1} per day or placebo until considered ready for extubation (the control group then received a pre-extubation bolus of caffeine, whereas the intervention group received a pre-extubation bolus of placebo). Caffeine treatment did not reduce age of first successful extubation (>24 h) nor total duration of mechanical ventilation, incidence of BPD, severe BPD or the composites of BPD or death. Furthermore, a nonsignificant trend towards higher mortality in the early caffeine group led to a cautious decision to stop the trial (22% *versus* 12%; p=0.22). However, one-third of the deaths in the caffeine group occurred after the first successful extubation, when both groups were receiving caffeine. Furthermore, a recent external analysis of the study [75] highlights that, given the early termination of the trial, the differences in prognostic variables for mortality between groups (gender, Apgar score at 5 min and birthweight) and the imprecision in the estimates of the treatment effect of early caffeine on mortality, no confident conclusions can be determined regarding the effect of early caffeine on mortality.

Currently there are two main ongoing trials exploring the use of early caffeine initiation (data sourced from ClinicalTrials.gov database (https://clinicaltrials.gov)). The first is a double-blind, randomised, placebo-controlled trial evaluating the need for endotracheal intubation within the first 12 h of life and the cardiac output in neonates born at <32 GW receiving caffeine either within 2 h after birth or at 12 h after birth (clinicaltrials.gov identifier NCT0308647). The second is a randomised, double-blind controlled trial of extremely low birthweight newborns (birthweight ⩽1000 g and <28 GW) aiming to evaluate the cumulative incidence of death and BPD between groups receiving caffeine (20 mg·kg^{-1} *i.v.* bolus, then *i.v.* or by mouth 5 mg·kg^{-1} daily for 14 days), or placebo (dextrose) within 24 h of life and then for the subsequent 14 days (clinicaltrials.gov identifier NCT02524249). The results of these trials will be able to shed further light on the best timing for caffeine administration in order to potentially reduce these short- and long-term outcomes.

Table 1 summarises the studies conducted to date in this area. Overall, caffeine administered within the first 3 days of life seems to provide a reduction in BPD rates, PDA and IVH, but does not reduce the risk of CPAP and extubation failure. In addition, there are still contrasting results of the effect of early caffeine initiation on duration of mechanical ventilation and death. There is an urgent need for RCTs addressing this issue, as most results stem from retrospective studies or trials with small sample sizes.

Caffeine dosage: high *versus* low/standard dose

Similar to timing of caffeine treatment initiation, there is still uncertainty regarding the optimal dose of caffeine in preterm infants. In 1977 ARANDA *et al.* [76] administered 20 mg·kg^{-1} *i.v.* caffeine citrate to 18 preterm infants followed by 5 or 10 mg·kg^{-1} once or twice daily, demonstrating a reduction in mean frequency of apnoeic spells from 13.6 to 2.1 per day (p<0.01). Subsequent studies investigating the relationship of dose and plasma concentrations of caffeine indicated a rapid rise in minute ventilation followed by a plateau in the ventilatory response with increasing doses of the drug [77]. These

TABLE 1 Summary of retrospective studies, *post hoc* analyses, randomised controlled trials (RCTs) and systematic reviews and meta-analyses comparing early *versus* late caffeine treatment in preterm infants

First author, year [ref.]	Study characteristics, regimen, limitations	Patient characteristics		Main significant findings	
		Early caffeine	Late caffeine	Benefits of early caffeine	Drawbacks or no effect of early caffeine
Davis, 2010 [34]	*Post hoc* subgroup analysis of the CAP trial Caffeine citrate 20 mg·kg^{-1} load ⩽3 DoL *versus* >3 DoL *Post hoc* analysis for treatment indication, not as primary outcome			Larger reduction in days of respiratory support (p=0.02) Lower PMA at time of discontinuing PPV (mean difference 1.35 weeks (0.90–1.81) *versus* 0.55 weeks (−0.11–0.99))	
Abbasi, 2010 (abstract) [65]	Retrospective cohort study Early caffeine (0–2 DoL) *versus* late caffeine (⩾3 DoL) Retrospective, many data not available; Newcastle–Ottawa score for risk of bias 4	166 case/control pairs, BW 500–1250 g		Reduced odds of IVH (OR 0.37)	
Patel, 2013 [61]	Retrospective cohort study Caffeine initial dose <3 DoL *versus* ⩾3 DoL Retrospective, single-centre; indication for caffeine therapy unknown; no protocol on caffeine use	83 neonates BW 940 (730–1100) g GA 27.3 (25.6–28.7) weeks	57 neonates BW 910 (715–1035) g GA 26.6 (25.3–27.7) weeks	Decreased incidence of death or BPD (25.3% *versus* 52.6%) by a reduced rate of BPD (23.6% *versus* 50.9%) Reduced need for treatment of PDA (10.4% *versus* 36.4%) Lower duration of MV (6 *versus* 22 days)	
Saeidi, 2014 (abstract) [69]	RCT Caffeine citrate 20 mg·kg^{-1} load within first 3 DoL *versus* ⩾3 DoL Single-centre; small sample size; many data not available	16 neonates BW 1123±244 g GA 29.5±2.0 weeks (BW and GA for all 36 included infants)	20 neonates	Marginal reduction in BPD and significant reduction in apnoea	
Dobson, 2014 [32]	Retrospective analysis Caffeine initial dose <3 DoL *versus* ⩾3 DoL Retrospective; variable indications for early caffeine use among centres (hypothetically: apnoea, prophylactically, weaning from MV and reduction in BPD); possible changes in clinical practice during the study period	14 535 neonates BW 1055 (630–1447) g GA 28.1 (25.0–31.0) weeks	14 535 neonates BW 1054 (590–1460) g GA 28 (24.0–32.0) weeks	Reduced risk of BPD by 7.6% (23.1% *versus* 30.7%); Reduction in MV days at 36 weeks PMA (median 11 *versus* 17 days) Reduction in PDA requiring treatment (12.3% *versus* 19%)	Higher odds of death (OR 1.23, 95% CI 1.05–1.43; 4.5% *versus* 3.7%)

TABLE 1 Continued

First author, year [ref.]	Study characteristics, regimen, limitations	Patient characteristics		Main significant findings	
		Early caffeine	Late caffeine	Benefits of early caffeine	Drawbacks or no effect of early caffeine
LODHA, 2015 [57]	Retrospective cohort study (Canadian Neonatal Network) Caffeine initial dose <3 DoL versus ⩾3 DoL Retrospective; variations and inconsistency in the protocol for early caffeine use at various centres and unknown indications for caffeine use; potential variations in maintenance dose of caffeine	3806 neonates BW 1070 (850–1310) g GA 28 (26–29) weeks	1295 neonates BW 1050 (790–1360) g GA 28 (26–30) weeks	Reduction in BPD or death (aOR 0.81), stemming on BPD (aOR 0.79) Reduced incidence of PDA (40.5% versus 46.2%) and of surgical treatment for PDA (13.3% versus 25%) Reduced duration of MV, HFV and CPAP on day 2; reduction in the use of postnatal steroids	No difference in mortality (aOR 0.98) No difference in NEC ⩾stage 2, ROP ⩾stage 3, severe neurological injury (presence of parenchymal echolucency, periventricular echogenicity or PVL)
TAHA, 2014 [66]	Retrospective data analysis (Alere Neonatal Database) Caffeine initial dose <3 DoL (0–2) versus ⩾3 DoL (3–10) Retrospective; unknown indications for use of early caffeine	1986 neonates BW 938±201 g GA 27.5±2.0 weeks	965 neonates BW 899±216 g GA 27.2±2.1 weeks	Reduced incidence of BPD (36.1% versus 46.7%, OR 0.69) and rate of BPD or death (45.5% versus 54.9%, OR 0.77) Lower age at first extubation (7.1 versus 10.8 days), decreased duration of MV (16.7 versus 23.7 days) and PMA to room air (34.7 versus 35.6 days) Lower odds of severe IVH and PDA	Higher odds of NEC (OR 1.41)
DEKKER, 2017 [12]	Unblinded RCT Caffeine in the delivery room versus caffeine in the NICU Small sample size; no placebo-controlled group	13 neonates BW 870 (767–1198) g GA 27 (26–28) weeks	10 neonates BW 960 (731–1450) g GA 28.5 (27–29) weeks	Increased minute volumes (189±74 versus 162±70 mL·kg^{-1}·min^{-1}) and tidal volumes (5.2, IQR 3.9–6.4 mL·kg^{-1}) versus 4.4, IQR 3.0–5.6 mL·kg^{-1}) at 7–9 min after birth	No differences in short-term clinical outcomes (intubation rates, surfactant administration) and IVH
KATHERIA, 2015 [40]	Pilot RCT Caffeine citrate 20 mg·kg^{-1} load within the first 2 h of life versus at 12 h of life Small sample size underpowered to achieve differences in the outcome of reducing intubation	11 neonates BW 1007±169 g GA 27±0.9 weeks	10 neonates BW 1005±239 g GA 27±0.9 weeks	Reduced incidence of intubation in the first 12 h (27% versus 70%, p=0.08) Reduced vasopressor requirement in the first 24 h (0% versus 20%, p=0.21) Higher SVC flow (101±25 mL·kg^{-1}·min^{-1} versus 77±24 mL·kg^{-1}·min^{-1}) and RVO (273±62 mL·kg^{-1}·min^{-1} versus 219±43 mL·kg^{-1}·min^{-1})	Similar duration of oxygen treatment, MV, IVH, PDA requiring treatment
PARK, 2015 [64]	Systematic review and meta-analysis Early caffeine (0–2 DoL) versus late caffeine (⩾3 DoL) Only one RCT included; one retrospective study in the meta-analysis; no analysis on the effect of caffeine on apnoea as the studies did not report it as an outcome	30 974 neonates for primary outcomes	23 873 neonates for primary outcomes	Reduced mortality (3.8% versus 4.2%, OR 0.90), incidence of BPD (20% versus 34.6%, OR 0.5) and rate of BPD or death (23.7% versus 37.9%, OR 0.52) Reduced risk of IVH, PVL, ROP requiring photocoagulation, PDA requiring treatment	Risk of NEC and NEC requiring surgery not associated with the early use of caffeine (OR 0.97 and 1.06, respectively)

Continued

First author, year [ref.]	Study characteristics, regimen, limitations	Patient characteristics		Main significant findings	
		Early caffeine	Late caffeine	Benefits of early caffeine	Drawbacks or no effect of early caffeine
KUA, 2017 [67]	Systematic review and meta-analysis Early caffeine (initiated <3 DoL) in preterm infants No information on the indications for early *versus* late caffeine treatment from the studies; most of the RCTs had small sample size			Meta-analysis of cohort studies and RCTs: - Reduction of BPD 20–33% - 29% reduction in the incidence of PDA (cohort studies) - 59% decrease in the need for surgical closure of PDA (cohort studies) - Shorter duration of MV (WMD −7.5 days)	Increase in absolute risk of mortality with early caffeine therapy (4.7% *versus* 3.9%). No difference in rates of NEC, need for surfactant, home oxygen
BORSZEWSKA-KORNACKA, 2017 [63]	Prospective cohort study Early (initial dose on DoL 1) and late (initial dose on DoL ⩾2) caffeine therapy Possible differences in local practices between centres; no randomisation	143 neonates BW 1130 (895–1450) g GA 29 (27–30) weeks	143 neonates BW 1100 (850–1485) g GA 29 (27–30) weeks	Significant lower incidence of PDA (25% *versus* 37%, OR 0.56) Reduced incidence of IVH (42.1% *versus* 60.1%, OR 0.48) Reduced duration of MV (IQR 0–4 *versus* IQR 1–15.9)	No statistically significant difference in the incidence of BPD (36.4% *versus* 45.8%, p=0.31) and mortality rates (8.6% *versus* 8.5%, nonsignificant)
PATEL, 2017 [73]	Multicentre, observational cohort study Early caffeine (initiation on DoL 0) *versus* late caffeine (initiation on DoL 1–6) No adjustment for factors possibly associated with doctor's decision to start caffeine; highly selected infants excluding those with need of surfactant or lower Apgar score	4528 neonates BW <1500 g GA 29 (28–30) weeks	6605 neonates BW <1500 g GA 30 (29–31) weeks		Similar incidence of CPAP failure (22% *versus* 21%, OR 1.05) No difference in exposure to a max F_{iO_2} >0.3 (27% *versus* 32%, OR 1.05) No difference in duration of CPAP therapy (3 *versus* 2 days, OR 1.02)

CAP: Caffeine for Apnoea of Prematurity; DoL: day of life; PMA: post-menstrual age; PPV: positive pressure ventilation; BW: birthweight; IVH: intraventricular haemorrhage; GA: gestational age; BPD: bronchopulmonary dysplasia; PDA: patent ductus arteriosus; MV: mechanical ventilation; aOR: adjusted odds ratio; HFV: high-frequency ventilation; CPAP: continuous positive airway pressure; NEC: necrotising enterocolitis; ROP: retinopathy of prematurity; PVL: periventricular leukomalacia; NICU: neonatal intensive care unit; IQR: interquartile range; SVC: superior vena cava; RVO: right ventricular output; WMD: weighted mean difference; F_{iO_2}: fraction of inhaled oxygen.

TABLE 1   Continued

observations, coupled with the unusual pharmacokinetic profile of caffeine, described later, led to the standard dose regimen that is widely used today: an *i.v.* loading dose of 20 mg·kg^{-1} of caffeine citrate (10 mg·kg^{-1} of caffeine base) followed by a maintenance dose of 5–10 mg·kg^{-1} per day started 24 h after the loading dose. This regimen was the one adopted in the CAP trial and recommended by the US Food and Drug Administration to treat apnoea of prematurity [78, 79].

In 1992 an RCT was published comparing two different regimens of caffeine with theophylline in a group of preterm infants (gestational age <31 GW), showing a loading dose of 50 mg·kg^{-1} caffeine citrate to be more effective in reducing apnoeic episodes within 8 h after administration than a loading dose of 25 mg·kg^{-1}, with no particular side-effects [80]. In 2003, a randomised double-blind clinical trial of three dosing regimens of caffeine citrate for periextubation management of ventilated preterm infants (<32 GW) demonstrated that the higher daily maintenance doses (of 15 and 30 mg·kg^{-1} per day) significantly reduced documented apnoea, but with no statistically significant difference in the incidence of extubation failure [81]. However, in a subsequent multicentre double-blind RCT the same authors found that a dose of 20 mg·kg^{-1} given 24 h before a planned extubation or within 6 h of an unplanned extubation in infants <30 GW reduced the rate of extubation failure within 48 h compared to a low maintenance dose of 5 mg·kg^{-1}, with no effect on infant mortality and major neonatal morbidities in the first year of life. Furthermore, a significant reduction in duration of mechanical ventilations was shown in infants <28 GW receiving the high dose regimen [82]. Confirming these results, an RCT demonstrated that the use of high loading and maintenance doses of caffeine citrate (loading/maintenance doses of 40/20 *versus* 20/10 mg·kg^{-1}) was associated with a significant decrease in extubation failure in preterm infants <32 GW and a decreased frequency of apnoea, with no differences in the incidence of major disabilities, but with more episodes of tachycardia [83].

Three systematic reviews and meta-analyses have summarised the results of RCTs assessing the efficacy and safety of higher dosage regimens of caffeine in preterm infants. A review by VLIEGENTHART *et al.* [84] identified six RCTs (620 patients, <32 GW) with considerable variation in loading and maintenance doses, as well as duration of therapy between allocation arms. The meta-analysis of data showed a potential benefit of a higher caffeine dosing regimen on the combined outcome of death or BPD and on BPD alone at 36 weeks PMA when therapy was given for >14 days. Meta-analysis for apnoea frequency could not be performed due to variation in definitions. One study reported an increased risk of cerebellar haemorrhage (CBH) with higher doses of caffeine [85]. However, this study was powered only to detect differences in the primary outcome of microstructural brain development at term-equivalent age, and long-term neurodevelopment is a better outcome compared to single cerebellar lesions or other short-term neurological effects. In addition, a recent retrospective study of 218 preterm infants <28 GW divided into two groups to receive either a median loading dose of the drug of 80 mg·kg^{-1} or of 20 mg·kg^{-1} within the first 36 h of age, has shown no difference in the incidence of neonatal morbidities, including CBH, between the two groups (2.5% *versus* 1.7%) [86]. A second review and meta-analysis published by BRATTSTRÖM *et al.* [87] comparing a high *versus* low dose of caffeine [88, 90–] identified six RCTs (total of 816 infants, <32 GW), with loading and maintenance doses varying between 20 and 80 mg·kg^{-1} per day and 3–20 mg·kg^{-1} per day, respectively, and diverse times of starting treatment. The use of high dose had no impact on mortality, but showed a reduction of BPD [91] with a risk ratio of 0.76 (0.60–0.96), very similar to Vliegenthart's calculation [92]. Furthermore, it resulted in fewer cases of extubation failure and apnoea and a shorter duration of mechanical ventilations, despite higher rates of tachycardia.

The last systematic review and meta-analysis by PAKVASA *et al.* [70] included three RCTs comparing high-dose caffeine with the standard dose [82, 83, 85], showing a decreased risk of BPD in the first group. In addition, the meta-analysis of three studies demonstrated an increased efficacy of high-dose caffeine in reducing AOP [81–83].

One additional review and meta-analysis published in 2018 [92] has evaluated efficacy and safety of different maintenance doses of caffeine citrate to treat AOP. The review included 13 RCTs, of which five were written in English. It concluded that the high-dose group (maintenance doses of 10–20 mg·kg^{-1}) exhibited greater effective treatment rate (defined as successful extubation within 72 h after treatment onset, fewer than three apnoea episodes per day, and no significant abnormalities in respiratory rhythm), success rate for ventilator removal, lower extubation failure rate, frequency of apnoea, apnoea duration and rate of BPD.

The evidence so far (summarised in table 2) suggests that higher doses of caffeine treatment may be more effective in reducing apnoea rates and extubation failure, as well as BPD at 36 weeks PMA. However, future RCTs of high *versus* low/standard dose of caffeine with larger sample sizes are needed to ameliorate allocation concealment and outcome reporting. Importantly, lack of data on long-term outcomes and safety limits the use of caffeine regimens other than those used in the CAP trial in standard neonatal care.

TABLE 2 Summary of retrospective studies, *post hoc* analyses, randomised controlled trials (RCTs) and systematic reviews and meta-analyses comparing high *versus* low/standard doses of caffeine citrate in preterm infants

First author, year [ref.]	Study characteristics Patient characteristics Limitations	Regimen		Main significant findings	
		High caffeine dose	Standard/low caffeine dose	Benefits of high caffeine dose	Drawbacks or no effects of high caffeine dose
ROMAGNOLI, 1992 [88]	Single-centre RCT 37 total neonates, 14 (controls) *versus* 13 *versus* 10 neonates, born <32 GW Single centre; small sample size; unclear risk of most biases with incomplete outcome data	Group I: LD 10 mg·kg^{-1}; MD 5 mg·kg^{-1}	Group II: LD 10 mg·kg^{-1}; MD 2.5 mg·kg^{-1}	Decrease in the number of apnoeic spells in both treated groups compared with a control group (p<0.01)	Significantly lower frequency of side-effects such as tachycardia (p<0.001) and gastrointestinal intolerance in the low-dose group (nonsignificant)
SCANLON, 1992 [80]	Single-centre RCT 44 total neonates, 14 *versus* 16 neonates (14 infants treated with theophylline), born <31 GW, with frequent apnoeic attacks (⩾10 in 8 h or 4 in 1 h) Single centre; small sample size; unclear risk of most biases with incomplete outcome data	LD 50 mg·kg^{-1}; MD 12 mg·kg^{-1}	LD 25 mg·kg^{-1}; MD 6 mg·kg^{-1}	Number of apnoea events·day^{-1} reduced by 1/3 within 24 h by standard dose treatment *versus* a reduction by >50% by the higher dose treatment within the same time period	
STEER, 2003 [81]	Single-centre RCT 45 *versus* 40 *versus* 42 neonates <32 GW ventilated for >48 h Single centre; small sample size	High dose: LD 60 mg·kg^{-1}; MD 30 mg·kg^{-1} Moderate dose: LD 30 mg·kg^{-1}; MD 15 mg·kg^{-1}	LD 6 mg·kg^{-1}; MD 3 mg·kg^{-1}	Reduction in documented apnoea episodes (p<0.02); Trend to decrease in failure of extubation in the two highest dose groups (24% *versus* 25% *versus* 45%, p=0.06)	
STEER, 2004 [82]	Multicentre RCT Total of 234 neonates, 113 *versus* 121 neonates, born <30 GW ventilated for >48 h; Data on long-term neurodevelopment to be considered with caution due to 18% loss at follow-up and not being the primary outcome	MD 20 mg·kg^{-1} before a planned extubation or 6 h within an unplanned extubation	MD 5 mg·kg^{-1} before a planned extubation or 6 h within an unplanned extubation	Reduced rate of extubation failure (15.0% *versus* 29.8%, RR 0.51; NNT 7) Reduction in documented apnoea episodes (4 (1–12) *versus* 7 (2–22), p<0.01) Significant difference in duration of MV in infants <28 GW (mean 14.4 days *versus* 22.1 days, p=0.01)	No difference in mortality, major morbidities, severe disability
GRAY, 2011 [89]	Multicentre RCT Total of 287 neonates, 120 *versus* 126 neonates, born <30 GW Some incomplete outcome data (*e.g.* age at starting treatment)	LD 80 mg·kg^{-1}; MD 20 mg·kg^{-1}	LD 20 mg·kg^{-1}; MD 5 mg·kg^{-1}	Significantly greater mean general quotient in the high-dose group (98.0±13.8 *versus* 93.6±16.5, p=0.048) Nonsignificant trend for benefit in the high-dose caffeine group for death or major disability (15.4% *versus* 24.2%; RR 0.75, 95% CI 0.49–1.14)	No difference in temperament and behaviour

TABLE 2 Continued

First author, year [ref.]	Study characteristics Patient characteristics Limitations	Regimen		Main significant findings	
		High caffeine dose	Standard/low caffeine dose	Benefits of high caffeine dose	Drawbacks or no effects of high caffeine dose
MOHAMMED, 2015 [83]	Single-centre RCT 60 versus 60 neonates, born <32 GW Single centre; small sample size	LD 40 mg·kg^{-1}; MD 20 mg·kg^{-1}	LD 20 mg·kg^{-1}; MD 10 mg·kg^{-1}	Reduction in extubation failure (p<0.05) Reduction in frequency of apnoea (p<0.001)	Significant increase in episodes of tachycardia (p<0.05) No difference in the incidence of BPD No difference in the incidence of ROP, IVH, PVL or LOS
MCPHERSON, 2015 [85]	Single-centre RCT Total of 74 neonates, 37 versus 37 neonates, born ⩽30 GW Pilot study with small sample size only powered to detect differences in the primary outcome of microstructural brain development at term-equivalent age	LD 80 mg·kg^{-1} over a 36-h period (40–20–10); MD 10 mg·kg^{-1}	LD 30 mg·kg^{-1} over a 36-h period (20–10); MD 10 mg·kg^{-1}		Increased incidence of cerebellar haemorrhage in the high-dose group (36% versus 10%, p=0.03), more deviant neurological signs (p=0.04) at term-equivalent age No differences in diffusion measures at term-equivalent age and developmental outcomes at 2 years
ZHAO, 2016 [90]	Single-centre RCT 164 total infants, 82 versus 82 neonates, born <32 GW Single-centre; possible selection, detection and reporting biases	LD 20 mg·kg^{-1}; MD 15 mg·kg^{-1}	LD 20 mg·kg^{-1}; MD 5 mg·kg^{-1}	Reduction in the frequency of apnoea (10 versus 18, p=0.009) Higher success rate of ventilator removal (85% versus 70%, p=0.015)	No significant difference in death during hospitalisation, CLD and duration of hospital stay No significant difference in tachycardia, irritability, difficulty in feeding, hyperglycaemia, hypertension, digestive disorders and electrolyte disturbances
VLIEGENTHART, 2018 [84]	Systematic review and meta-analysis including 6 RCTs with a total of 620 preterm infants; GA ⩽32 GW Overall quality of the outcome measures (GRADE) considered low to very low due to imprecision and inconstancy of the effect estimates; small sample sizes of the included studies	LD 10–80 mg·kg^{-1}; MD 5–30 mg·kg^{-1}	LD 6–30 mg·kg^{-1}; MD 2.5–20 mg·kg^{-1}	In the subgroup analysis for therapy duration >14 days, significant reduction in the combined outcome of mortality or BPD at 36 weeks PMA (3 studies, 428 patients) (TRR 0.76, 95% CI 0.59–0.98) and in BPD rates alone (TRR 0.72, 95% CI 0.54–0.97) Reduction in extubation failure (TRR 0.51, 95% CI 0.37–0.70)	No difference in mortality at discharge or at 12 months Increased risk of tachycardia in the HD group (RR 3.39, 95% CI 1.50–7.64) No difference in NEC, SIP, ROP, IVH, hyperglycaemia. Considerations: no meta-analysis on differences in apnoea frequency due to diverse definition of the outcome No meta-analysis on duration of respiratory support due to data reported in IQR Inadequate power to detect small but clinical relevant differences Considerable differences in administered caffeine doses between studies

TABLE 2 Continued

First author, year [ref.]	Study characteristics Patient characteristics Limitations	Regimen		Main significant findings	
		High caffeine dose	**Standard/low caffeine dose**	**Benefits of high caffeine dose**	**Drawbacks or no effects of high caffeine dose**
BRATTSTRÖM, 2019 [87]	Systematic review and meta-analysis including 6 RCTs with a total of 816 preterm infants (GA ⩽32 GW); LD 20–80 mg·kg^{-1}; MD 3–20 mg·kg^{-1} Low quality of evidence mainly due to imprecision of the estimates, few events, small sample sizes and the wide confidence intervals of the meta-analysis	LD >20 mg·kg^{-1}; MD >10 mg·kg^{-1}	Doses lower than the high-caffeine group	Reduction in BPD at 36 weeks PMA (RR 0.76, 95% CI 0.60–0.96) Fewer cases of extubation failure (as defined by study authors, RR 0.51, 95% CI 0.36–0.71) and apnoeas (mean difference −5.68, −6.15— 5.22), and shorter duration of MV (mean difference −1.69, −2.13— 1.25) in the HD group	No difference in mortality (RR 0.85, 95% CI 0.53–1.38) No difference in IVH ⩾3 (RR 1.41, 95% CI 0.71–2.79)
CHEN, 2018 [92]	Systematic review and meta-analysis including 13 RCTs with 1515 infants, GA <32 GW Variable maintenance doses within the high- and low-dose range; only few trials assessing outcomes such as extubation failure, frequency of apnoea, apnoea duration; most studies in Chinese with low quality	Variable LD MD 10–20 mg·kg^{-1}	Variable LD MD 5–10 mg·kg^{-1}	Higher efficacy rate in the HD group (RR 1.37, 95% CI 1.18–1.45) Higher success rate of ventilator removal (3 studies, RR 1.74, 95% CI 1.04–2.90) Lower extubation failure rate in the HD group (3 studies, RR 0.5, 95% CI 0.35–0.71) Lower frequency of apnoea and shorter apnoea duration in the HD group (MD −1.55, 95% CI −2.72−−0.39 and MD −4.85, 95% CI −8.29−−1.40) Lower incidence of BPD in the HD group (RR 0.79, 95% CI 0.68–0.91)	Higher incidence of tachycardia in the HD group (RR 2.02, 95% CI 1.30–3.12)

GW: gestational weeks; LD: loading dose; MD: maintenance dose; RR: risk ratio; NNT: number needed to treat; MV: mechanical ventilation; BPD: bronchopulmonary dysplasia; ROP: retinopathy of prematurity; IVH: intraventricular haemorrhage; PVL: periventricular leukomalacia; LOS: late-onset sepsis; CLD: chronic lung disease; GRADE: Grading of Recommendations Assessment, Development and Evaluation; PMA: post-menstrual age; TRR: typical risk ratio; HD: high dose; NEC: necrotising enterocolitis; SIP: spontaneous intestinal perforation; IQR: interquartile range; GA: gestational age.

Caffeine pharmacokinetics

Caffeine metabolism and pharmacokinetics

Most of the studies investigating the metabolism of caffeine in premature newborns were conducted between the 1970s and the 1990s by ARANDA and co-workers [93, 94]. Using high-performance liquid chromatography (HPLC), these authors were able to show a strict correlation between administered dose of drug and plasma level [77], as well as between plasma and cerebrospinal fluid levels [95]. The route of caffeine administration does not affect its pharmacokinetics, as there is almost complete bioavailability after its oral or *i.v.* administration. Oral caffeine citrate is rapidly and completely absorbed by the gastrointestinal tract, as there is almost no first-pass metabolism, with the peak plasma concentration often reached in <1 h [96].

Caffeine metabolism occurs in the liver, mainly by CYP1A2, with a subsequent N-demethylation at positions 1, 3 and 7 and hydroxylation at position 8. In preterm neonates, ~86% of caffeine citrate is excreted unchanged in the urine [97], as the processes of caffeine metabolism maturates progressively through time (N7-demethylation at the post-natal age of ~4 months [98], acetylation by N-acetyltransferase (NAT2) completely developed by 1 year of postnatal age [99] and 8-hydroxylation activity starting as early as 1 month of age [100]). Thus, the maturity of the hepatic enzymes, dependent mainly by the postnatal age regardless of birthweight and gestational age, affects the plasma half-life of the drug [98, 101].

Due to this difference in metabolism, and to the slow urinary excretion of unmetabolised drug at the earlier gestational ages, the serum half-life of caffeine in infants ranges from 40 to 230 h (>17-fold greater than that in adults), decreasing with the advance of PMA to ~2–4 h by 6–8 months [102]. Of note, because of the long half-life, caffeine may persist in an infant's plasma for some days after cessation of therapy [102, 103].

Elimination of caffeine occurs mainly by renal excretion in the first weeks of life, which is slower in premature and term neonates compared with older children and adults, because of immaturity of renal functions [96]. Clearance of caffeine in neonates is influenced by gestational age, postconceptional age, parenteral nutrition and comorbidities [96, 99, 100, 103, 104], with values ranging from 0.08 to 0.13 mL·kg^{-1}·min^{-1} compared to that of adults and older children of 1.5 and 4.4 mL·kg^{-1}·min^{-1}, respectively [100, 105].

These data highlight that extremely premature infants do not behave as "little adults" with respect to caffeine pharmacokinetics, as caffeine metabolism and urinary elimination are strongly determined by the maturity of liver enzymes and renal function, which are influenced by gestational and postnatal age and by the presence of morbidities affecting these organs.

Therapeutic drug monitoring

Caffeine dosing and therapeutic drug monitoring (TDM) vary from practice to practice. Caffeine has a wider therapeutic range than theophylline, therefore the role of TDM for the control of therapeutic ranges of caffeine has often been challenged [106]. A therapeutic level of caffeine is considered between 5 and 25 mg·L^{-1} (or μg·mL^{-1}), while toxic levels are reached with >40–50 mg·L^{-1} [107, 108]. An observational study by NATARAJAN *et al.* [109] in neonates born between 23 and 32 GW found that caffeine citrate doses of 2.5–10.9 mg·kg^{-1} (median 5 mg·kg^{-1}), obtained plasma levels ranging between 5.1 and 20 mg·L^{-1} in 94.8% of cases (within the normal therapeutic ranges), independent of gestation, thus indicating against the necessity of TDM. However, in the subgroup of infants in whom caffeine plasma concentrations were obtained for lack of clinical efficacy, three-quarters of the levels were within the normal range (15 mg·L^{-1}), which suggests that higher doses and plasma concentrations may be required for optimal efficacy in some preterm neonates. In addition, the numbers of infants with renal or hepatic dysfunction in the study were small at the time of caffeine level, and no data on relation to efficacy with regard to apnoea was reported. Importantly, another study demonstrated that a standardised regimen leads to a high variation of serum levels of caffeine metabolites in infants <33 GW, with no correlation between episodes of apnoea and caffeine serum concentrations in the post-extubation period [110]. Therefore, caffeine TDM may help dose individualisation in order to minimise the incidence of toxic adverse effects, optimise efficacy and the performance of diagnostic tests, especially for patients who are unresponsive to therapy (breakthrough apnoea, bradycardia or desaturations without other obvious disease-related aetiologies) [106, 111, 112]. In addition, a retrospective chart review of infants born ⩽29 GW demonstrated that those with an average caffeine concentration >14.5 μg·mL^{-1} had lower incidence of chronic lung disease and PDA, lesser number of days on ventilator and oxygen, less need for diuretics and lower length of stay and total hospital charges (all p<0.05) [113]. If these findings are confirmed prospectively, it could become useful to introduce TDM in routine practice.

Caffeine levels can be measured in plasma, saliva or urine by enzyme immunoassay technique, which is simple, convenient and rapid, or using HPLC, which is the most accurate technique for caffeine TDM in the clinical setting [114, 115]. In recent years, minimally invasive techniques have been proposed for the detection of caffeine levels, with promising results. In 2013, PATEL et al. [116] used dried blood spots (DBS) to measure caffeine dosage with liquid chromatography triple quadrupole mass spectrometry from 67 preterm infants at random time intervals following either oral or i.v. doses. The study showed a good agreement between pharmacokinetic parameters estimated using DBS samples and historical caffeine pharmacokinetic parameters based on plasma samples.

In 2016, BRUSCHETTINI et al. [117] confirmed the importance of limiting the size of blood samples to avoid anaemia due to blood sampling for TDM in preterm infants and highlighted the advantages of DBS over conventional sampling techniques. To overcome the problem of haematocrit, alternative strategies based on new microfluidic sampling procedures or volumetric microsampling devices have been described and proved to be a reliable sampling approach for caffeine [118, 119]; however, the drawback is the use of expensive devices for routine TDM analyses or for pharmacokinetic studies. To overcome the problem of blood sample size, invasiveness and cost, in 2017, CHAABANE et al. [120] determined caffeine concentrations in both saliva and serum of preterm infants (mean gestational age 32.2±0.7 weeks), showing a proportional increase in both saliva and serum caffeine concentration to the administered dose, with the saliva caffeine concentrations strongly correlating with those from serum.

Despite different studies exploring the best minimally invasive and cost-effective methods to monitor therapeutic ranges of caffeine in clinical practice, few have tried to develop a pharmacokinetic model to adjust caffeine dosage and none has investigated the relationship between caffeine biofluid levels in the first weeks of life and clinical outcomes, such as apnoea frequency [121, 122]. Interestingly, in 2017 KOCH et al. [122] developed simulation models of caffeine concentrations, proposing the need of adjusting the maintenance doses through time in preterm neonates, with the administration of 6 mg·kg^{-1}·day^{-1} in the second week of life, 7 mg·kg^{-1}·day^{-1} in weeks 3–4 and 8 mg·kg^{-1}·day^{-1} in weeks 5–8.

Further studies are needed to determine whether caffeine dosage can be optimised for the individual patient through TDM in particular situations. Drug levels could be performed minimising the drawn blood volume (for instance with DBS) or, even better, non-invasively (for example in urine or saliva samples). Prospective pharmacokinetic studies of caffeine with relation to both clinical outcomes (apnoea episodes, extubation failure, respiratory support at 36 weeks PMA, respiratory morbidity in the first year of life), and adverse events (tachycardia, hypoglycaemia, seizures, weight loss, neurodevelopment at 2 and 5 years) should be conducted in order to identify the appropriate dosage of the drug.

Conclusions

In preterm infants, caffeine is effective in reducing apnoea frequency, the need for IPPV and mechanical ventilation, as well as enhancing the success of extubation. In addition, caffeine-treated newborns have lower rates of BPD, IVH and PDA, with positive long-term outcomes on pulmonary function and neurodevelopment. Despite the longstanding use of caffeine in the neonatal intensive care units, controversies regarding the optimal timing and dosage of caffeine therapy still remain [123], as the majority of data on long-term outcomes and safety stem from one randomised placebo-controlled trial [33]. Furthermore, the role of therapeutic drug monitoring needs to be addressed. The paucity of data on caffeine metabolism related to clinical outcomes in extremely preterm neonates highlights the importance of further research in this field in order to better refine the respiratory management of these subjects.

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