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Use of Methylxanthine Therapies for the Treatment and Prevention of Apnea of Prematurity

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Abstract

Apnea of prematurity (AOP) is a common complication of preterm birth, which affects more than 80 % of neonates with a birth weight less than 1,000 g. Methylxanthine therapies, including caffeine and theophylline, are a mainstay in the treatment and prevention of AOP. Despite their frequent use, little is known about the long-term safety and efficacy of these medications. In this review, we systematically evaluated the literature on neonatal methylxanthine therapies and found that caffeine is associated with fewer adverse effects and a wider therapeutic window when compared with theophylline. When used as a therapeutic agent, larger doses of caffeine citrate have been shown to improve acute neonatal outcomes when administered promptly, although further studies are needed to assess the long-term neurological consequences associated with the use of large loading doses. In a secondary analysis of data obtained from a randomized controlled trial, the prophylactic use of caffeine was associated with substantial cost savings and improved clinical outcomes. However, there remains a paucity of well-controlled, randomized clinical trials that have examined the use of caffeine as a prophylactic agent, and further prospective trials are needed to determine if caffeine is a safe and effective prophylactic agent. Additionally, measuring plasma concentrations longitudinally as a marker of therapeutic efficacy and/or toxicity has not been shown to be clinically useful in neonates who are responsive to treatment and exhibit no signs or symptoms of toxicity. However, in cases where toxicity is of concern or for neonates with congenital or pathophysiologic process that may alter the pharmacokinetics of these drugs, therapeutic drug monitoring may be warranted to monitor for methylxanthine toxicity.

1 Introduction

Apnea in preterm neonates occurs as a result of immature respiratory control [1]. Episodes of apnea of prematurity (AOP) and its associated hypoxemia and bradycardia are characterized by a pause in breathing for greater than 15 s, accompanied with an oxygen saturation (SpO₂) less than 80 % for more than 4 s, and a heart rate less than 67 % from baseline for more than 4 s in neonates less than 37 weeks' gestation [2]. The incidence of apneic episodes corresponds inversely to the gestational age and birth weight of the neonate.

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Neonates born at 30–31 weeks' gestation experience AOP at a higher incidence rate than neonates born at 32–33 or 34–35 weeks' gestation (54 % vs. 15 % vs. 7 %) [2]. Additionally, there is an 84 % incidence rate of apnea occurring in neonates weighing less than 1 kg at birth, regardless of gestational age [3]. Thus, preterm neonates are at an increased risk of apnea than term neonates due to their low gestational age and low birth weight.

Although AOP is a time-limited developmental disorder that resolves with maturation, pharmaceutical interventions are frequently used to reduce the frequency of apneic events, decreasing hypoxemic and bradycardic events [4]. Methylxanthine therapies, such as caffeine citrate and theophylline, are the primary pharmaceutical agents used in the treatment and prevention of AOP [1]. Methylxanthines act as central nervous system stimulants and have been proven to increase respiratory drive, lower the threshold of sensitivity to hypercapnia, and increase the contractility of the diaphragm [5, 6]. Methylxanthines are frequently prescribed to prevent apneic episodes around the perixtubation period and to facilitate weaning off of mechanical ventilation [7].

Methylxanthine therapies act as non-specific adenosine receptor antagonists [8]. Caffeine and theophylline are both substrates for cytochrome P450 (CYP) 1A2, which accounts for more than 95 % of the primary metabolism of caffeine [9, 10]. Caffeine primarily undergoes hepatic *N*-demethylation to paraxanthine, theobromine, and theophylline [11]. Theophylline (1,3-dimethylxanthine) is closely related to caffeine; however, it undergoes *N*-demethylation to give rise to 1-methylxanthine, which is also a product of CYP1A2-mediated metabolism of caffeine via the intermediate metabolite paraxanthine [12, 13]. In neonates, this typical metabolic pathway may be disrupted by retrograde conversion of theophylline to caffeine, which occurs via methylation [14]. The standard dosing regimen of caffeine citrate includes an intravenous loading dose of 20 mg/kg followed by a maintenance dose of 5 mg/kg/day [15]. The standard theophylline regimen involves an oral loading dose of 5–6 mg/kg, followed by a maintenance dose of 1–3 mg/kg/12 h [16]. Although caffeine and theophylline feature similar molecular structures, caffeine and theophylline display slight variations in their clinical efficacy when used in the treatment and prevention of AOP.

Systematic meta-analyses have sought to evaluate the comparative safety and efficacy of caffeine versus theophylline for the prevention and treatment of AOP [17]. Evidence has shown that caffeine therapy may be preferred to theophylline for individuals at risk of AOP as caffeine has a wider therapeutic window and a longer serum half-life [17, 18]. This finding has been established in multiple independent studies and has led to the widespread adoption of caffeine as the first-line treatment for AOP [17, 19].

Therapeutic drug monitoring (TDM) is frequently conducted when administering methylxanthine agents, which provides a quantitative measurement that allows clinicians to adjust the quantity and duration of the methylxanthine dosing regimen to avoid sub- and supratherapeutic drug concentrations [20]. Currently, the utility of routine TDM is controversial, both in clinical practice and the literature [20].

The purpose of this article is to review the available literature on methylxanthine therapies for the treatment and prevention of AOP, and to examine the utility of TDM in achieving

optimal clinical outcomes among pre-term neonates. Published studies were identified through a query of MEDLINE, EBSCOhost, and PubMed using the key words 'caffeine' or 'caffeine citrate' or 'theophylline' and 'apnea' or 'premature' or 'neonate' or 'preterm'. Identified articles were then reviewed and evaluated for their contribution to the treatment of AOP. Only studies that enrolled and treated preterm neonates with caffeine or theophylline were included. No limits were applied on the basis of publication dates. All publications were manually reviewed by two authors (KS and CS) and duplicate publications were excluded from further review. All doses are expressed as caffeine citrate, which are double the dose of base caffeine.

2 Results

2.1 Clinical Efficacy

Caffeine and theophylline both act to reduce the number of apneic events in neonates with AOP [17]. Several small studies conducted in the 1980s and 1990s evaluated the comparative effectiveness of caffeine versus theophylline in terms of improving respiratory function (Table 1) [21–25]. In an aggregate meta-analysis of these five studies, Henderson-Smart and Steer examined outcomes from 108 enrolled infants and found no difference in the therapeutic effectiveness of caffeine versus theophylline [17]. However, adverse effects, including tachycardia and feeding intolerance, were less frequent in the caffeine-treated group [17]. More recently, in a prospective study, 53 preterm neonates were randomized to receive either theophylline or caffeine [26]. Within 24 h, neonates who received caffeine had significantly improved respiratory function and a decreased requirement for supplemental oxygen in comparison to those who received theophylline. However, after 7 days of treatment, there was no difference in respiratory effort between those neonates who received caffeine and those who received theophylline. Thus, caffeine resulted in an earlier onset of action in the improvement of neonatal respiratory function than theophylline, although both were effective in improving overall neonatal respiratory function.

Research has been conducted to investigate the efficacy of several caffeine maintenance dose regimens in neonates. In a randomized, double-blind clinical trial, the efficacy of caffeine citrate dosages in the periextubation period were examined in 120 enrolled neonates <28 weeks' gestation [15]. Two intravenous dosing regimens of caffeine citrate (5 or 20 mg/kg/day) were administered to neonates for periextubation management. Table 2 shows the treatment failure rate in neonates administered 5 mg/kg/day or 20 mg/kg/day maintenance-dose regimens. A significant reduction in the rate of extubation failure was achieved for the 20 mg/kg/day dosing group compared with the 5 mg/kg/day group (17 % vs. 49 %; 95 % CI 0.20–0.65). Additionally, a significant reduction in the mean duration of mechanical ventilation was noted in neonates receiving the higher dosage of caffeine compared with those in the lower dosage group ($p < 0.01$). Thus, neonates in the higher dosage group were less likely to fail extubation or require re-intubation or doxapram treatment in the subsequent 7 days following initial extubation than those in the lower dosage group. Although neonates administered the higher maintenance dose regimen experienced delayed weight gain, there was no difference in the overall amount of weight gained between the two

dosing groups. These data suggest that 20 mg/kg/day of caffeine citrate results in better clinical outcomes than a 5 mg/kg/day maintenance dose.

In addition to comparing dosing amounts, studies have also investigated the timing of the initiation of caffeine dosing and its impact upon reduced apneic events [27]. In one retrospective study, the effectiveness of early caffeine intervention was investigated by comparing the efficacy of caffeine therapy initiated in neonates less than 3 days old with that in neonates greater than 3 days of age [27]. Neonates who received early caffeine therapy ($n = 83$) were less likely to die or develop bronchopulmonary dysplasia when compared with neonates who received late caffeine therapy ($n = 75$) [adjusted odds ratio 0.26; 95 % CI 0.09–0.70; $p < 0.01$]. Moreover, a smaller proportion of neonates receiving early caffeine citrate therapy required patent ductus arteriosus (PDA) treatment (10 %) and the mean duration of mechanical ventilation was 6 days, whereas 36 % of neonates receiving late caffeine citrate therapy required PDA treatment and the mean duration of mechanical ventilation was 22 days ($p = 0.01$ for both). Similarly, Davis et al. conducted a post hoc subgroup analysis and found that early initiation of intravenous caffeine citrate resulted in larger reductions in the duration of respiratory support [28]. Therefore, prompt initiation of caffeine citrate therapy is recommended.

Further studies have been conducted to evaluate the prophylactic use of methylxanthine therapies for the prevention of AOP. Although both caffeine citrate and theophylline are effective treatments for AOP, results from a randomized controlled trial suggest that only caffeine has a prophylactic effect [29]. Therefore, caffeine may be preferred over theophylline for prophylaxis to prevent AOP in at-risk neonates. One trial randomized 50 preterm neonates to receive short-term caffeine prophylaxis versus placebo and reported no difference in the number of apneic, bradycardic or hypoxemic events [30], whereas a large clinical trial demonstrated that prophylactic caffeine improved survival without leading to developmental disability in infants assessed at 18–20 months corrected age when compared with the control group [15, 31, 32]. Additionally, there was a significant decrease in PDA treatment in the prophylactic caffeine group compared with the control group. However, it is unclear whether prophylactic caffeine use results in better clinical outcomes compared with the use of caffeine strictly as a therapeutic agent in the management of established apnea. In light of a recent post hoc analysis demonstrating a reduction in death and major morbidity among caffeine-treated mechanically-ventilated neonates [28], the likelihood of conducting a definitive study to address the comparative effectiveness of prophylactic versus therapeutic caffeine is diminishing.

In addition to improving clinical outcomes, caffeine therapy may result in substantial cost savings. The economic impact of caffeine therapy was evaluated by comparing direct medical costs of neonates receiving caffeine with that of neonates receiving placebo [33]. In this multicenter, international study of 1,869 neonates, it was reported that caffeine treatment improved outcomes and reduced costs when compared with placebo in >99 % of 1,000 bootstrap replications. Thus, caffeine therapy may be a cost-effective treatment for preterm neonates.

2.2 Safety

As methylxanthine therapies are powerful central nervous system stimulants, there are some concerns regarding their safety profile in the neonatal population. Caffeine citrate is generally well-tolerated, although tachycardia, tachypnea, glucose instability, jitteriness, restlessness, tremors, irritability, vomiting, and feeding intolerance have been infrequently reported [15, 34–36].

Several studies have investigated the short-term adverse effects of caffeine on the growth and development of the newborn child. In a randomized, double-blind clinical trial, the effects of caffeine maintenance dose regimens were assessed by administering a 5 or 20 mg/kg/day intravenous dose of caffeine citrate [15]. There were no significant differences in the overall rates of severe disability, morbidity, or death between the two groups (Table 3). A follow-up neurological assessment was conducted at 12 months' corrected age to assess long-term neurologic function. The results from this neurological assessment showed that there was a statistically significant reduction in major disability in the 20 mg/kg/day caffeine citrate maintenance dose group compared with the 5 mg/kg/day maintenance dose group ($p = 0.05$). Additionally, no significant differences in general quotients or death rates were observed between the two groups.

Another study evaluated the long-term clinical safety of caffeine therapy with regard to the cognitive development, temperament, and behavior of 287 neonates treated with intravenous caffeine citrate [37]. This multicenter, randomized, controlled trial compared 5 and 20 mg/kg/day maintenance-dose regimens and reported no statistical difference in adverse outcomes related to temperament and behavior at 1 and 2 years of age, respectively ($p = 0.075$) [37]. Additionally, the study found that the higher caffeine citrate maintenance regimen of 20 mg/kg/day may be beneficial for the cognitive development of the preterm neonate when assessed at 1 year of age. This study found that high-dose caffeine therapy does not adversely affect the development of preterm neonates. The results of the neurological assessment evaluating the effects of the two dosing regimens with regard to the adverse events of disability, morbidity and mortality at 1 year of age are seen in Table 3. A non-significant benefit for reduced deaths and major disability was shown to be associated with the use of 20 mg/kg/day rather than 5 mg/kg/day of caffeine citrate. Overall, these results show that an elevated dose of caffeine was not associated with undesirable clinical or neurological outcomes in this preterm neonatal population.

Nevertheless, caffeine therapy has the potential to result in adverse events when elevated loading doses are administered to neonates. A previous study has shown that a loading dose of 25 mg/kg of caffeine citrate reduced blood flow velocity in cerebral and intestinal arteries of preterm neonates by 20 % within 2 h [38], whereas a loading dose of 10 mg/kg of caffeine citrate administered via a nasogastric tube over 15–20 min did not alter cerebral hemodynamics in preterm neonates at 2 h post-administration [39]. The decrease in blood flow velocity in cerebral and intestinal arteries following a high caffeine loading dose has been attributed to vasoconstriction, which may increase the risk of periventricular leukomalacia, hemorrhage, and necrotizing enterocolitis [38]. Owing to concern over the risk of cerebral and intestinal ischemia, Hoecker et al. [40] investigated the use of a divided loading dose of two 25 mg/kg caffeine citrate doses separated by 4 h, and reported a

decrease in cerebral blood flow velocity following the second dose, although blood flow velocity in intestinal arteries and left ventricular output were unaffected. It is well appreciated that high loading doses are more effective in the treatment of neonatal apnea, although further research is needed to develop an optimal loading-dose regimen.

Compared with caffeine, theophylline therapy has been associated with increased adverse events in the neonatal population, including seizures and hypokalemia [41]. In randomized and quasi-randomized trials comparing the toxicities of caffeine and theophylline, theophylline therapy was associated with increased tachycardia and feeding intolerance in neonates [17]. Additionally, it was reported that theophylline exhibited unique toxicokinetics of sinus tachycardia and agitation in preterm neonates due to developmental differences between neonates and adults [42].

In addition to the toxic effects, methylxanthines can exert physiologic effects. Studies have shown that both theophylline and caffeine increase energy expenditure [43, 44]. This physiologic effect has the potential to increase oxygen demand and result in diminished growth and delayed weight gain in preterm neonates [45]. To combat this effect, some authors advocate for extra caloric supplementation among neonates treated with theophylline and caffeine at high doses [43, 44, 46]; however, larger randomized controlled trials have generally found no long-term difference in weight gain among neonates who did and did not receive caffeine [31, 32].

2.3 Methylxanthine Pharmacology

It is widely known that drug dosing cannot be naively extrapolated based on the size of the child compared with that of the adult dose. This is due to the unique physiological changes that accompany the growing and developing child [47]. However, few studies have evaluated the pharmacokinetics and pharmacodynamics of caffeine administered to preterm neonates for the treatment and prevention of AOP.

Neonates exhibit unique metabolic and elimination profiles in comparison to adults due to the developmental differences in their physiology. Theophylline has been reported to feature a serum half-life ranging from 24.7 to 36.5 h, and estimated clearance from 0.02 to 0.05 L/kg/h in premature neonates, compared with healthy adults, who have an estimated elimination half-life of 6.3 h [11]. In contrast to the relatively short half-life of theophylline, caffeine exhibits a longer serum half-life of 101 h in neonates [18], whereas its half-life ranges from 3 to 6 h in adults [11]. Thus, caffeine therapy has proven to be more efficacious in the treatment of AOP than theophylline, not only due to caffeine's reduced toxicity but also because caffeine can be conveniently dosed once daily.

Due to the extensive hepatic metabolism and renal elimination of methylxanthine agents, studies have been conducted to assess the need for maturation-dependent dose modifications in the neonatal population. It has been shown that there is a strong relationship between age and the demethylating activity of CYP1A2 [47, 48]. Demethylation activity is detected in infants older than 4 months of age, which increases until adult values are reached at 6 months of age [48]. Renal clearance of caffeine differs between preterm and full-term neonates, with a glomerular filtration rate (GFR) of 0.6–0.8 mL/min/1.73 m² in preterm

neonates and 2–4 mL/min/1.73 m² in full-term neonates [47]. The GFR increases rapidly during the first 2 weeks of life and then rises steadily until 8–12 months of age, when adult values are reached [49, 50]. As caffeine and theophylline are metabolized and eliminated by developing organ systems in the neonate, a lower effective dose may be required in preterm neonates compared with that required for full-term neonates, children, and adults [47].

In clinical practice, neonatal apnea improves with increased postmenstrual age, such that the evolving condition is often treated with caffeine until respiratory function improves and the incidence of clinically significant apneic events has decreased. AOP typically resolves around 34–36 weeks postmenstrual age; however, in more immature infants apnea may persist until 43–44 weeks of age [51, 52]. For these infants, the persistence of cardiorespiratory depression may delay hospital discharge or require home cardiorespiratory monitoring [53, 54].

Further pharmacokinetic studies have been conducted to assess how various doses of caffeine affect its metabolism and elimination in neonates. A previous parallel-group study assessed the pharmacokinetics of caffeine citrate after intravenous administration to neonates with AOP [55]. The study evaluated the administration of 3, 15, and 30 mg/kg/day maintenance doses of caffeine citrate maintenance over 7 days. The mean clearances for the low, medium, and high caffeine dosages were calculated to be 0.0044, 0.0043, and 0.0047 L/kg/h, respectively. The mean clearance of 0.0049 L/h/kg was smaller among neonates when compared with that of adults, and the volume of distribution was found to be 0.97 L/kg among neonates, which was larger than that of adults. The study showed that clearance increased with increasing weight and postnatal age, which were attributed to renal maturation. Additionally, the analysis showed no difference between a one-compartment pharmacokinetic model and a two-compartment model in fitting the data. These results suggest that the metabolism and clearance of caffeine among neonates is governed primarily by the acquisition of hepatic and renal function, which may be estimated using gestational age.

Although studies have addressed the developmental aspects of the pharmacokinetics of methylxanthines, the pharmacodynamics of these drugs in the developing neonate has not been well established. It has been proposed that the pharmacodynamics of drug metabolism is an age-dependent process with regard to the number of receptors present and their affinity for the target xenobiotic [56]. Caffeine and theophylline exert effects on multiple organ systems by antagonizing adenosine A2A and A1A receptors that are present in the brain, blood vessels, kidneys, heart, gastrointestinal tract, and respiratory system. The stimulatory effects of these drugs on the respiratory system may be attributed to blockade of A2A receptors, resulting in inhibition of GABAergic neurons of inhibitory pathways. However, these pharmacodynamic effects are strongly age-dependent and warrant consideration when evaluating the clinical response to therapy among preterm neonates [56].

Drug–drug interactions have been reported for both caffeine and theophylline [11, 57]. Concomitant administration of drugs that are known to induce CYP1A2, and drugs that depress or stimulate the central nervous system, should be avoided [11]. Additionally, concomitant administration of ciprofloxacin may increase serum concentrations of caffeine,

which has the potential to result in methylxanthine toxicity [58]. Furthermore, maturation of neonatal hepatic metabolism and renal excretion with increasing age also has the potential to exacerbate drug-disease interactions [56]. Methylxanthines are dependent upon both hepatic metabolism and renal elimination, such that other pathophysiologic conditions that alter these processes may influence the safety and effectiveness of caffeine and theophylline [59, 60].

2.4 Therapeutic Drug Monitoring

Although caffeine is preferred over theophylline as the first-line pharmaceutical treatment for AOP, the clinical utility of routine TDM remains controversial [17, 26]. By measuring caffeine plasma concentrations regularly, TDM can help clinicians ensure that drug concentrations stay within the therapeutic range, potentially avoiding supra-therapeutic toxicity and subtherapeutic treatment failure. However, caffeine TDM has not been shown to be useful when administering standard doses of caffeine to neonates [20]. An observational study of 101 preterm neonates reported that caffeine citrate doses ranging from 2.5 to 10.9 mg/kg resulted in plasma concentrations that ranged from 3.0 to 23.8 mg/L among preterm neonates. It was shown that 94.8 % of concentrations fell within the therapeutic range of 5.1–20.0 mg/L, regardless of gestational age. Thus, TDM is not required in preterm neonates since the majority of doses result in concentrations within the normal reference range.

Other studies have assessed the utility of caffeine TDM following varying loading doses in neonates [61]. In a prospective study, 154 preterm neonates (mean gestation of 29 weeks) were administered a 20 or 25 mg/kg caffeine citrate loading dose followed by 6 mg/kg/day maintenance doses [61]. Additionally, it was reported that by 14 days of life, the serum concentrations were no longer dependent upon gestational age, weight, or postnatal age. The results of this study lend further evidence supporting the claim that routine monitoring of steady-state serum caffeine concentrations in preterm neonates is of limited utility.

Additionally, caffeine toxicity is not commonly associated with the administration of standard doses of caffeine [29]. A randomized controlled trial evaluated the utility of caffeine TDM in 70 neonates [29]. It was found that the majority of cases fell within the recommended therapeutic range (5.5–23.7 mg/L), obviating the need for TDM. Furthermore, none of the patients in the study experienced toxicity when administered standard dosing regimens. It was also reported that apneic events were not significantly associated with supratherapeutic concentrations. The authors concluded that TDM is not likely to be necessary when administering standard doses of caffeine; however, for cases in which toxicity is suspected or there is an absence of an appropriate clinical response, TDM may be warranted.

In contrast, some studies have shown that TDM may benefit preterm neonates, as caffeine pharmacokinetics and pharmacodynamics are maturation-dependent. It has been suggested that continuous monitoring of preterm neonates with apnea should be mandatory as TDM has the potential to aid in defining the pathophysiology and type of apnea, and can be used to monitor the efficacy and tolerability of caffeine for each neonate in real-time [41]. Additionally, it has been suggested that continuous monitoring could aid in weaning neonates off therapy. In one review, the authors reported that TDM may be used to define

clinical success in the treatment and prevention of AOP. TDM could prevent this vulnerable population from exposure to toxic levels of caffeine as a result of hepatic and renal underdevelopment. TDM may also be clinically beneficial in neonates who do not respond to therapy or for neonates who have additional clinical conditions that may alter their response to therapy, including hepatic or renal impairment. Some clinicians find TDM to be beneficial in monitoring the course of caffeine therapy; however, TDM is widely believed to be unnecessary when administering standard doses and a clinical response is observed. If TDM is initiated, serum or plasma specimens are typically obtained from the neonate via a heel puncture [62]. Immunoassays are widely available in clinical chemistry laboratories and are expected to be precise if the analytical coefficient of variation does not exceed 10 % [63].

3 Discussion

Caffeine and theophylline therapies are effective pharmacological interventions in treating and potentially preventing AOP. Caffeine features a more rapid onset of action, reduced toxicity, and longer half-life when compared with theophylline [11, 17, 26, 42]. However, as an orphan drug, caffeine may not be universally available and theophylline may be a reasonable alternative in the treatment of AOP [64].

In this review, strong evidence from multiple randomized trials supports the use of caffeine for the treatment of AOP. When caffeine citrate is used as a therapeutic agent, early initiation of therapy is associated with improved clinical outcomes, which include a dramatic reduction in the number of apneic events [27]. Large maintenance doses of 20 mg/kg/day have been shown to be more effective in treating AOP without a concomitant increase in short-term adverse effects [15]; however, additional research is needed to evaluate the long-term clinical impact associated with large maintenance doses [10, 15]. Although a few studies have begun to evaluate the long-term effects of these doses at 1, 2, and 5 years of age, further research is needed to determine if long-term neurological outcomes depend upon the loading- and maintenance-dose administration [10]. Administration of large loading and maintenance doses should be accompanied by supplemental calories to compensate for the increased energy expenditure from the increased oxygen demand, ensuring that growth and development proceed at an age-appropriate rate [43, 44, 46].

The use of caffeine as a prophylactic agent has been briefly studied and appears to reduce adverse events in preterm neonates at risk of AOP [29, 65]. Limited data from a small number of preterm neonates revealed that prophylactic treatment may reduce recurrent AOP; however, these studies were not powered to permit important subgroup analyses [29, 65]. Therefore, larger studies, with long-term follow-up, are needed to address the use of caffeine as a prophylactic agent.

Methylxanthines undergo extensive hepatic metabolism and renal elimination, demanding an age-appropriate dosing regimen to account for developmental changes that occur during the neonatal period [47, 48]. Due to individual characteristics in hepatic metabolism and renal elimination, further research is necessary to determine an age-dependent therapeutic dose of caffeine for administration with the first few days of life [47, 56, 61]. By altering the dosing

regimen to be age and developmentally appropriate with consideration of the pharmacokinetics of each drug, optimal therapy will be delivered and toxicities will be avoided. Nevertheless, further studies are needed to evaluate neonatal methylxanthine pharmacodynamics, for which little data currently exist.

Although there has been controversy surrounding the use of routine TDM for neonatal caffeine dosing, TDM aids in maintaining serum concentrations within the therapeutic window [41]. TDM of neonates could be used to construct a comprehensive model of the pharmacokinetics of caffeine therapy in this vulnerable population. With this strategy, improved dosing regimens based on demographic information, individual physiological characteristics, and disease states could be developed. The literature does not support routine TDM when administering standard doses of caffeine, as the majority of neonates are expected to have plasma concentrations within the normal therapeutic window [20, 29, 61]. However, TDM may be warranted when toxicities are suspected or when neonates fail to respond to therapy [20, 29, 61].

4 Conclusion

AOP is a common problem affecting preterm and low birth weight neonates. This review addressed the use of caffeine citrate and theophylline for the treatment and prevention of AOP. Caffeine is the preferred first-line pharmaceutical therapy as it is associated with fewer adverse events and has a wider therapeutic window than theophylline. Prompt initiation of caffeine therapy and larger doses may lead to better clinical outcomes for those at risk of AOP. Further research is needed to assess the potential for long-term adverse neurological effects that may occur as a consequence of elevated caffeine citrate maintenance doses and prophylactic administration. TDM does not appear to provide additional benefit when administering standard doses of caffeine citrate. However, TDM may be warranted for neonates who fail to respond to therapy or are suspected of exhibiting methylxanthine toxicity. Further research is needed to evaluate the effectiveness of caffeine citrate as a prophylactic agent and to assess the long-term neurological consequences of larger doses when caffeine citrate is used as a therapeutic agent.

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Table 1

Comparative effectiveness of caffeine citrate and theophylline in the acute treatment of apnea of prematurity

Reference	Parameter	Caffeine	Theophylline	Mean difference (95 % CI)
Brouard et al. [22]	Number of participants	8	8	
	Mean ($\pm$ SD) apnea rate per 100 min	0.13 ($\pm$ 0.26)	0.12 ($\pm$ 0.11)	0.01 (−0.19 to 0.21)
Bairam et al. [21]	Number of participants	10	10	
	Mean ($\pm$ SD) apnea rate per 100 min	0.66 ($\pm$ 0.46)	0.37 ($\pm$ 0.32)	0.29 (−0.06 to 0.64)
Fuglsang et al. [23]	Number of participants	9	9	
	Mean ($\pm$ SD) apnea rate per 100 min	0.12 ($\pm$ 0.22)	0.08 ($\pm$ 0.17)	0.04 (−0.14 to 0.22)
Kumar et al. [25]	Number of participants	11	13	
	Mean ($\pm$ SD) apnea rate per 100 min	0.29 ($\pm$ 0.39)	0.20 ($\pm$ 0.54)	0.09 (−0.28 to 0.46)
Scanlon et al. [24]	Number of participants	16	14	
	Mean ($\pm$ SD) apnea rate per 100 min	0.72 ($\pm$ 0.10)	0.26 ($\pm$ 0.60)	0.46 (0.14–0.78)
Cumulative		54	54	0.11 (0.14–0.78)

Outcome measure: mean apnea rate per 100 min for the first 3 days of therapy

Adapted from Henderson-Smart and Steer [17], with permission. © 2013 Cochrane Collaboration

Table 2

Caffeine citrate dosing regimens associated with extubation failure in neonates <28 weeks' gestational age

Characteristic	20 mg/kg (n = 63)	5 mg/kg (n = 57)	Risk ratio (95 % CI)	p-Value
Extubation failure ^a	11 (17 %)	28 (49 %)	0.36 (0.20–0.65)	
Median duration of mechanical ventilation (days)	14.4	22.1		<0.01
Median number of documented apneic episodes (interquartile range) ^b	4 (0–92)	7 (0–56)		<0.01

Adverse effects associated with a maintenance dose of 5 or 20 mg/kg

^aExtubation failure was defined as one or more of the following: not extubated within 48 h of initiating caffeine therapy, reintubation, or doxapram within 7 days of caffeine loading

^bDocumented apnea reflects the number of apneic episodes recorded by the nursing staff within 7 days of initiating caffeine therapy Data taken from Steer et al. [15]

Table 3

Outcomes at 1 year of age following adjustment for prematurity

Reference	Parameter	20 mg/kg	5 mg/kg	Risk ratio (95 % CI)	p-Value
Gray et al. [37]	Number of participants	116	120		
	Death	7 (6.0)	10 (8.3)	0.73 (0.29–1.95)	0.62
	GQ ^a	98.0 (13.8)	93.6 (16.5)	–	0.048
	Major disability ^b	9 (9.3)	15 (16.1)	0.73 (0.43–1.25)	0.28
	Death or disability	16 (15.4)	25 (24.2)	0.75 (0.49–1.14) ^c	0.16
Steer et al. [15]	Number of participants	87	86		
	Death	7 (8.0)	8 (9.3)	0.86 (0.33–2.28)	0.78
	GQ ^a	96.6 (13.2)	92.2 (17.3)	–	0.08
	Major disability	6 (6.9)	14 (16.3)	0.42 (0.17–1.05)	0.05
	Death or disability	13 (14.9)	22 (25.6)	0.58 (0.32–1.08)	0.08

Clinical outcomes, including disability, morbidity, and mortality associated with two caffeine citrate dosing regimens at 1 year of age from two studies [10, 23]. Both studies evaluated patients enrolled in The Caffeine Collaborative Study, although their analyses differed with respect to the populations that were analysed. The Steer et al. report evaluated only children who received caffeine before they were extubated, in an intent-to-treat analysis. The Gray et al. report also included children who were randomized to receive high versus low dose caffeine after they had been extubated. This study also excluded a number of neonates ($n = 37$) who did not receive >7 days of caffeine therapy owing to a shortage of the study drug. Data presented as n (%) unless otherwise stated

GQ general quotient

^aMean ($\pm$ SD)^bMajor disability was defined as one or more of the following: cerebral palsy, bilateral blindness, need for a hearing aid, or a GQ <76 %^cDeath risk ratio was calculated from data presented by Steer et al. [15]

Adapted from Steer et al. [15], with permission from the BMJ Publishing Group Ltd, and from Gray et al. [37], with permission from John Wiley and Sons [© 2011 Paediatrics and Child Health Division (Royal Australasian College of Physicians)]