MedicalExpress

Clinical Pharmacology of Caffeine Citrate in Preterm Infants

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ABSTRACT

BACKGROUND: Apnea of prematurity consists in 15 to 20 sec. of breathing cessation and is the most important disorder in the control of breathing in preterm infants. It is treated with caffeine citrate.

OBJECTIVES: The objectives of this article are to review: (1) the mechanisms of action, (2) the effects, (3) the metabolism, (4) the pharmacokinetics, and (5) the adverse effects of caffeine citrate in preterms.

METHODS: The bibliographic search was performed using PubMed and EMBASE databases as search engines and April 2014 was the cutoff point.

RESULTS: Caffeine citrate is a stimulant of the respiratory and central nervous systems. It binds competitively to the receptors for adenosine A1 and A2$_A$, causing inhibition. Caffeine increases respiratory rate and minute volume, stimulates respiratory centers, and increases pulmonary blood flow and the sensitivity of central medullary areas to hypercapnia. Orally administered caffeine citrate is rapidly and completely absorbed. It is N-demethylated by CYP1A2 and is N-acetylated by N-acetyltransferase. The half-life of caffeine citrate is 100 hours at birth and 5 hours at a gestational age >29 weeks. There is a remarkable shortening of the half-life during neonatal maturation. Adverse effects of caffeine are usually mild, and include restlessness, vomiting, and functional cardiac symptoms.

CONCLUSIONS: Caffeine citrate is the drug of choice for the treatment of apnea of prematurity. It is an easy drug to use. Administered orally or intravenously once a day, it does not require monitoring of serum concentrations and has few side effects.

KEYWORDS: caffeine citrate; metabolism; neonate; pharmacodynamics; pharmacokinetics.

■ INTRODUCTION

Apnea is the most important disorder in the control of breathing in the neonate.[1] Apnea of prematurity is defined as the cessation of breathing for over 15–20 sec and may be accompanied by oxygen desaturation (i.e. <80%) and/or bradycardia (i.e. <80 beats per min) or cyanosis in neonates with a gestational age under 37 weeks.[2]

The frequency of apnea has an inverse correlation to gestational age; it occurs in 7% of neonates with a gestational age from 34 to 35 weeks, 15% of neonates with a gestational age from 32 to 33 weeks, 54% of neonates with a gestational age from 30 to 31 weeks, and in nearly 100% of neonates with a gestational age under 29 weeks or weighing less than 1,000 g.[3] Apnea of prematurity may be classified as one of three types: central apnea (10 to 15% of cases) is a complete cessation of breathing; obstructive apnea (10 to 25% of cases) refers to an absence of nasal airflow in spite of respiratory efforts; and mixed apnea (50 to 75% of cases), the most common type, observed in premature infants, refers to a central respiratory pause that either precedes or follows airway obstruction.[4–6]

Pharmacological therapy to stimulate breathing consists of the methylxanthines. Caffeine citrate is more effective than theophylline or aminophylline in stimulating the central nervous and respiratory systems; it also penetrates the cerebrospinal fluid more readily than theophylline or aminophylline.[5–6] Caffeine citrate is the first choice drug to treat apnea.

The efficacy of caffeine citrate in the treatment of apnea of prematurity has been demonstrated in several studies.[5–9] Caffeine citrate decreases the number of apneic spells, PCO$_2$ tension, hydrogen ion concentration as well as the need for and the duration of mechanical ventilation in premature infants.

Schoen et al.[10] reviewed the use of caffeine citrate and of theophylline in premature infants. They found that the

therapy with caffeine is associated with fewer adverse effects and a wider therapeutic window when compared with theophylline. A recent multinational clinical trial in preterm infants demonstrated pulmonary and neurodevelopmental benefit from caffeine therapy.[10] Indications for caffeine use were predominantly for treatment of apnea and facilitation of extubation rather than prophylaxis.[11] These authors observed that prophylactic use of methylxanthine therapy for apnea of prematurity can possibly be attributed to the beneficial effects of caffeine therapy.

Caffeine citrate has a longer half-life, is associated with fewer adverse events, has easier administration than theophylline or aminophylline[12] and, finally, has a wider therapeutic value than theophylline and aminophylline.[13]

Information on the effects of caffeine citrate, and on the fate of this drug in preterm infants has been published in different journals during the last thirty years, but it is scattered. The objectives of this article are (1) to gather together and (2) to review the published data on (a) the mechanisms of action, (b) the effects, (c) the metabolism, (d) the pharmacokinetics, and (e) the adverse effects of caffeine citrate in preterm infants. (f) The comparison of the efficacy of caffeine citrate, theophylline, and aminophylline in treating the apnea of prematurity is also reviewed. The main objective of this work is to provide neonatologists with a tool that embraces all aspects of the clinical pharmacology of caffeine citrate in preterm infants.

■ BIBLIOGRAPHIC SEARCH

The bibliographic search was performed electronically using PubMed and EMBASE databases as search engines; April 2014 was the cutoff point. The following key words "caffeine citrate neonate", "caffeine citrate therapy for apnea of prematurity", "caffeine citrate therapy", "caffeine citrate pharmacokinetics neonate", "caffeine citrate metabolism neonate", and "caffeine citrate adverse effects neonate" were used. In addition, the books NEOFAX: a Manual Used in the Neonatal Care by Young and Mangum[13] and the Neonatal Formulary[14] were consulted.

■ RESULTS

Dosage of caffeine citrate in preterms infants

There is 1 mg of caffeine base in 2 mg of caffeine citrate.[14] Young and Mangum suggest giving a loading dose of a 20 to 25 mg/kg caffeine citrate intravenously or orally.[13] For maintenance, the recommended dose is 5 to 10 mg/kg of caffeine citrate every 24 hours. The maintenance dose should be started 24 hours after the loading dose. Later apnea occurs in few infants at a postmenstrual age of more than 52 weeks. On occasion, it may be necessary to give a maintenance dose of 5 mg/kg of caffeine citrate four times a day.[14]

Mechanism of action of caffeine citrate in preterm infants

The mechanism most likely to mediate most of the pharmacological effects of caffeine citrate is antagonism to the actions of adenosine at A1 and A2$_A$ receptors in the central nervous system.[15−20] These two receptors have different properties. Caffeine citrate binds to adenosine A1 and A2$_A$ receptors with inhibition constant (Ki) values of 44 and 44 μmol/l, respectively.[17−22]

Activation of the A1 receptor can produce sedation, antinociception, anticonvulsant effects, bradycardia, vasoconstriction, bronchoconstriction, antidiuresis and decreased glomerular filtration, as well as an increase in insulin sensitivity; it is associated with inhibition of adenylate cyclase, inhibition of transmitter release, potassium channel activation and changes in phosphoinositide turnover.[15−17] Activation of the A2$_A$ receptors stimulates adenylate cyclase and causes vasodilatation, bronchodilation, central respiratory depression and peripheral respiratory stimulant, platelet inhibition, decreased locomotor activity and immunodepression.[15−20]

Genetic basis of apnea of prematurity

Recent data raise the possibility that apnea of prematurity is genetically linked.[21] Kumral et al. investigated the role of A1 and A2$_A$ polymorphism in the development of apnea of prematurity and the individual differences in caffeine response. Polymorphisms in the A1 and A2$_A$ adenosine receptor genes account for variability in the subject's response to caffeine. They also observed that the adenosine receptor genes are responsible for the interindividual caffeine response variability in apnea of prematurity. Single-nucleotide polymorphism on the A2$_A$ is associated with a greater risk of apnea of prematurity.[21] These authors assessed the variability of the response to caffeine treatment in relation to polymorphisms in the A1 and A2a receptor genes, and assessed the role of these polymorphisms in predicting vulnerability to apnea. They also determined whether the polymorphisms in A1 and A2$_A$ have any effect on bronchopulmonary dysplasia development.[21]

Recent evidence, relating to the use of caffeine citrate for apnea of prematurity suggests that it decreases the likelihood of bronchopulmonary disease development.[22] Caffeine's limiting action on bronchopulmonary disease development is apparent in the subgroup that was administered caffeine within the first 3 days after birth.[23] Several factors including gestational age, genetic variations in the hepatic enzyme system involved in caffeine metabolism and genetic variations in caffeine receptors may contribute to variability in caffeine response. Although the reason for the interindividual caffeine response variability is unclear, there is evidence that some of the variability in the acute response to caffeine may have a genetic basis.

Effects of caffeine citrate in preterm infants

Table 1 summarizes the properties and the effects of caffeine citrate for the treatment of apnea of prematurity in neonates. It increases the mean respiratory rate, stimulates respiratory centers, increases pulmonary blood flow and increases the sensitivity of central medullary areas to hypercapnia.[15] The drug has a direct effect on the myocardium, increasing ventricular output, stroke volume and mean blood pressure in neonates.[15]

Caffeine citrate is a central stimulant agent: it inhibits adenosine receptors, affects release, turnover, and levels of several other transmitters, including biogenic amines (dopamine, noradrenalin, serotonin), acetylcholine, and excitatory and inhibitory amino acids.[24,25] The increased lung volume associated with an increased pulmonary compliance and decreased pulmonary vascular resistance by caffeine citrate may result in increased oxygenation.[26]

Preterm infants treated with an oral loading dose of 10 mg/kg of caffeine citrate, followed by a maintenance dose

Table 1 - Summary of the properties and effects of caffeine citrate for the treatment of apnea of prematurity in neonates.

Mechanisms of action	Increase central inspiratory drive
	Increase minute ventilation
	Increase respiratory rate
Route of administration	Intravenously or orally
Onset of toxicity	Plasma levels $>50\,\mu g/ml$
Therapeutic range	5 to 25 µg/ml*
Half-life at birth	100 hours
Loading dose	20 to 25 mg/kg*
Daily maintenance dose	5 to 10 mg/kg*
Time to steady-state	14 days
Effects of caffeine citrate	Increases mean respiratory rate, stimulates respiratory centers, increases pulmonary blood flow, increases the sensitivity of central medullary areas to hypercapnia, increases ventricular output, stroke volume, mean blood pressure, increases glomerular flow rate, urinary flow rate, and creatinine clearance.
Adverse-effects	Tremors, opisthotonous, tonic-clonic seizures, vomiting, hyperglycaemia, hypokalemia, and jaundice. Infrequent adverse events are tachycardia, constipation, and gastro-oesophageal reflux.
Monitoring of plasma concentrations	Infrequently

*Data reproduced from Young and Mangum.[13] The loading dose is given intravenously over 30 min or it isgiven it by mouth. The daily maintenance dose should be started 24 hours after the loading dose.

of 5 mg/kg once daily, exhibited a significant improvement in the compliance of the respiratory system ($p < 0.01$), a related reduction in the strength of the Hering Breuer reflex ($p < 0.05$), and a lower inspired oxygen requirement ($p < 0.01$) in 20 premature infants from baseline to day 7[t]of the study.[27]

Clinical stimulation of preterm infant breathing with methylxanthines can evoke seizures.[28] Inspiratory-related pre-Botzinger complex interneuronal plus spinal (cervical/phrenic) was studied in cranial hypoglossal or motoneuronal bursting in newborn rats. Non-respiratory bursting perturbed inspiratory cervical nerve activity was observed at concentrations $>0.25\,mM$ theophylline or caffeine.

Aranda et al.[18] administered 20 mg/kg caffeine citrate intravenously to 18 preterm infants followed by 5 or 10 mg/kg once or twice daily. Mean frequency of apneic spells decreased from 13.6 ± 2.5 to 2.1 ± 0.6 ($p < 0.01$) per day, after initiation of caffeine treatment.

Saliba et al.[29,30] observed that a dose of 20 mg/kg caffeine citrate did not affect cerebral blood flow velocity of premature infants. Caffeine citrate was administered intravenously to 31 infants at the dosages of 5, 10 or 20 mg/kg.[31] Cardiac index increased in all infants by $14.6 \pm 16.3\%$ ($P < 0.001$). Stroke volume increased in 24 of 31 subjects, by $7.8 \pm 12.2\%$ ($p < 0.001$). Heart rate increased in 28 of 31 infants, by 7.7 ± 7.2 beats per min ($p < 0.001$) and blood pressure increased in 25 of 31 infants, by 4.1 ± 5.8 mm Hg ($p < 0.001$). These authors observed that caffeine increased left ventricular CO_2 tension in all of the 31 infants, by an average of approximately 15%.

Walther et al.[32] studied the effects of caffeine in 20 clinically stable preterm infants. Ten received a loading dose of 20 mg/kg caffeine citrate, followed by a maintenance dose of 5 mg/kg after 24 hours. The mean caffeine citrate plasma level was $9.44 \pm 2.82\,\mu g/ml$. Twenty clinically stable preterm infants were studied. Ten infants received a loading dose of 20 mg/kg caffeine citrate, followed by a maintenance dose of 5 mg/kg after 24 hours. The other ten infants were the controls. The mean caffeine plasma level was $9.44 \pm 2.82\,\mu g/ml$. Left ventricular output and stroke volume were significantly increased on days 1 to 7 of caffeine citrate therapy. This was accompanied by a higher mean arterial blood pressure on days 1 to 3. Linear regression analysis showed a significant relation between caffeine citrate levels and left ventricular output ($r = 0.56$, $p = 0.003$) and, to a lesser extent, between caffeine levels and stroke volume ($r = 0.39$; $p = 0.016$).

Metabolism of caffeine citrate in preterm infants

Oral caffeine citrate is rapidly and completely absorbed, and there is almost no first-pass metabolism. In neonates, approximately 86% of caffeine citrate is excreted unchanged in the urine, with the remainder metabolized via CYP1A2 enzyme system.[13] In infants, the serum half-life ($t_{1/2}$) ranged from 40 to 230 hours, decreasing with the advance of postmenstrual age until 60 weeks.[13]

Caffeine was used as a probe to study development of CYP1A2 in neonates. Model development involved the scale-up of in vitro metabolic parameters, and adjusting metabolic function for the ontological pattern of CYP1A2. Model runs were able to simulate the large difference in $t_{1/2}$ and Cl between neonates and adults.[33]

Caffeine is also acetylated by N-acetyltransferase (NAT2).[33] N-acetyltransferase activity is not completely developed before 1 year of age implying that acetylator status cannot be reliably determined before that age.[34] 8-Hydroxylation of caffeine is absent in newborn infants[33]. It develops as early as 1 month of age, and may be higher in infants than in adults.[35,36]

al-Alaiyan et al.[37] determined the influence of postnatal age, birthweight, gestational and postmenstrual ages on the maturation of caffeine metabolism in 80 premature infants. The caffeine base loading dose was 10 mg/kg, followed by a maintenance dose of 2 mg/kg every 24 hours. When the patients were stratified into four postnatal age groups, each older group showed a consistently higher level for caffeine N-3-demethylation, N-7-demethylation, and all N-demethylation pathways. In contrast, no significant differences were seen for N-1-demethylation rate.

Cattarossi et al.[38] correlated plasma and urinary levels of caffeine citrate in preterm infants (n = 56), treated with an oral loading dose of 10 mg/kg caffeine citrate, with a maintenance oral dose of 2 mg/kg. The infants were divided in 6 groups according to the gestational age. Plasma and urinary levels correlated ($p < 0.001$) at all examined gestational ages. Thus, urinary levels of caffeine might be a useful means to assess therapeutic ranges of caffeine citrate.

Romagnoli et al.[39] studied the effectiveness of caffeine citrate in preventing idiopathic apnea to 37 premature infants. After an intravenous loading dose of 10 mg/kg of caffeine citrate, two different oral maintenance regimens were adopted: 5 mg/kg or 2.5 mg/kg. A significant decrease

in the number of apneic spells occurred in both groups. It is significant that they report that in the "2.5 mg/kg" group, the frequency of side effects such as tachycardia and gastrointestinal intolerance was significantly lower than in the "5 mg/kg" group.

De Carolis et al.[40] administered 10 mg/kg of caffeine citrate intravenously to 5 premature infants on the 15th day of postnatal life. They also administered 10 mg/kg of caffeine citrate to 10 preterm infants on entry to the unit. A daily maintenance oral dose of 2.5 mg/kg was administered for 15 days. Ten min after a single intravenous dose of 10 mg/kg, the mean blood concentration of caffeine was $14.5 \pm 1.4 \mu g/ml$ and $14.4 \pm 1.6 \mu g/ml$ on the 15th day of postnatal life, suggesting that caffeine does not accumulate in blood.

Drug monitoring of caffeine citrate

Doses of caffeine citrate ranging from 2.5 to 10.9 mg/kg (median 5.0 mg/kg) were administered to 101 neonates whose median gestational age was 28 weeks.[41] Caffeine administration was initiated at a median of 6 days (range: 1 to 70 days), with the third day of life being the most frequent day of therapy initiation. The median caffeine plasma concentration was $10.7 \pm 4.0 \mu g/ml$ (range: 3 to 23.8 μg/ml). The overwhelming majority (95%) of preterm infants achieve plasma concentrations of caffeine between 5 and 20 μg/ml, independently of gestational age, following administration of standard doses of caffeine. Thus, therapeutic drug monitoring is unnecessary when caffeine is used for the treatment of apnea of prematurity in neonates.

Pharmacokinetics of caffeine citrate in preterm infants

The pharmacokinetic parameters of caffeine citrate are summarized in Table 2. At birth, the serum $t_{1/2}$ of caffeine citrate ranges from 40 to 230 hours, decreasing with the advancing of postmenstrual age until 60 weeks of postmenstrual age. Clearance of caffeine citrate occurs mostly via the kidneys.[13]

Le Guennec et al.[41] measured $t_{1/2}$ of caffeine citrate in 23 low birth weight infants with ages ranging from birth to >29 weeks of postnatal age. An oral loading dose of 20 mg/kg was followed by oral daily maintenance doses of 3 to 5 mg/kg. At postnatal age 0 to 4 weeks, caffeine $t_{1/2}$ was 97.6 ± 32.7 hours, but dropped to 5.2 ± 5 at an age >29 weeks. A high variability of caffeine citrate $t_{1/2}$ was observed among normal neonates at similar conceptional ages. The peak concentration of caffeine citrate was obtained at 1 to 1.5 hours after oral administration.

Early work has demonstrated an exceedingly slow elimination rate of caffeine citrate in premature and term infants.[42] The $t_{1/2}$ was 17-fold lower than that of adults. By 1.5 months of age, it had decreased from neonatal levels, and it attains the adult value (2.2 hours) at 4 – 6 months of age.[45] The long caffeine citrate $t_{1/2}$ in premature infants is due to a lower activity of N-demethylation.[33,34] Approximately 85% of unchanged caffeine citrate was recovered in the neonatal urine;[43,44] whereas about 2% of unchanged caffeine citrate is recovered in the urine of adults.[45]

Lelo et al.[46] studied the pharmacokinetics of caffeine in man; the clearance was 2.07 min/kg per min and $t_{1/2}$ was 4.1 hours. Gorodischer and Karplus[47] studied the pharmacokinetics of caffeine citrate in 13 premature infants. A single intravenous dose of 15 mg/kg caffeine citrate was administered. $t_{1/2}$ was 65 ± 3.7 hours, clearance was 0.14 ± 0.01 ml/kg per min, and volume of distribution was 0.87 ± 0.04 l/kg. No correlation was found between Cl, $t_{1/2}$ and postnatal age.

De Carolis et al.[40] administered 10 mg/kg of caffeine citrate intravenously to 5 premature infants. $t_{1/2}$ of caffeine citrate was 72 ± 12 hours, that is, 18 times greater than that of adults.[46] Gorodischer and Karplus[47] studied the pharmacokinetics of caffeine citrate in 13 preterm infants after a single intravenous dose of 15 mg/kg caffeine citrate was administered. The $t_{1/2}$ value was 65.3 hours, clearance was 0.14 ± 0.01 ml/kg per min, and volume of distribution was 0.87 ± 0.01 l/kg. Pearlman et al.[48] measured the caffeine citrate $t_{1/2}$ in 17 preterm infants and found it to be 52.0 ± 23.9 hours.

Bonati et al.[45] report the pharmacokinetics of caffeine citrate in adults. Table 2 summarizes the pharmacokinetic parameters of caffeine citrate obtained in 5 selected studies. Charles et al.[49] performed a large multicenter, randomized, blinded clinical trial of caffeine citrate pharmacokinetics in 110 infants. The loading dose of caffeine citrate was 80 mg/kg and the daily maintenance dose 20 mg/kg. The median caffeine treatment period was 7 days. Clearance for infants increased in a nonlinear manner from about 1 ml/kg per min, on the first day of life, to about 12 ml/kg per min after 45 days. The mean clearance was 0.116 ml/kg per min, which is markedly reduced compared with that reported in adults (1.50 ml/kg per min)[43,48] and in older children (4.40 ml/kg per min).[48] The mean volume of distribution in the Charles et al. study[49] was 0.85 l/kg, larger than that reported in healthy adults (0.63 l/kg).[45] This increased volume of distribution is attributed to an increased residence time of caffeine in the extracellular fluid, which represents a greater percentage of total body water and body mass in the newborn infant than in older children and adults.[52]

Table 2 - Demographic data of the infants and pharmacokinetic parameters of caffeine citrate obtained in neonatal population studies.

Number of cases	GA (weeks)	PNA (days)	BW (g)	Cl (ml/kg/min)	Vd (l/kg)	$t_{1/2}$ (hours)	Reference
110	27.6	12	1,009	0.116	0.85	101	48
89	28.2	4	1,167	0.082	0.97	144	8
75	na	na	na	0.13	0.91	na	49
60	23	31	na	0.13	0.82	na	50
4	30*	–	–	1.50	0.63	4.8	33

Figures are the mean; GA = gestational age; PNA = postnatal age; BW = body weight; Cl = clearance; Vd = volume of distribution; $t_{1/2}$ = elimination half-life; na = not available; *years.

Lee et al.[8] administered an intravenous loading dose of 60, 30 or 6 mg/kg, either 24 hours before a planned extubation or within 9 hours of an unanticipated extubation to 89 premature infants who were ventilated for >48 hours. A maintenance dose of 30 mg/kg (n = 42) or 15 mg/kg (n = 39) or 3 mg/kg (n = 38) was continued at 24-hour intervals for 6 days. Mean clearance estimates were similar after administration of the low, medium, and high doses either at entry or exit from the study. The mean $t_{1/2}$ was 144 hours, clearance was 0.082 ml/kg per min and volume of distribution was 0.971 l/kg. $t_{1/2}$ was longer, clearance was smaller, and volume of distribution was larger than the values reported in infants 1 to 2.5 months old.[42] In these children $t_{1/2}$ was 103 hours.[42]

Falcao et al.[50] report an oral or intravenous loading dose of 20 mg/kg and a maintenance daily dose of 50 mg/kg.[50] Individual estimates of clearance were obtained using the population estimates and a "posthoc" Bayesian analysis. Clearance was estimated at 0.13 ± 0.02 ml/kg per min which is consistent with the average clearance values of 0.13 ± 0.03 ml/kg per min, 0.15 ± 0.02 ml/kg per min and 0.14 ± 0.01 ml/kg per min reported by Thomson et al.,[51] Aranda et al.[42] and Gorodischer and Karplus,[47] respectively. Volume of distribution was 0.91 l/kg which was similar to those reported by Charles et al.[49] (0.85 l/kg), by Lee et al.[8] (0.97 l/kg) and by Thomson et al.[51] (0.82 l/kg).

Thomson et al.[51] studied the population pharmacokinetics of caffeine citrate in 60 neonates and young infants with a median postmenstrual age of 31 weeks and a median postnatal age of 23 days. A loading dose of 20 mg/kg of caffeine citrate was administered orally or intravenously, with a maintenance dose of 5 mg/kg, adjusted as necessary to maintain the serum caffeine concentration within the range 25–100 μmol/l. The clearance estimate was 0.13 ± 0.03 ml/kg per min and was consistent with the average clearance of 0.15 ± 0.02 ml/kg per min reported by Aranda et al.,[42] and the 0.15 ± 0.01 ml/kg per min found by Gorodischer and Karplus.[47] The estimate of volume distribution was 0.82 l/kg, consistent with the data by Charles et al.[49] (0.85 l/kg), Lee et al.[8] (0.97 l/kg) and Falcao et al.[50] (0.91 l/kg).

Comparative efficacy: caffeine citrate, theophylline and aminophylline for prematurity apnea

Skouroliakou et al.[52] report a study which enrolled 70 neonates <33 weeks of gestation breathing spontaneously. They were randomly assigned (open-label) to receive either theophylline or caffeine citrate for prevention of apnea. The primary outcome measure was to assess the difference in apnea frequency between theophylline and caffeine patient groups. The intravenous loading dose of theophylline was 4.8 mg/kg and the maintenance dose was 2 mg/kg every 12 hours (n = 37). Thirty-three infants received caffeine citrate orally or intravenously, with a loading dose of 20 mg/kg, and a maintenance dose of 5 mg/kg. The plasma concentrations of caffeine citrate ranged from 5.5 and 23.7 μg/ml, and those of theophylline ranged from 2.2 and 13.9 μg/ml, and reached the steady-state after 3 days. After caffeine citrate, a significant decrease in the number of apnea events was observed on days 1–3 (p = 0.001) and 4–7 (p = 0.001).

Laubscher et al.[27] determined the effects of theophylline and caffeine citrate on neonatal respiratory function. Forty-five preterm infants received either theophylline (loading dose 4 mg/kg followed by a maintenance dose of 4 mg/kg per day) or caffeine citrate (loading dose 10 mg/kg followed by 5 mg/kg per day). Twenty four hours after dosing, there was a significant improvement in the compliance of the respiratory system and reduction in supplementary oxygen requirements in the caffeine group (p < 0.001). After seven days of treatment, compliance was improved in both the theophylline and caffeine groups (p < 0.05 and p < 0.01, respectively). A significant reduction in the strength of the Hering Breuer reflex was only observed in the caffeine group (p < 0.05). The requirement of inspired oxygen was lower in the caffeine group 24 hours after treatment (p < 0.05). Laubscher et al.[27] conclude that theophylline and caffeine have similar effects on neonatal respiratory function, but their results suggest that caffeine administration may be associated with an earlier onset of action.

Scanlon et al.[53] compared caffeine citrate and theophylline on the improvement of apnea in 44 preterm infants who were suffering from frequent apneic attacks. Caffeine was administered in two doses. The first was 12.5 mg/kg (loading), and 3 mg/kg daily (maintenance); the second was 25 mg/kg (loading), and 6 mg/kg daily (maintenance). Theophylline dosage was 7.5 mg/kg (loading), and 3 mg/kg thrice daily (maintenance). All three regimens produced significant reductions in apneic attacks within 24 hours, but only the higher dose of caffeine citrate and theophylline showed a significant improvement in apnea within 8 hours. The use of caffeine citrate for the treatment of neonatal apnea is recommended, because a single daily dose is more easily administered, and because it was found that plasma concentrations are more predictable than those of theophylline.

Brouard et al.[54] compared the efficacy of theophylline and caffeine citrate in the treatment of idiopathic apnea in 24 premature infants. The infants showed similar significant decreases of apnea frequency in both theophylline-treated infants (n = 8) and caffeine-treated infants (n = 8). They preferred caffeine to theophylline because caffeine is efficient and easier to administer.

Larsen et al.[55] compared the effects of aminophylline versus caffeine citrate for apnea and bradycardia prophylaxis in premature neonates. An aminophylline loading dose (6.2 mg/kg) with a maintenance dose of 3.1 mg/kg; the caffeine citrate loading dose was 20.2 mg/kg (n = 82), with a maintenance dose of 2.5 mg/kg. Both treatments lasted 10 days. Aminophylline and caffeine citrate decreased the incidence of neonatal apnea and bradycardia to the same extent. No differences were found between the two groups regarding the number of neonates who needed respiratory therapy and the number of episodes of apnea of bradycardia. The caffeine citrate group had a lower median heart rate on day 3 and a smaller amount of gastric aspirate on day 7. Furthermore, the caffeine citrate group had fewer premature neonates with tachycardia (heart rate > 160 beats per min) than the aminophylline group (p = 0.003). Aminophylline reduced the cerebral blood flow. There were no differences in the frequency of respiratory distress syndrome or necrotizing enterocolitis between groups. Based on these results, caffeine citrate seems to be the drug of choice for apnea and bradycardia prophylaxis in premature neonates.

Lundstrom et al.[56] compared the acute effects of bolus administration of caffeine citrate or aminophylline on left ventricular output, heart rate, blood pressure and global cerebral blood flow. Fourteen infants received 20 mg/kg

caffeine citrate and 19 infants received 5 mg/kg aminophyl-line. All infants were breathing spontaneously since birth. Cerebral blood flow was higher in the caffeine than in the aminophylline groups 17.1 ± 7.1 versus 13.2 ± 2.9 ml/100 g/min (p = 0.01). As in the previously discussed studies, caffeine citrate was preferred to aminophylline.

Adverse effects of caffeine citrate in preterm infants

Caffeine citrate is incompatible with acyclovir, furosemide, ibuprofen lysine, lorazepam, nitroglycerin and oxacillin.[13] Adverse events associated with caffeine citrate involve tremors, opisthotonous, tonic-clonic seizures, vomiting and metabolic effects such as hyperglycemia, hypokalemia, and jaundice.[35] Other, infrequently reported, adverse events include tachycardia,[32] constipation, gastro-oesophageal reflux,[57] increased levels of urinary output, creatinine clearance,[58] sodium and calcium excretion.[59] Jitteriness occurred in an infant with plasma concentration of caffeine of 61.7 µg/ml. The onset of toxic effects usually takes place at concentrations ranging from 160 to 300 µg/ml.[60] In the event of toxicity, supportive therapy is required: correction of hypokalemia and hypercalcemia, and ministration of anticonvulsants in the event of seizures.

Romagnoli et al.[39] verified the efficacy and the side effects of two different dosages of caffeine for the prevention of idiopathic apnea in 23 preterm infants. Infants (n = 14, group 1) received a 10 mg/kg intravenous loading dose (maintenance 5 mg/kg), while 10 neonates (group 2) received a daily maintenance dose of 2.5 mg/kg. Before the loading dose, the mean caffeine citrate concentrations were $1.58 + 0.27$ µg/ml in group 1 and $0.56 + 0.25$ µg/ml in group 2. Tachycardia (heart rate >180 beats per min) was observed in 11 infants in group 1 (5 mg/kg caffeine) and 0 infants in group 2 (2.5 mg/kg, p < 0.001). Vomiting and other feeding problems were observed in 11 infants in group 1 and 2 infants in group 2 (NS). A higher caffeine maintenance dose could stimulate a more rapid metabolism of caffeine into theophylline and other methylxanthines. The only side effects observed were hyperglycemia, vomiting, regurgitation, and tachycardia. These were transitory manifestations, and sometimes regressed spontaneously during treatment. Romagnoli et al.[39] believe that the observed side effects were not due to caffeine itself, but to the theophylline blood concentrations or, more likely, to the cumulative effect of caffeine and theophylline.

Dayanim et al.[61] proposed that hyperoxia-induced alveolar inflammation and hypoplasia is associated with alterations in the adenosine signaling pathway. They suggested a potential adverse role of caffeine on alveolar development in a murine model of hyperoxia-induced alveolar hypoplasia. The use of caffeine may reduce the incidence of bronchopulmonary dysplasia. The precise mechanisms remain unknown.

If a caffeine licensed product is unavailable, extemporaneous caffeine citrate can be and has been used by many hospital pharmacies. Vatlach et al.[62] prospectively compared the safety profile of extemporaneous with the licensed product of caffeine. 562 preterm infants with 14,590 extemporaneous citrate treatment days were compared with 538 infants with 12,813 licensed product treatment days. The gestational age was similar in both groups. No relevant differences were seen concerning tachycardia, gastric residuals, or vomiting, and seizures risk ratio: 1.91,

p = 0.35. Safety profiles were thus similar for both forms of caffeine citrate.

■ DISCUSSION

Drugs employed to manage the apnea of prematurity have been in use for many years. The last drug which entered into clinical use to treat apnea was caffeine citrate, introduced by Aranda et al.[18] in 1977. Since 1973, when theophylline was first used, clinical studies have demonstrated its effectiveness.[7] In the first weeks of life, caffeine is mainly eliminated by renal excretion.[60] Physiological variables related to the development of renal function influence caffeine clearance in this age range.

Caffeine citrate is a more potent central and respiratory acting agent with fewer side effects than theophylline.[5,6] Caffeine citrate is used to increase the mean respiratory rate, to stimulate the respiratory centers, to increase the transmission of neural impulses and pulmonary blood flow, to improve the diaphragm's activity, skeletal muscle contraction, metabolic homeostasis, and oxygenation secondary to increased cardiac output.[6,7] Caffeine citrate decreases the number of apneic spells, the PCO_2 tension, the hydrogen ion concentration, the respiratory depression by hypoxia, and periodic breathing.[63,64]

Caffeine citrate penetrates into the cerebrospinal fluid more readily than theophylline because of its higher lipophilicity[7], and is effective in infants who are refractory to standard theophylline treatment.[8,60] Caffeine is rapidly absorbed in preterm infants, with plasma concentrations reaching 6 to 10 µg/ml within 30 min to 2 hours after administration of an oral dose of 10 mg/kg.[10]

In preterm infants, the administration of caffeine base (10 or 20 mg/kg) had no effect on cerebral blood flow.[29,30] Oxygen desaturation and bradycardia episodes can clearly cause alterations in cerebral hemodynamics which may compromise the subsequent neural development in neonates. In a trial conducted on 175 preterm infants monitored up to the age of three, Janvier et al.[65] highlighted that the number of days of apnea, in addition to male sex, had a significant association with the increased probability of an alteration in neuronal development.

The recommended loading dose of caffeine citrate is 20 mg/kg, followed, 24 hours later, by a single daily maintenance dose of 5 mg/kg.[16] This dose regimen will achieve plasma concentrations of caffeine of 8 to 14 µg/ml after the loading dose, and 7 to 20 µg/ml during the maintenance dose.[16] Therapeutic drug monitoring for caffeine citrate is unnecessary in preterm infants because the overwhelming majority (95%) of preterm infants achieves serum concentrations of caffeine citrate between 5 and 20 µg/ml, which are the therapeutic serum concentrations for this drug.[16]

Recent data suggest that apnea of prematurity may be genetically linked.[19] Polymorphism in the A1 and $A2_A$ receptor genes may account for variability in subjective response to caffeine.[19] High incidence of apnea of prematurity was observed in infants born to first-degree consanguineous parents.[64] This supports a genetic link. The heritability of apnea of prematurity was 87% among twins of the same gender.[66] The possibility that developmentally regulated genes may contribute to the vulnerability of preterm infants to apnea was raised by Bloch-Salisbury et al.[66]

Caffeine citrate is metabolized by CYP1A2. It is N-demethylated at positions 1, 3 and 7 and is hydroxylated at position 8.[13] N-3- and N-7-demethylation rates increase exponentially with postnatal age and a plateau is reached by 120 days.[67] The delay in the maturation of N-1- activity compared with N-3- and N-7-demethylation rates observed in vitro, and the delay of hydroxylation at position 8, are in agreement with in vivo data.[36,67] Caffeine is also acetylated by N-acetyltransferase (NAT2)[33] and its activity is not complete till the age of 1 year, implying that the acetylator status cannot be reliably determined before that age.

At birth, the serum $t_{1/2}$ of caffeine citrate ranges from 40 to 230 hours, decreasing with advancing postmenstrual age until 60 weeks of post-conceptional age.[13] The half life is 21 to 30-fold longer, clearance is 11 to 18-fold smaller, and volume distribution is 1.3 to 1.5-fold larger at birth than in adults. These findings must be taken into consideration when planning a therapeutic regimen with caffeine citrate in neonates. Le Guennec et al.[41] found that the $t_{1/2}$ of caffeine citrate was 97.6 hours at a postnatal age from 0 to 4 weeks, and became 5.2 hours at a postnatal age >29 weeks. There is a considerable shortening of caffeine citrate $t_{1/2}$, which is due to a rapid increase in CYP1A2 activity, during neonatal maturation. The adult values (2.2 hours) are reached at an age of from 4 to 6 months.[45]

In conclusion, theophylline produces tachycardia[56] and aminophylline reduces the cerebral blood flow.[55] Caffeine citrate does not have these effects, and reduces the apneic spells more effectively than theophylline or aminophylline. Theophylline and aminophylline require 2 to 3 daily administrations whereas caffeine citrate is administered once daily, and its concentrations are more predictable than those of theophylline and aminophylline. This body of information makes caffeine citrate the first choice drug for the treatment of apnea of prematurity.

■ ACKNOWLEDGEMENTS

■ RESUMO

OBJETIVO: A apneia de prematuridade é definida como a interrupção respiratória de 15 a 20 segundos; é o distúrbio respiratório mais importante em prematuros. A apnéia é normalmente tratada com citrato de cafeína. Os objetivos deste artigo são rever: (1) os mecanismos de ação, (2) os efeitos, (3) o metabolismo, (4) a farmacocinética, e (5) os efeitos adversos do citrato de cafeína em prematuros.

MÉTODOS: A pesquisa bibliográfica foi realizada utilizando as bases de dados PubMed e EMBASE como motores de busca e abril 2014 foi o ponto de corte.

RESULTADOS: O citrato de cafeína é um estimulante dos centros respiratórios do sistema nervoso central. Liga-se competitivamente aos receptores de adenosina A2$_A$ e A1, causando sua inibição. A cafeína aumenta a frequência respiratória e o volume minuto, estimula os centros respiratórios e aumenta o fluxo sanguíneo e a sensitividade das áreas medulares centrais à hipercapnia. O citrato de cafeína administrado por via oral é rápida e completamente absorvido. O fármaco é desmetilado pelo CYP1A2 e N-acetilado pela N-acetil-transferase. A meia-vida de citrato de cafeína é de 100 horas ao nascimento. Há uma redução notável da meia vida durante a maturação neonatal. Os efeitos adversos da cafeína geralmente são pouco importantes e incluem agitação, vômito e sintomas cardíacos funcionais.

CONCLUSÕES: O citrato de cafeína é a droga de escolha para o tratamento da apneia da prematuridade. É droga fácil de usar. Administrado por via oral ou por via intravenosa, uma vez por dia, não requer monitorização das concentrações de soro e tem poucos efeitos colaterais.

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