RISKS AND BENEFITS OF METHYLXANTHINES THERAPY – CASE STUDY

Mariana Boia[1,2], Delia Maria Nicoara[2], Aniko Maria Manea[1,2]
[1] *„Victor Babes" University of Medicine and Pharmacy, Timisoara*
[2] *„Louis Turcanu" Children's Emergency Hospital, Timisoara*

ABSTRACT

Introduction. Apnea of prematurity (AOP), a developmental disorder of respiratory control present in approximately 80% of extremely low birth weight (ELBW) infants, that, if prolonged, may cause hypoxemia and low cardiac output, with subsequent neurodevelopmental compromise.
Material and method. Retrospective study in a regional referral level III neonatal intensive care unit, sought to evaluate our experience with methylxanthines treatment for recurrent apneic spells in 84 preterm infants with gestational age of < 32 weeks and birth weight of < 1,500 g.
Results. The median maintenance dose was 5 mg/kg/d for caffeine citrate, and 3 mg/kg/d for theophylline. There was no difference in mean apnea rate between caffeine and theophylline groups after one to week of treatment, with similar need for continuous positive airway pressure and supplementary oxygen requirements in both groups. Adverse effects, such as tachycardia, feeding intolerance and failure to gain weight leading to change in dosage, were lower in the caffeine group.
Conclusions. Lower postmenstrual age (less than 28,2 weeks) were associated with increased need for methylxanthines weight adjustments and mini-loads, as these infants required longer courses of therapy. While both methylxanthines are as effective in treating apneic preterms, caffeine citrate was the preferred drug given its wider therapeutic margin, and fewer adverse effects.

Keywords: apnea of prematurity, methylxanthines, adverse effects

INTRODUCTION

Apnea of prematurity (AOP), a developmental disorder of respiratory control (1), is one of the most commonly encountered disorders in the neonatal intensive care unit (2,3), with an incidence inversely related to gestational age, occuring in approximately 80% of extremely low birth weight (ELBW) infants (3,4). If prolonged, it can cause hypoxemia and low cardiac output, that may compromise the subsequent neural development of the neonate (5). Improved survival rates of low birth weight (LBW) infants due to advances in neonatal care have led to an increased incidence of this disease (6). Because nonpharmacologic therapies such as protracted mechanical ventilation and supplemental oxygen increase the risk of developing Bronchopulmonary dysplasia (BPD) (7), complementary agents such as methylxanthines are used to stimulate the respiratory drive (8). Although having been used in the treatment of AOP for over 3 decades, it was not until recent years that evidence surfaced regarding the safety of their routine use in preterm infants (9). The current study sought to evaluate our Units experience with methylxanthines in AOP.

METHODS

This study was a retrospective analysis, carried out over a 3 years period (January 2010 – December 2013), in a regional referral level III neonatal intensive care unit. The study included 84 preterm infants, with gestational age of < 32 weeks and birth weight of < 1,500 g that had received eihter caffeine or aminophyline treatment for apnea of prematurity. Infants with other causes of apnea (e.g., central nervous system disorders, sepsis, primary lung disease, and cardiovascular abnormalities) were excluded from the study. Parameters obtained

Corresponding author:
Mariana Boia, „Victor Babes" University of Medicine and Pharmacy, 2 Murgu Eftimie Pta, Timisoara

by individual chart review included: gestational age, birth weight, loading and maintenance dose, episodes of apnea, bradycardia, and desaturation, number of weight dose adjustments, time to first elective extubation, total duration of mechanical ventilation and of oxygen supplementation, and adverse reactions regarding methylxanthines therapy.

RESULTS

The studied lot included 84 preterm infants with recurrent apneic spells, of which 43 treated with theophylline and 41 with caffeine citrate.

The median gestational age was 29.1 weeks (interquartile range 26.5 to 31.9 weeks) and the median birth weight was 1,290 g (interquartile range 712 to 1,468 g). There were no significant differences in sex, twin gestation, antenatal steroid use, chorioamnionitis, 1 and 5 min Apgar scores, and surfactant therapy between the two groups.

The median duration of caffeine therapy was similar between the two groups (caffeine 40 days, theophylline: 42 days). The median loading dose of caffeine citrate was 20 mg/kg (range 18.7 to 28.5 mg/kg), while the initial maintenance dose most frequently chosen was 5 mg/kg. Maintenance dose of theophylline was 2 mg/kg/12 h, while the median loading dose was 5 mg/kg/12 h.

Infants with GA < 29 weeks required weight adjustments and maintenance dose increases (median 2-3/week).

There was no difference in mean apnea rate between caffeine and theophylline groups after one to week of treatment.

The need for continuous positive airway pressure was similar in both groups:

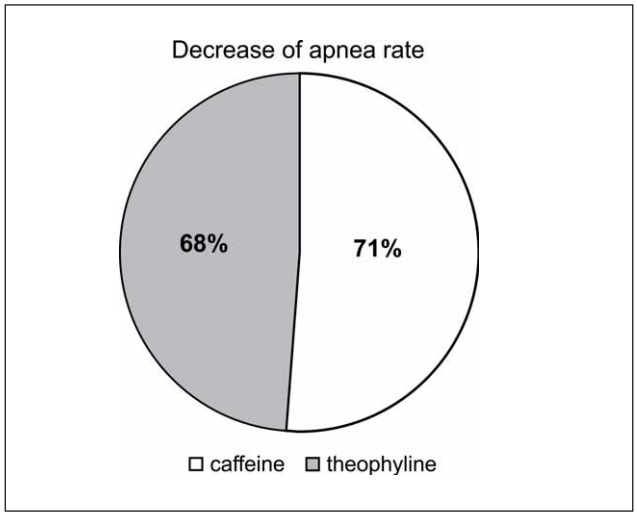

FIGURE 1. *Decrease of apnea rate after 1 week of methylxanthines treatment*

TABLE 1. *Need for continuous positive pressure therapy*

	Caffeine group	Theophylline group
Extubated at 72 hours	6 (14.6%)	6 (13.9%)
Extubated at 1 week	31 (75.6%)	30 (69.7%)
Extubated at 2 weeks	38 (92.6%)	39 (90.6%)
O_2 dependency at 36 weeks	13 (31.7%)	15 (34.8%)

Adverse effects, such as tachycardia and feed intolerance leading to change in dosing, were lower in the caffeine group.

TABLE 2. *Most common encountered side effects of methylxanthines*

	Caffeine group	Theophylline group
Tachycardia	11 (26,8%)	12 (27,9%)
Feeding intolerance	8 (19,5%)	11 (25,5%)

None of the infants from the studied lot developed necrotizing enterocolitis; the rates of ultrasonographic signs of brain injury did not differ between the two groups.

DISCUSSION

Apnea of prematurity, one of the most frequent pathologies in the Neonatal Intensive Care Unit, has an incidence inversely related to gestational age (GA): less than 10% of infants with GA of 34-35 weeks, as opposed to 54% of neonates 32-33 weeks gestational age, and 84% in infants with birth weights less than 1,000 g (10). With increased survival of ELBW infants due to constant medical advances, maintaining adequate respiration and corresponding oxygenation represents a clinical challenge for the neonatologist (11). The incidence of apnea was similar in our study group: lower postmenstrual ages were associated with high rates of apneic spells (95% of infants with GA < 29 weeks), while only 15% of infants with GA = 34-35 weeks demonstrated these disorder. Preterm infants are more prone to respiratory distress due to certain anatomical particularities: a large occiput, hypotonic neck muscles and smaller airways, decreased pulmonary reserves (12). Immaturity of the pathways involved in respiratory drive and exaggerated inhibitory reflexes are thought to be the main physiological pathways involved (13).

Despite being a self-limiting developmental disorder which regresses with the maturation of the newborn, it may affect the neurodevelopmental outcome due to frequent episodes of profound and recurrent hypoxemia (14). Up to date no studies identified with certainty a threshold in either fre-

quency or severity of accompanying bradycardia or hypoxemia that increases the risk of neurodevelopmental impairment (15).

Central effects of methylxanthines, obtained by adenosine receptor blockade, include: stimulating central inspiratory drive and increasing minute ventilation by augmenting the medullary respiratory sensitivity to carbon dioxide (16,17). Peripheric effects include improving the preterm's chest wall mechanics by increasing diaphragmatic contractility (18), and decreasing diaphragmatic fatigability (19). Apart from improving respiratory morbidity, recent evidence of improved white matter microstructural development in infants treated with caffeine suggests additional unidentified mechanisms of action (20). In addition, methylxanthines stimulate catecholamine release and increase metabolic rate (21).

Recommended doses of caffeine include IV loading doses of 20 mg/kg caffeine citrate followed 24 hours later by maintenance doses of 5 to 10 mg/kg caffeine citrate (22,23). The prolonged half-life of caffeine in preterm infants results in less fluctuation in plasma concentrations and allows single daily doses (24). Therapeutic drug monitoring and dosing differ from practice to practice (25). The initial maintenance dose of caffeine citrate most frequently used in our study was 5 mg/kg, while the median loading dose was 20 mg/kg. Most infants achieve therapeutic caffeine plasma concentrations (5-20 mcg/mL) using standard doses (26). Current practice in our Unit is to not routinely monitor caffeine levels. Indications for caffeine serum monitoring include: infants with clinical signs of toxicity or with intractable apnea (26). Given its wider therapeutic index, longer half-life, and more reliable oral absorption, caffeine citrate is the preferred methylxanthine (27).

Most centers use initial maintenance doses of aminophylline in the range of 1 to 2 mg/kg/dose given every 8 to 12 hours. Therapeutic dosis of theophylline used in our study were similar to those cited in the literature: median loading dose was 2 mg/kg/12h, while the maintenance dose was 5 mg/kg/12h. Serum theophylline concentrations should be monitored 72 hours after initiation of therapy or after dosage adjustment. The generally accepted therapeutic range of theophylline for apnea of prematurity is 7 to 12 mcg/mL (28). Indications for monitoring theophylline serum levels include: an increase in the number of apneic episodes, toxicity signs or symptoms, or a significant increase in weight. Once steady-state levels are obtained in asymptomatic neonates, theophylline levels may be monitored once every 2 weeks (24).

No significant short-term effects of methylxanthines on death rates, ultrasonographic signs of brain injury, or NEC were identified. Adverse effects such as tachycardia, CNS excitation, and feeding intolerance are cited more frequently with theophylline than with caffeine (29). Our study did not identify any significant adverse effects associated with methylxanthine therapy, however, the small sample size limited detection of clinically significant differences. Prior studies have raised concerns regarding the vasoconstrictive effects of caffeine therapy (30).

CONCLUSIONS

Lower postmenstrual age (less than 28.2 weeks) is associated with increased need for caffeine citrate weight adjustments and mini-loads, as these infants require longer courses of therapy.

REFERENCES

1. **Abu-Shaweesh J.M., Martin R.J.** Neonatal apnoea: what's new? *Pediatr Pulmonol.* 2008; 43: 937-44.
2. Committee on Fetus and Newborn. American Academy of Pediatrics. Apnea, sudden infant death syndrome, and home monitoring. *Pediatrics*. 2003; 111(4 Pt 1):914-922.
3. **Erenberg A., Leff R.D., Haack D.G.** Caffeine citrate for the treatment of apnea of prematurity: a double-blind, placebo controlled study. *Pharmacotherapy*. 2000; 20(6):644-652.
4. **Scanlon J.E., Chin K.C., Morgan M.E.** Caffeine or theophylline for neonatal apnea? *Arch Dis Child*. 1992; 67(spec no 4):425-428.
5. **Martin R.J., Abu-Shaweesh J.M. and Baird T.M.** Pathophysiologic Mechanisms Underlying Apnea of Prematurity. *Neoreviews* Vol. 3 No. 4 April 1, 2002 pp. e59 -e65
6. **Erenberg A., Leff R.D., Haack D.G.** Caffeine citrate for the treatment of apnea of prematurity: a double-blind, placebo controlled study. *Pharmacotherapy*. 2000; 20(6):644-652.
7. **Northway W.H., Rosan R.C., Porter D.Y.** Pulmonary disease following respirator therapy of hyaline membrane disease. *N Engl J Med* 1967; 276:357-68.

8. **Gerhardt T., McCarthy J., Bancalari E.** Effect of aminophylline on respiratory center activity and metabolic rate in premature infants with idiopathic apnea. *Pediatrics* 1979;63:537-42.
9. **Clark R.H., Bloom B.T., Spitzer A.R.** Reported medication use in the neonatal intensive care unit: data from a large national data set. *Pediatrics*. 2006;117(6):1979–1987.
10. **Henderson-Smart D.J.** The effect of gestational age on the incidence and duration of recurrent apnea in newborn babies. *J Paediatr.* 1981; 17:273-6.
11. **Di Fiore J.M., Martin R.J., Gauda E.B.** *Respir Physiol Neurobiol* 2013 Nov 28; 189(2):213-22. Epub 2013 May 28.
12. **Atkinson E., Fenton A.C.** Management of apnoea and bradycardia in neonates. *Ped and Child Health* 2009; 19: 550-554.
13. **Abu-Shaweesh M., Martin R.J, Jalal J.** Apnea of prematurity: past, present and future. *Arab Neonatal Forum*; 2005; 2:63-73.
14. **Piermichele P., Simonetta P.** Apnea of prematurity. *Journal of Pediatric and Neonatal Individualized Medicine;* 2013;2(2):e020213 doi: 10.7363/020213
15. **Taussig M., Landau L.I., Le Souëf P.N.** chapter 30 Apnea of Prematurity Christian Poets, page 413
16. **Henderson-Smart D.J., Steer P.A.** Caffeine versus theophylline for apnea in pre-term infants. *Cochrane Database Syst Rev*. 2010; 1:CD000273.
17. **Schmidt B., Roberts R.S., Davis P.** Caffeine therapy for apnea of prematurity. *N Engl J Med*. 2006; 354(2):2112–2121.
18. **Supinski G.S., Deal Jr E.C., Kelsen S.G.** The effects of caffeine and theophylline on diaphragm contractility. *Am Rev Respir Dis* 1984; 130(3): 429–433.
19. **Bhandari A., Bhandari V.** Bronchopulmonary Dysplasia: An *Update***.** - *Indian Journal of Pediatrics*, Volume 74 – January 2007
20. **Doyle L.W., Cheong J., Hunt R.W., Lee K.J., Thompson D.K., Davis P.G. et al.** Caffeine and brain development in very preterm infants. *Ann Neurol* 2010; 68(5): 734-742.
21. **Anderson D.E., Hickey M.S.** Effects of caffeine on the metabolic and catecholamine responses to exercise in 5 and 28 degrees. *Med Sci Sports Exerc.* 1994 Apr;26(4):453-8.
22. **Sayles R., McCarthy J. ACH Neonatal Formulary 1995.** (Available from the Department of Neonatology, Box 7565, All Children's Hospital, 801 Sixth Street, South, St. Petersburg, FL 33701.)
23. **Taketomo C.K., Hodding J.H., Kraus D.M.** Pediatric Dosage Handbook 1997, 4th ed. Hudson, Ohio: Lexi-Camp.
24. **Alldredge R.L., Corelli M.E., Ernst B.J., Pamala A.J., Wayne A.K., Bradley R.** Koda-Kimble & Young's Applied Therapeutics: The Clinical Use of Drugs; 10th edition published by Wolters Kluwer
25. **Charles B.G., Towsend S.R., Steer P.A.** Caffeine citrate treatment for extremely premature infants with apnea: population pharmacokinetics, absolute bioavailability, and implications for therapeutic drug monitoring. *Ther Drug Monit*. 2008; 30(6):706-716.
26. **Natarajan G. et al.** Therapeutic drug monitoring for caffeine in preterm neonates: an unnecessary exercise? *Pediatrics***.** 2007:119:936.
27. **Erenberg A., Leff R.D., Haack D.G.** Caffeine citrate for the treatment of apnea of prematurity: a double-blind, placebo controlled study. *Pharmacotherapy*. 2000; 20(6):644-652. et al.
28. **Yaffe Sumner J., Aranda Jacob V.** Neonatal and Pediatric Pharmacology: Therapeutic Principles in Practice, 3rd Edition. 2005
29. **Steer P.A., Henderson-Smart D.J.** Caffeine versus theophylline for apnea in preterm infants. *Cochrane Database of Systematic Reviews* 1998, Issue 2. Art. No.: CD000273.
30. **Gibbs F.A., Gibbs E.L., Lennon W.G.** Cerebral blood flow in man as influenced by adrenalin, caffeine, amyl nitrite and histamine. *Am Heart J* 10: 916-924, 1935