

# Failure of Caffeine to Ameliorate Respiratory Syncytial Virus-Induced Apnea

Dante Allen Pappano\*

*Department of Emergency Medicine, East Tennessee Children's Hospital, Knoxville, TN, USA*

**Abstract:** Caffeine and other methylxanthines have been reported to be effective in preventing the need of invasive airway support in cases of respiratory virus-associated apnea. However, the reliability of the reported effect is not known. We report a case of RSV-induced apnea in an infant in which 10mg/kg of intravenous caffeine did not prevent the need for intubation and mechanical ventilation.

**Keywords:** Apnea, caffeine, respiratory syncytial virus.

## INTRODUCTION

Respiratory syncytial virus (RSV)-induced apnea is a potentially deadly manifestation of RSV infection in infants. Those born prematurely, and those in the first few months of life are most susceptible [1]. The best pathophysiological explanation for the phenomenon appears to be the combined effects of the laryngeal chemoreflex stimulated by hypotonic secretions in the setting of lethargy and neurotoxin mediated reduction in respiratory drive [2].

Perhaps because of their well-established efficacy for neonatal apnea [3], or because of their purported ability to increase respiratory drive, methylxanthines have been tried for RSV-induced apnea. However, our understanding of its effectiveness in this role is very limited.

## CASE REPORT

A 22 day white male infant was transferred to the East Tennessee Children's Hospital (ETCH) emergency department (E.D.) with apnea. He was an ex-36 week premature infant whose neonatal course was uncomplicated. He was seen by his primary care physician 3 days prior to admission for nasal congestion, a nasal washing indicated the presence of RSV. One day prior to admission he vomited several times. The child was briefly checked by a family friend who is a pediatrician and felt to be "ok". On the morning of admission he was felt to be lethargic. En route to the pediatrician's office the infant had several cyanotic episodes and instead went to a nearby EMS facility. From there he was transferred to a local emergency department, and finally to East Tennessee Children's Hospital (ETCH). During transfer he required stimulation several times, and bag-mask ventilation once.

In the ETCH E.D. his vital signs were as follows: T 95.7F, HR 190 RR 36 BP 84/40 SaO<sub>2</sub> 100% on non-rebreather supplemental oxygen mask. He appeared well except for many episodic respiratory pauses. All events

appeared to be central, characterized by a complete lack of respiratory effort. Observers allowed only 1 or 2 to go to a full 20 seconds to satisfy the definition of apnea. All episodes responded to tactile stimulation, except once he also received bag mask stimulation. The frequency of the events was such that the infant required near constant stimulation. IV access was obtained and the infant was loaded with 5mg/kg caffeine citrate. Thirty minutes after initiating the first caffeine load a second 5mg/kg was given for continued apnea. Twenty minutes after the second load the apneic episodes still had not abated so the infant was intubated and received mechanical ventilation. Nasal washings were positive for RSV by DFA. Culture of tracheal secretions resulted in heavy growth of *S. pneumoniae* for which he was treated with cefotaxime. Blood cultures were negative, and chest xrays did not reveal infiltrates at anytime during the hospitalization. On hospital day number three the patient failed a CPAP trial. He was extubated on hospital day 5, and had an uneventful recovery from that point. He was discontinued from caffeine and discharged home on hospital day #9.

## DISCUSSION

The first use of a methylxanthine for RSV-induced apnea was in 1979 [4]. Debusse and Cartright provided an oral load of theophylline to a 9 ½ week-old ex-29-week premature infant suffering from RSV-induced apnea and noted a favorable response after several hours. In 1992 Johnston and Kuzemko reported cessation of apnea within 30 seconds after 5mg/kg intravenous aminophylline for both of two apneic infants, one infected with RSV one with echovirus 2 [5]. Most recently Tobias reviewed 7 cases of RSV-induced apnea treated with 10mg/kg intravenous caffeine benzoate at his institution [6]. While individual responses are not reported, as a group in the 3 hours following caffeine the number of episodes of apnea ranged from 0-2 per infant compared to 7-12 episodes per infant per hour during the 2 to 3 hours before caffeine. In all 10 cases authors report that intubation for apnea was averted by the therapy.

We report a case of RSV-induced apnea for which the administration of caffeine failed to prevent the need to intubate and provide mechanical ventilation. This has not previously been reported. The appropriate dose of caffeine for

\*Address correspondence to this author at the Department of Emergency Medicine, East Tennessee Children's Hospital, 7150 Sir Arthur Way, Knoxville, TN 37919, USA; Tel: 865-531-7223; Fax: 865-531-7223; E-mail: epappano@aol.com

respiratory virus induced apnea is not known. We provided a total of 10mg/kg of caffeine citrate, the lower end of the recommended loading dose for apnea of prematurity [7] and equivalent to about half the dose of caffeine base used by Tobias in his series [6]. It is possible that a larger dose of caffeine, or a different intravenous methylxanthine may have resulted in the desired effect. An alternative explanation is that our infant may have been affected too severely for caffeine to have been of benefit, as it was our patient suffered far more frequent apneic spells than any of the infants described by Tobias [6].

## CONCLUSION

To be an effective tool in the emergency department, the ideal respiratory stimulant for the treatment of RSV-induced apnea would be fast acting and efficacious even for those patients who are severely effected by the illness. Caffeine citrate, at least as delivered as a 10mg/kg loading dose, does not appear to satisfy this need. More clinical experience with these medications is necessary to optimize our understanding of their use for respiratory virus-associated apnea. Other medications and treatment modalities which deserve research attention for their potential use in this setting [2] include doxapram [8], diphenhydramine [9], anti-RSV immune globulin [10], and nebulized lidocaine [11].

## PROPRIETARY STATEMENT

The author has no proprietary interest, ownership, or financial interest in any products or services discussed in this manuscript.

## CASE REPORT

This case report describes the failure of caffeine to prevent the need to intubate an infant suffering from RSV-induced apnea. The author has once previously cared for a similar case that went unreported. It is important for those who care for infants to understand that caffeine may not work in all cases of respiratory virus-associated apnea. Publication bias may make this therapy appear to have greater

effectiveness then it actually has. Because the failure rate of this medication in this setting is not known research should be directed at other potential therapies as well.

## KEY POINTS

RSV-induced apnea, a form of respiratory virus-associated apnea, may require invasive respiratory support.

Methylxanthines have been used for respiratory virus-associated apnea to decrease the need to intubate an apneic infant.

The effectiveness of these medications is not known.

## REFERENCES

- [1] Bruhn FW, Mokrohisky ST, McIntosh K. Apnea associated with respiratory syncytial virus infection in young infants. *J Pediatr* 1977; 90(3): 382-6.
- [2] Pappano D, Bass E. Respiratory Virus-Associated Apnea. *Pediatr Emerg Med Rep* 2007; 12(1): 1-12.
- [3] Henderson-Smart DJ, Steer P. Methylxanthine treatment for apnea in preterm infants. *Cochrane Database Syst Rev* 2001; (3): CD000140.
- [4] DeBuse P, Cartwright D. Respiratory syncytial virus with apnoea treated with theophylline. *Med J Aust* 1979; 2(6): 307-8.
- [5] Johnston DM, Kuzemko JA. Virus-induced apnoea and theophylline. *Lancet* 1992; 340(8831): 1352.
- [6] Tobias JD. Caffeine in the treatment of apnea associated with respiratory syncytial virus infection in neonates and infants. *South Med J* 2000; 93(3): 294-6.
- [7] Robertson J, Shilkofski N, Eds. *The Harriet Lane Handbook*. Philadelphia, PA: Mosby; 2005.
- [8] Yost CS. A new look at the respiratory stimulant doxapram. *CNS Drug Rev* 2006; 12(3-4): 236-49.
- [9] Downs DH, Johnson K, Goding GS Jr. The effect of antihistamines on the laryngeal chemoreflex. *Laryngoscope* 1995; 105(8 Pt 1): 857-61.
- [10] Sabogal C, Auais A, Napchan G, *et al*. Effect of respiratory syncytial virus on apnea in weanling rats. *Pediatr Res* 2005; 57(6): 819-25.
- [11] McCulloch TM, Flint PW, Richardson MA, Bishop MJ. Lidocaine effects on the laryngeal chemoreflex, mechanoreflex, and afferent electrical stimulation reflex. *Ann Otol Rhinol Laryngol* 1992; 101(7): 583-9.

Received: October 01, 2009

Revised: January 15, 2010

Accepted: January 16, 2010

© Dante Allen Pappano; Licensee *Bentham Open*.

This is an open access article licensed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0/>) which permits unrestricted, non-commercial use, distribution and reproduction in any medium, provided the work is properly cited.