Caffeine in the Treatment of Apnea Associated With Respiratory Syncytial Virus Infection in Neonates and Infants

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ABSTRACT

Background. The xanthines have been shown to be effective in the treatment of apnea of prematurity. Limited reports are available in the literature concerning the use of these agents with apnea related to respiratory syncytial virus (RSV) infections.

Methods. A retrospective review was done to identify infants who received caffeine therapy for RSV-associated apnea. The number of apneic episodes during the 2 hours before the use of caffeine and the number of apneic episodes after the administration of caffeine were compared using a Wilcoxon nonparametric test.

Results. The 7 infants ranged in age from 14 to 64 days and in weight from 2.8 to 4.4 kg. The number of apneic episodes per hour for the 2 to 3 hours before the administration of caffeine ranged from 7 to 12, and the number of episodes during the 3 hours after the administration of the first dose of caffeine ranged from 0 to 2. The apneic episodes after caffeine responded to external stimulation. Apnea recurred in 3 infants, 18 to 24 hours after the first dose of caffeine. These infants received a second dose of caffeine (5 mg/kg).

Conclusions. Caffeine should be considered in the treatment of apnea related to RSV infections in neonates and infants.

THE ASSOCIATION between RSV and central apnea has been well documented.[1-3] Despite the recognized association of apnea and RSV infections, the mechanisms responsible remain obscure. Treatment options for apnea include external stimulation, supplemental oxygen, continuous positive airway pressure, pharmacologic management with xanthine derivatives such as theophylline or caffeine, and mechanical ventilation. Despite the widespread use of xanthines in the treatment of apnea of prematurity,[4-6] I am unaware of previous reports concerning the use of caffeine for the treatment of RSV-associated apnea. This manuscript retrospectively reviews the use of intravenous caffeine to treat apnea associated with RSV infection in seven neonates and infants.

METHODS

The records of infants who received caffeine to treat RSV-associated apnea were retrospectively reviewed. Demographic data obtained were current age, gestational age, weight, underlying medical problems including chronic lung disease, previous history of apnea during the neonatal period, and current drug therapy. Treatment measures before the use of caffeine were noted. The initial dose and subsequent doses of caffeine were noted. The number of apneic episodes during the 2 hours before the use of caffeine and the number of apneic episodes after the administration of caffeine were compared using a Wilcoxon nonparametric test for pairs. The data are presented as the mean ± SD.

RESULTS

The study population included 7 neonates and infants admitted to the pediatric intensive care unit for the treatment of apnea. Demographic data and patient characteristics are summarized in the Table. All infants received an initial dose of caffeine benzoate (10 mg/kg of caffeine base) intravenously over 30 minutes. The number of apneic episodes per hour for the 2 to 3 hours before the administration of caffeine ranged from 7 to 12 (9.7 ± 2.6), whereas the number of apneic episodes during the 3 hours after the administration of the first dose of caffeine ranged from 0 to 2 (0.4 ± 0.8, $P = .0078$). The apneic episodes that occurred

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TABLE. Patient Demographics and Characteristics

No. of infants	7
No. with respiratory syncytial virus infection	7/7
Age (at presentation)	14-64 days (40.4 ± 17.2)
Weight (at presentation)	2.8-4.4 kg (3.5 ± 0.5)
Gestational age	32-38 weeks (34 ± 2.2)
History of apnea as neonate	2/7
Previous treatment of apnea	0/7
Home apnea monitor	0/7
Chronic lung disease	2/7
Home oxygen therapy	2/7 (both at 0.2 L/min)
Treatment preceding caffeine therapy*	
Oxygen	7/7 (F_1O_2 0.4-0.6)
Nasal CPAP†	3/7
Bag/mask ventilation	3/7
Attempted endotracheal intubation**	2/7

*These treatments had all proved ineffective and apnea had persisted.

†CPAP = Continuous positive airway pressure.

**Before transfer to the pediatric intensive care unit, endotracheal intubation had been attempted for severe apnea in 2 infants, but both became vigorous during laryngoscopy and the attempts were aborted.

after caffeine therapy responded to external stimulation. None of the infants required endotracheal intubation for apnea. From the time of 2 to 18 hours after the caffeine dose, no infant had episodes of apnea or bradycardia. Three infants had recurrence of apnea, 18 to 24 hours after the first dose of caffeine. These infants received a second dose of caffeine (5 mg/kg). One infant required a third dose of caffeine (2.5 mg/kg) on day 3. Two infants subsequently required endotracheal intubation and mechanical ventilation on days 4 and 5 for treatment of RSV pneumonia unrelated to apnea. All infants were observed on the infant ward and with an apnea monitor for at least 5 to 7 days after the last dose of caffeine and were discharged home in good condition. All infants are doing well without further episodes of apnea.

DISCUSSION

Despite reports concerning the efficacy of xanthines in the treatment of apnea of prematurity, limited information is available concerning its use for apnea related to viral infections. A literature search revealed only two reports, both of which were letters to the editor,[7,8] concerning the use of theophylline for this purpose. No reports described the use of caffeine for the treatment of RSV-associated apnea. DeBuse and Cartwright[7] reported the successful use of theophylline in an infant with apnea and RSV infection. Their dosing regimen included an initial dose of 2 mg/kg, which proved ineffective, and was followed in 2 hours by a second dose of 4 mg/kg. After the second dose, no further episodes of apnea occurred. The theophylline (4 mg/kg) was administered every 6 hours for 24 hours. The dosage was then decreased to 1 mg/kg every 6 hours. A similar letter from Johnston and Kuzemko[8] describes the successful use of theophylline in two infants with apnea, one case due to RSV infection and the other due to echovirus type II. The authors administered an initial intravenous dose of aminophylline (5 mg/kg) followed by oral theophylline for 5 to 7 days.

Although the most common indication for the xanthines in the treatment of apnea remains apnea of prematurity, these agents have been shown to be effective in the control of central ventilation abnormalities related to other causes, including viral-associated problems,[7,8] congenital central hypoventilation syndrome,[9] and apnea after general anesthesia in former preterm infants.[10,11] Welborn et al[11] randomized 32 former preterm infants undergoing general anesthesia for inguinal herniorrhaphy repair to receive either placebo or intravenous caffeine 10 mg/kg after the induction of general anesthesia. None of the infants given caffeine had postoperative apnea, whereas 13 of 16 infants who received placebo had apnea.

Options for xanthine use include aminophylline, theophylline, and caffeine. These agents can be given orally or intravenously. Because of the potential benefit of achieving rapid serum concentrations, the intravenous route was chosen for the current group of patients. Caffeine was chosen on the basis of several factors, including my personal experience with its use during the perioperative period as described by Welborn et al,[10,11] as well as its potential pharmacokinetic advantages, including a longer half-life that allows for once-a-day dosing.[12,13] If aminophylline or theophylline is used, these agents are generally administered three or four times a day. Although the efficacy of theophylline preparations in most studies has been shown to be equivalent to that of caffeine in the treatment of apnea of prematurity,[13,14] the previously mentioned pharmacokinetic differences have prompted some investigators to suggest that caffeine remains the drug of choice for this indication.[13,14] Larsen et al[14] compared the efficacy of caffeine and aminophylline in the treatment of apnea of prematurity. Although the efficacy of the two agents was similar, they noted fewer

cardiovascular and gastrointestinal side effects with caffeine. Also, Davis et al[5] showed that caffeine was effective in 11 neonates whose apnea had been unresponsive to therapeutic theophylline levels.

Although significant, life-threatening adverse effects such as ventricular tachycardia have been reported with the methylxanthines, the effects are generally mild. They include tachycardia and increased cardiac output,[15] feeding intolerance, and direct gastrointestinal irritant effects.[17] Romagnoli et al[16] showed that the efficacy in preventing apnea was similar with oral maintenance doses of caffeine of 2.5 mg/kg versus 5 mg/kg, with a lower incidence of cardiovascular and gastrointestinal side effects with the lower dose.

In conclusion, this review of 7 infants with RSV-associated apnea showed that caffeine was effective in decreasing the occurrence of apnea and avoiding the need for mechanical ventilation. The current dosing regimens were extrapolated from the literature on apnea of prematurity and included a loading dose of 10 mg/kg (caffeine base) followed in 18 to 24 hours by additional doses of 5 mg/kg as needed. In this report, only caffeine benzoate was used, though caffeine is also available as caffeine citrate. Because RSV-associated apnea is usually of short duration, maintenance doses were not routinely started, but rather additional doses were given as needed. Since the therapy was short term (1 to 3 doses), serum concentrations were not measured. All infants were subsequently monitored for 5 to 7 days after the administration of caffeine. Although no infant in the current population was sent home with an apnea monitor, each case should be individualized, and infants who have ongoing apnea may require further investigation or home monitoring.

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