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Anesthesiology
68:796–798, 1988

The Use of Caffeine in the Control of Post-anesthetic Apnea in Former Premature Infants

LEILA G. WELBORN, M.D.,* HERNANDO DE SOTO, M.D.,† RAAFAT S. HANNALLAH, M.D.,‡ ROBERT FINK, M.D.,§ URS E. RUTTIMANN, PH.D.,¶ ROGER BOECKX, PH.D.**

Premature infants undergoing general anesthesia within the first few months of life are prone to develop apnea and/or bradycardia in the postoperative period.[1–5] The incidence of perioperative apneic episodes is inversely correlated with gestational age and weight.[1–6]

Methylxanthines have been widely used by neonatologists for the management of apnea of prematurity. Although therapeutic blood concentrations and pharmacokinetic profiles in premature infants have been established for both theophylline[7] and caffeine,[8,10] caffeine has the distinct advantage of being a more potent central nervous system and respiratory stimulant, and possesses fewer cardiac side effects than does theophylline.[11]

We designed a prospective, double blind, randomized study to examine the possible effectiveness of caffeine in the prevention of apnea following anesthesia and surgery in premature infants.

* Associate Professor of Anesthesiology.
† Fellow in Anesthesiology. Currently Assistant Professor of Anesthesiology, Medical College of Georgia, Augusta, Georgia.
‡ Associate Professor of Anesthesiology.
§ Associate Professor of Pulmonary Medicine.
¶ Research Associate Professor.
** Professor of Laboratory Medicine.

Received from the Departments of Anesthesiology, Pulmonary Medicine, Laboratory Medicine, and Child Health and Development, Children's Hospital National Medical Center and George Washington University, Washington, DC. Accepted for publication December 8, 1987. Presented in part at the Annual Meeting of the American Society of Anesthesiologists, Atlanta, Georgia, October, 1987.

Address reprint requests to Dr. Welborn: Department of Anesthesiology, Children's Hospital National Medical Center, 111 Michigan Avenue, N.W., Washington, DC 20010.

Key words: Anesthesia: pediatric. Complications: apnea; periodic breathing. Pharmacology: caffeine.

MATERIALS AND METHODS

Informed consent and institutional approval for the study were obtained. Twenty otherwise healthy (ASA PS 1 or 2) premature infants born at ≤37 weeks gestational age undergoing general anesthesia for inguinal hernia repair were studied. All were ≤44 weeks conceptual age at the time of operation (range 35–44 weeks). Infants with pre-existing cardiac, neurologic, or metabolic diseases, as well as those already receiving methylxanthines, were not included.

No preoperative medication was used. General endotracheal inhaled anesthesia supplemented with neuromuscular blockade was used in all cases. Heart rate and sounds, arterial blood pressure, electrocardiogram, temperature, oxygen saturation, and end-tidal CO_2 were monitored. No barbiturates or narcotics were administered in the perioperative period.

Infants were randomly divided into two groups. Group 1 patients received iv caffeine 5 mg/kg injected over a 2-min period. The drug was administered immediately following induction of anesthesia, so that its peak effect would be evident at the end of surgery. Patients in group 2 received iv saline and served as controls. The solutions were supplied by the hospital pharmacy in a double-blinded fashion. At the completion of surgery, the trachea was extubated in the operating room when the patient was fully awake, and a venous blood sample was drawn to measure caffeine level using the Emit® caffeine assay.[12] The pattern of respiration and heart rate were continuously monitored and recorded[13] using an impedence pneumograph (Healthdyne 16000®) with an Oxford® recorder for at least 12 h postoperatively. The recorded data were analyzed by a pulmonologist for evidence of apnea, periodic breath-

ing, and/or bradycardia in all patients. The pulmonologist was blinded with regard to which group the patients were assigned.

Brief apnea was defined as a respiratory pause less than 15 s. Prolonged or life-threatening apnea was a respiratory pause 15 s or longer, or less than 15 s if accompanied by bradycardia. Bradycardia was indicated by heart rate less than 100 bpm for at least 5 s, and periodic breathing by three or more periods of apnea of 3–15 s, separated by less than 20 s of normal respiration. The incidence of these events in the two groups were compared using Fisher's exact test. Results were considered significant if P values were less than 0.05.

Results

Twenty infants were studied. Nine received caffeine (group 1), and eleven received saline and served as controls (group 2).

Although there were no significant differences between the two groups in gestational or conceptual ages (table 1), the incidence of prior history of apnea in the caffeine group was significantly higher than in the control group ($P < 0.001$).

The incidence of postoperative apnea and periodic breathing in the two groups is also shown in table 1. None of the patients who received caffeine developed prolonged apnea or periodic breathing, although eight of them had a prior history of apnea. Eight infants, however, experienced brief episodes of apnea lasting less than 15 s. In the control group, eight of the patients developed prolonged apnea and bradycardia 4–6 h postoperatively. Two of these developed postoperative periodic breathing as well. None of the patients in either group required tracheal intubation or controlled ventilation postoperatively. The difference in the incidence of prolonged apnea with bradycardia between the two groups is statistically significant ($P < 0.002$).

TABLE 1. Age, Number of Infants with Apnea, Periodic Breathing (PB), and Postoperative Ventilation in Groups 1 and 2

	Group 1 Caffeine (n = 9)	Group 2 Control (n = 11)
Gestational age (weeks)		
Mean ± SD	29.8 ± 3	31.6 ± 3
Range	25–35	26–36
Conceptual age (weeks)		
Mean ± SD	40.6 ± 2	40.6 ± 2
Range	38–44	35–44
History of preop. apnea	8 (89%)*	5 (45%)
Postop. apnea 15 s (no bradycardia)	8 (89%)	1 (9%)
Postop. prolonged apnea with bradycardia	None†	8 (73%)
Postop. PB > 1%	None	2 (18%)
Postop. intubation or ventilation	None	None
Postop. caffeine level mg/L (range)	5–8.6	Zero

Fisher's exact test.
* $P < 0.001$.
† $P < 0.002$.

Discussion

Premature infants are at a significant operative risk, mainly related to the presence of immature organ systems.[1-4] Although advanced knowledge and modern techniques have increased the chance of survival for premature infants in their first few months of life, apnea and/or bradycardia still pose the greatest risk following anesthesia and surgery in these infants.[1-5]

In a retrospective chart review of otherwise healthy infants undergoing herniorrhaphy, Steward[3] reported that preterm infants who require surgery in the first months of life are more likely than full-term infants to develop apnea and other respiratory complications during and following anesthesia.

In a prospective study of 41 premature infants, Liu *et al.*[2] found that the 18 patients who required postoperative ventilation were all less than 41 weeks conceptual age. Infants greater than 46 weeks conceptual age did not develop prolonged apnea postoperatively. Liu's study, however, included infants undergoing neurosurgical, as well as thoracic surgery, procedures. Narcotics and/or barbiturates were given to some patients.

Kurth *et al.*[4] observed a 37% incidence of post-anesthetic prolonged apnea in infants 32–55 weeks conceptual age, and that the initial episode of apnea may occur as late as 12 h following anesthesia. This study also included infants undergoing complex surgical procedures, such as laparotomy for necrotizing enterocolitis and ventriculo-peritoneal shunts.

In a previous study of otherwise healthy premature infants undergoing elective hernia repair,[1] we found that, although none of the patients developed prolonged apnea or required postoperative endotracheal intubation or mechanical ventilation, periodic breathing was noted in 14 of 38 (37%) of preterm infants whose conceptual age was ≤44 weeks. In the present study, however, using identical selection criteria, eight of 11 infants in the control group developed postoperative apnea and bradycardia. Since both studies were performed more than 3 yr apart, it is impossible to compare these results. Subtle and unknown differences in the overall care and management of these patients may have occurred during that period. This finding emphasizes the importance of using randomization and including a concurrent control group in all such studies.

In 1973, Kuzemko and Paala[15] first reported that

aminophylline significantly decreased the frequency of apneic episodes in newborns. Since then, a number of other authors have reported successful treatment of neonatal apnea with various theophylline preparations.[16] Theophylline increases ventilatory response to CO_2 and decreases periodic breathing.[17] Aranda *et al.*[8-10] described similar findings with caffeine, and further suggested that caffeine may be a more appropriate agent for treating neonatal apnea, since it has less side effects than theophylline.

In adults and children, theophylline undergoes extensive demethylation and oxidation.[18] In contrast, demethylation and oxidation pathways are markedly deficient in neonates, who, instead, tend to methylate theophylline to produce caffeine.[19]

The elimination rate of all methylxanthines is significantly decreased in the newborn infant. In adults, the half-lives of caffeine and theophylline are 6 h[20] and 9 h[21] respectively; but, in newborns, the elimination half-lives are prolonged (caffeine 37–231 h, theophylline 12–64 h). In a study of the maturation of caffeine elimination, Aranda *et al.*[20] found that the caffeine elimination half-life decreases with age and reaches adult values by about 4 months of age.

We chose to use caffeine over theophylline in this study because it is a more potent central nervous system and respiratory stimulant,[11] and possesses fewer cardiac side effects than does theophylline. Other advantages of caffeine include wider therapeutic index, ease of administration, less fluctuation in plasma concentrations, less need for therapeutic drug monitoring, and fewer peripheral effects.[22] Although the dose of caffeine that we selected (5 mg/kg) has been shown to be effective in other studies,[23] the resultant caffeine level (5–8.6 mg/l) was on the low side of the ideal therapeutic range (8–20 mg/l). It is likely that a higher dose of caffeine (10 mg/kg), which has been recommended by other authors,[8] would result in a caffeine blood level that is well within the therapeutic range without increased incidence of side effects.

Our data suggest that caffeine is a useful drug in the prevention of postanesthetic life-threatening apnea in premature infants. Although a significant reduction in the severity of apnea was noted in our study, complete abolition of all types of apnea did not occur in all infants following caffeine treatment. It is, therefore, still recommended that, until more extensive experience is available, all infants at risk be monitored for apnea and/or bradycardia following general anesthesia.

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