Caffeine Citrate for the Prevention of Apnea Associated With Alprostadil Infusions

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OBJECTIVE To evaluate the incidence of apnea and requirement for positive pressure ventilation in patients who received caffeine for prevention while receiving alprostadil compared with those who did not receive caffeine.

METHODS This was a single-center, retrospective study of patients who received alprostadil over a 7-year time frame. Patients were divided into 2 groups based on whether they received caffeine for prevention of apnea while receiving alprostadil. The incidence of apnea and requirements for positive pressure ventilation were recorded.

RESULTS A total of 64 patients who received alprostadil were included for review. Thirty-two patients received caffeine for the prevention of apnea, and 32 patients received alprostadil only. Alprostadil doses were similar between the 2 groups (0.04–0.05 mcg/kg/min). Seven patients had a documented apneic event; 3 in the group given caffeine and 4 in the control group. One patient in each group required intubation because of apnea. All patients with documented apnea were on low-dose alprostadil therapy (<0.05 mcg/kg/min). Three patients had apnea after dose reductions had been made. Six out of the seven patients experienced apnea within the first 24 hours after the infusion. Only 1 patient experienced multiple apneic events.

CONCLUSIONS In this small sample, there was no difference in incidence of apnea between patients on low-dose alprostadil who received caffeine for prevention and those who did not. Despite the use of low-dose alprostadil therapy and dose reductions, the incidence of apnea remains low, and most patients did not have repeated apneic events or require intubation.

ABBREVIATIONS cPAP, continuous positive airway pressure; EMR, electronic medical record; IQR, interquartile range; IV, intravenous

KEYWORDS alprostadil; apnea; caffeine citrate; congenital heart disease; neonate

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Introduction

Dose-related adverse effects have frequently been reported with the use of alprostadil in infants with ductal-dependent congenital heart disease. Of these, 1 of the most clinically significant adverse effects is the development of apnea. Apneic events often lead to modification of alprostadil infusions, and repeated apneic events may lead to use of continuous positive airway pressure (cPAP) or intubation.¹ Early studies describing the use of alprostadil report an incidence of apnea of up to 12%, with events occurring more frequently on doses above 0.05 mcg/kg/min.^{2–5} In current practice, most institutions initiate alprostadil at a dose of 0.05 mcg/kg/min, with subsequent titrations to maintain an open ductus. Downward titration once the ductus has opened allows the lowest effective dose to be used to minimize adverse events. Studies have shown that the incidence of apnea is lowest on doses of 0.01 mcg/kg/min or less.^{6,7}

Aminophylline has been used to prevent apnea in in-

fants receiving alprostadil infusions. Lim et al⁸ reported that infants who received a bolus dose of aminophylline prior to initiation of alprostadil followed by maintenance dosing were less likely to experience apneic events (2 infants vs 11 infants, $p = 0.006$) or require intubation (0 infants vs 6 infants, $p = 0.02$) compared with those who received placebo. Caffeine citrate (caffeine), currently the preferred methylxanthine for apnea of prematurity, is used in some institutions to prevent or treat apnea in infants receiving alprostadil infusions; however, this use has not been previously described.⁹ The purpose of this study was to evaluate the incidence of apnea and use of positive pressure ventilation in patients receiving alprostadil who received caffeine for prevention of apnea compared with patients receiving alprostadil who did not receive caffeine.

Materials and Methods

Information was collected using a retrospective chart review of the electronic medical record (EMR). Patients

Figure 1. Flow diagram of study participant inclusion.

were included if they received alprostadil between July 1, 2011, and June 30, 2018. Patients were excluded if they were born at less than 28 weeks gestational age, had documented apnea or required respiratory support (including supplemental oxygen, cPAP, or intubation) prior to initiation of alprostadil, or if treatment was withdrawn as part of a redirection of care. Infants who received caffeine citrate were excluded if they had documented apnea or required respiratory support before receiving caffeine citrate.

Patient characteristics collected included weight, gestational age, gender, primary congenital heart defect, and length of alprostadil therapy. Additional data collected included titrations of the alprostadil dose and duration of the alprostadil infusion, caffeine dose and route of administration, documented apnea (defined as an apneic event lasting longer than 20 seconds as reported by the bedside nurse in a flowsheet in the EMR), and requirements for additional respiratory support indicating a change from initiation of alprostadil. Descriptive statistics were used to describe and evaluate the data. Continuous parameters were compared using the 2-tailed independent Student *t* test. A *p* value of < 0.05 was considered statistically significant. Microsoft Excel 2013 was used for descriptive statistics and *p* value calculation.

Results

During the study period, 397 infants received alprostadil and were included for initial review. Of those,

115 patients received both alprostadil and caffeine. In the group that received caffeine, 83 patients were excluded (Figure 1). Fifty patients required respiratory support prior to the initiation of alprostadil. Of these, 19 were intubated at an outside hospital upon initiation of treatment, 14 were intubated by the Neonatal Emergency Transport Service for transfer to our institution, and 17 required respiratory support at our institution. Ultimately, 32 patients who received caffeine for apnea prevention were included in the review. Thirty-two patients were selected using a random sequence from the group receiving alprostadil who were not given caffeine to serve as the control group.

Demographic information was similar between the 2 groups, and there were no statistically significant differences regarding weight, gestational age, or sex (Table 1). Hypoplastic left heart syndrome was the most commonly diagnosed heart defect in both groups, followed by transposition of the great arteries in the caffeine group and coarctation of the aorta in the control group. The median treatment duration for both groups was 7 days (IQR 4–13.75 in caffeine group, 4.75–9 in control group).

Alprostadil infusion rates were also similar between the 2 groups at all points of assessment (Table 2). The majority of patients received an initial dose of 0.04 to 0.05 mcg/kg/min consistent with current dosing recommendations.¹⁰ There were more rate changes in the group that received caffeine (2.1 ± 1.6 in caffeine group vs 1.3 ± 1.1 in control group, *p* = 0.038). This could indicate that this group was being titrated more frequently for efficacy or to prevent adverse effects.

Table 1. Patient Demographics

Characteristic*	Caffeine Citrate (n = 32)	Control Group (n = 32)
Weight, kg, mean $\pm$ SD	2.98 $\pm$ 0.6	3.06 $\pm$ 0.5
Gestational age, mean $\pm$ SD	38 wk, 1 day $\pm$ 12 days	38 wk, 5 days $\pm$ 9 days
Sex, male, n (%)	20 (63)	20 (63)
Congenital heart defect, n (%)		
Hypoplastic left heart syndrome	9 (28)	10 (31)
Coarctation of the aorta	4 (13)	8 (25)
Other	4 (13)	6 (19)
Transposition of the great arteries	7 (22)	1 (3)
Hypoplastic right heart	4 (13)	1 (3)
Double outlet right ventricle	1 (3)	1 (3)
Pulmonary atresia	1 (3)	2 (6)
Tetralogy of Fallot	2 (6)	1 (3)
Length of therapy, days, median (IQR)	7 (4–13.75)	7 (4.75–9)

* All comparisons were not statistically significant.

Nearly all of the patients in the caffeine group received an IV loading dose (97%), with 91% given a dose of 20 mg/kg (Table 3). Loading doses were administered at the time alprostadil was initiated. Nineteen patients (59%) were started on maintenance doses of caffeine following their loading dose, with a median of 3 maintenance doses received per patient (IQR 1–6.5).

Only 7 patients (11%) had a documented apneic event. Three patients in the caffeine group, and 4 in the control group. One patient in each group required intubation because of apnea. Alprostadil titrations were reviewed for each of the patients who experienced apnea (Figure 2). None of these patients were on a dose higher than 0.05 mcg/kg/min, and 6 out of the 7 experienced apnea on a dose less than or equal to 0.03 mcg/kg/min. Three patients had their apneic event after dose reductions had been made. Six out of the seven patients experienced apnea within the first 24 hours of the infusion. Of the 3 patients in the caffeine group, patients 1 and 3 received a loading dose of 20 mg/kg, whereas patient 2 received a loading dose of 10 mg/kg. Patients 1 and 2 were continued on maintenance caffeine, and patient 3 was intubated because of apnea.

Discussion

Apnea is a well-known adverse effect associated with the use of alprostadil, with a reported incidence of up to 12%.³ This is a dose-related effect, with a higher incidence of apnea associated with alprostadil doses greater than 0.05 mcg/kg/min. Repeated events may lead to further reductions in the alprostadil dose or the addition of assisted ventilation therapy. The incidence of apnea in our study was 11%, consistent with previous reports, despite the use of low-dose therapy (<0.05 mcg/kg/min). Three patients experienced apnea even after dose reductions were made. The lowest alprostadil dose necessary to maintain an open ductus arteriosus should be used, but practitioners should be aware that apneic events might still occur in susceptible infants.

Caffeine did not appear to decrease the rate of apnea or requirement for assisted ventilation therapy in this study. However, the group that received caffeine for prevention of apnea made up a small subset of the overall population. Of the 397 patients who received alprostadil, only 115 patients (29%) also received caf-

Table 2. Alprostadil Dosing

	Caffeine Citrate (n = 32)	Control Group (n = 32)	p value
Dose, mcg/kg/min, mean $\pm$ SD			
Initiation	0.041 $\pm$ 0.011	0.038 $\pm$ 0.012	0.395
Maximum	0.047 $\pm$ 0.019	0.043 $\pm$ 0.019	0.450
Minimum	0.02 $\pm$ 0.012	0.02 $\pm$ 0.01	0.921
Discontinuation	0.028 $\pm$ 0.018	0.024 $\pm$ 0.011	0.288
Number of dose changes, mean $\pm$ SD	2.1 $\pm$ 1.6	1.3 $\pm$ 1.1	0.038

Table 3. Caffeine Citrate Dosing

	Caffeine Citrate (n = 32)
Route for loading dose, n (%)	
IV	31 (97)
Orally	1 (3)
Loading dose, mg/kg, n (%)	
20	29 (91)
15	1 (3)
10	2 (6)
Number of patients receiving maintenance therapy, n (%)	19 (59)
Number of maintenance doses administered per patient, median (IQR)	3 (1–6.5)

feine. Of these 115 patients, only 32 patients (28%) received caffeine for prevention of apnea. At our institution, caffeine was initiated at the discretion of the attending physician. A larger sample size may have shown a difference between the 2 groups, however with only 32 patients who received caffeine citrate for apnea prevention over a 7-year period, it is unlikely that single center would be able to achieve an adequate sample size to provide the necessary numbers to determine a statistically significant difference. Caffeine is commonly used as the treatment of apnea, and 26 infants were excluded from this analysis because they were receiving caffeine as treatment for apnea rather than for prevention.

Infants may be electively intubated at the start of an alprostadil infusion when they require transportation to another institution for surgical repair of their cardiac defect. In our study, 14 patients were electively intubated in preparation for transfer to our institution and 19 were electively intubated by staff at an outside hospital at the time of initiation of alprostadil. In a previous study by Carmo et al,¹⁹ the authors suggested that infants receiving low-dose alprostadil during transport might not require mechanical ventilation. This subpopulation of patients may benefit from a preventive dose of caffeine citrate for transport as an additional safeguard against the need for mechanical ventilation.

Our study is limited by its retrospective design and small sample size. The retrospective nature of this study relies on appropriate documentation of apnea in the EMR. Using documentation in the EMR flowsheet was the most objective way to capture apneic events at our institution. It is possible that patients might have experienced an apneic event that was not appropriately documented in this flowsheet. There were also a large number of patients excluded from this study, the majority of which received respiratory support prior to initiation of alprostadil. It could be argued that only patients who received positive pressure ventilation before initiation should have been excluded because these patients were receiving treatment for apnea. Patients who received supplemental oxygen were also

excluded to avoid confounding the results by including patients with underlying respiratory distress prior to starting alprostadil. If further investigation is attempted to evaluate the efficacy of caffeine in preventing apnea in this setting, a multicenter prospective study will likely be needed to achieve the necessary sample size.

Conclusions

This analysis did not show a difference in the incidence of alprostadil-associated apnea in patients who received caffeine for prevention compared with those who did not. Analysis of our sample population, however, did show that even with initiation of low-dose alprostadil therapy or dose reduction, the incidence of apnea has not declined from that reported in studies dating from the initial approval of the drug in the United States. Although the incidence of apnea was not reduced, it was notable that only 1 patient experienced multiple apneic events. The remaining patients had a single event, typically occurring within the first days of treatment. If caffeine can be of benefit, it will most likely be when it is given at the time of alprostadil initiation, with a loading dose followed by 1 or 2 maintenance doses.

ARTICLE INFORMATION

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Ethical Approval and Informed Consent The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and have been approved by Institutional

Figure 2. Alprostadil dose titrations and documented apnea for the patients with an apneic event.

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