Aminophylline for the Prevention of Apnea During Prostaglandin E_1 Infusion

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ABSTRACT. *Background.* **Apnea is associated with prostaglandin E_1 infusion (PGE_1) used in the palliation of ductal-dependent congenital heart lesions.**

Hypothesis. **Aminophylline is a central respiratory stimulant and will decrease the incidence of PGE_1-associated apnea and the need for intubation for apnea in infants with ductal-dependent congenital heart disease.**

Methods. **Informed consent was obtained for all patients. In a prospective, double-blinded, placebo-controlled study, newborn infants with ductal-dependent congenital heart disease were randomized to receive either aminophylline or placebo during initiation and maintenance of PGE_1, which was started at 0.01 μg/kg/min and increased to 0.03 μg/kg/min. Aminophylline was given as a bolus dose of 6 mg/kg before or during initiation of PGE_1, and continued at 2 mg/kg dose every 8 hours for 72 hours. Serum aminophylline levels were checked at 18 and 36 hours. The primary study endpoint was intubation for apnea, with a secondary endpoint of apnea, as defined as acute cessation of breathing with associated hypoxia and bradycardia.**

Results. **The study evaluated 42 infants. The 2 groups were similar for gestational age, weight, hematocrit, and use of sedation. In the aminophylline group, serum levels were 7.6 ± 1.2 μg/mL. No significant side effects of aminophylline were seen. Infants receiving aminophylline ($n = 21$) were less likely to have apnea (2 vs 11) or be intubated for apnea (0 vs 6). Length of postoperative stay and survival to discharge were similar between the 2 groups.**

Conclusions. **Aminophylline was effective for the prevention of apnea and intubation for apnea associated with PGE_1 in infants with ductal-dependent congenital heart disease.** *Pediatrics* **2003;112:e27–e29. URL: http://www.pediatrics.org/cgi/content/full/112/1/e27;** ***prostaglandin, apnea, congenital heart disease.***

ABBREVIATION. PGE_1, prostaglandin E_1 (infusion).

Prostaglandin E_1 (PGE_1) was first demonstrated by Coceani and Olley[1,2] in 1973 to be involved in the patency of the ductus arteriosus in lambs and later in cyanotic neonates; it has become an integral part of palliative therapy in pediatric cardiology. However, PGE_1 has concomitant dose-dependent side effects, of which respiratory depression has been noted to occur in 12% of neonates.[3] This PGE_1-associated respiratory depression can be potentiated by use of sedatives for procedures, and the resultant apnea can lead to intubation and mechanical ventilation.

Concurrent with the discovery of the utility of PGE_1 in ductal-dependent neonates, aminophylline was reported to be a useful respiratory stimulant in premature neonates with apnea of prematurity.[4] Aminophylline has been demonstrated to have an excellent safety profile at standard dosing regimens when used for apnea of prematurity.[5,6] However, to date, the use of aminophylline in neonates with ductal-dependent congenital heart disease has not been described. Aminophylline was chosen as a respiratory stimulant for this study because of its excellent safety profile and low cost of serum level assays. The purpose of this study was to determine the utility of aminophylline to prevent apnea and intubation for apnea in ductal-dependent neonates palliated with PGE_1.

METHODS

Consecutive neonates with either known or suspected ductal-dependent congenital heart disease were recruited, and informed written consent was obtained from their parents before study enrollment. Families of infants with prenatal diagnosis of suspected ductal-dependent congenital heart disease were approached for study recruitment at time of fetal echocardiogram. All infants enrolled were born at the study facility, and no infant was transported from outlying facilities before study enrollment. The study was approved by the University of Michigan Institutional Review Board. Infants were excluded if they had prior initiation of PGE_1, were already intubated, or were thought to have imminent cardiovascular compromise.

Infants were prospectively randomized in a double-blinded fashion to receive either aminophylline or placebo, and this study drug was administered either before or during initiation of PGE_1 therapy. Aminophylline was given as an initial 6 mg/kg intravenous bolus, followed by a 2 mg/kg intravenous dose every 8 hours for 72 hours, at which time the study drug was discontinued. The 72-hour study endpoint was chosen, as review of PGE_1 use in the preceding year at the University of Michigan found that apneic events occurred within the first 48 hours. Serum aminophylline levels were obtained at the 3rd and 6th dose, with goal levels between 6 and 12 μg/mL. Serum levels were drawn in both groups to complete the blinding. Aminophylline levels were reviewed by study investigators who were not involved in clinical assessment or management of the patient. PGE_1 was started at a dose of 0.01 μg/kg/min and increased on an hourly interval to a maximum of 0.03 μg/kg/min or higher if clinically indicated.

Infants were monitored by continuous cardiorespiratory telemetry in the cardiac intensive care unit or a monitored cardiac step-down unit. Infants were prospectively evaluated during the 72 hours of the study for the following factors: birth weight, gestational age, lowest hematocrit, maximum dose of prostaglan-

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TABLE 1. Demographic Data on Infants During Study*

	Aminophylline Group	Placebo Group	*P* Value
N	21	21	
Birth weight (kg)	3.2 ± 0.5 (range: 2.3–4.2)	3.0 ± 0.5 (range: 1.9–4.3)	NS
Gestational age (wk)	39 ± 1 (range: 35–40)	39 ± 1 (range: 37–40)	NS
Hematocrit (%)	40 ± 4 (range: 34–47)	40 ± 6 (range: 32–55)	NS
Fetal diagnosis	17	21	NS
Single ventricle	9	16	
Coarctation ± VSD	5	0	
Shone's Complex	1	0	
IAA/VSD	2	1	
TGA	2	3	
TOF	2	1	
Highest PGE dose			NS
0.03	19	20	
0.05	2	0	
0.1	0	1	
Aminophylline level (μg/mL)	7.6 ± 1.6	—	
Inotropic support	4	2	NS
Arterial pH	7.34 ± 0.01	7.33 ± 0.01	NS
Prophylactic antibiotics	6	3	NS
Irritability	3	0	NS
Length of stay (d)	25 ± 18	25 ± 16	NS
Survival to discharge	18	16	NS

VSD, indicates ventricular septal defect; IAA, interrupted aortic arch; TGA, transposition of the great arteries, TOF, Tetralogy of Fallo; NS, not significant.

* Length of stay includes postoperative recovery. Arterial pH is the lowest pH during the study period; inotropic support, prophylactic antibiotics, and irritability are preoperative occurrences. Statistical *P* values > .05 are not significant.

din infusion, use of sedation, need for fluid bolus or inotropic support to treat hypotension, arterial pH, need for prophylactic antibiotics, apnea, intubation, length of postoperative recovery, and survival to discharge. Apnea was defined as >15 seconds of no respiratory effort, or >10 seconds of no respiratory effort with associated bradycardia. Indications for intubation were apnea without resumption of spontaneous respiration, recurrent apnea, or hemodynamic instability. Infants were prospectively monitored for side effects of aminophylline therapy such as irritability, arrhythmias, or seizures.

For statistical comparison, unpaired Student *t* test and Fisher exact test were performed, with statistical significance defined as a *P* value <.05.

RESULTS

Consent for participating in the study was obtained for 44 of the 48 families approached; however, 2 infants were excluded as 1 required intubation at birth and the other inadvertently had PGE_1 started before the study drug. Forty-two infants completed the study, and their demographic data are depicted in Table 1. The infants were randomly assigned to either aminophylline or placebo groups, with 21 infants in each group. No infant in the aminophylline group had a toxic or subtherapeutic drug level (mean serum level, 7.6 ± 1.2 μg/mL). The 2 groups were similar in terms of their gestational age, birth weight, and hematocrit. The highest dose of PGE_1 used was also similar between the 2 groups, with 2 infants in the aminophylline group receiving 0.05 μg/kg/min of PGE_1 without apnea, and 1 infant in the placebo group receiving 0.1 μg/kg/min of PGE_1 with resultant apnea and need for intubation. The majority of infants had prenatal diagnoses of ductal-dependent congenital heart disease (Table 1). There was no significant difference between the 2 groups in terms of their cardiac diagnoses. The high percentage of patients with single ventricle anatomy (hypoplastic left heart syndrome, unbalanced atrioventricular septal defect, and double inlet left ventricle) reflects the referral bias at the University of Michigan. The 2 groups were similar in their need for preoperative inotropic support, lowest arterial pH, antibiotic therapy, irritability, length of hospitalization, and survival to discharge.

Table 2 demonstrates the use of sedation and the incidence of apnea in the 2 groups. The frequency of sedation and the medications used were similar between the 2 groups. Although no subject in the aminophylline group became apneic with sedation, 4 of the 6 infants receiving sedation in the placebo group became apneic immediately after sedation ($P = .02$ vs aminophylline group), and 3 required intubation. Overall, 2 infants in the aminophylline group became apneic, 1 subject 30 minutes after initiation of PGE_1, and the other 26 hours later. Neither infant required intubation for apnea. In the placebo group, 11 subjects became apneic ($P = .006$ vs aminophylline group). Apnea in this group occurred from as short as a few minutes after initiation of PGE_1 to as long as 40 hours later (Fig 1). Of these 11 infants with apnea, 6 required intubation for apnea ($P = .02$ vs aminophylline group). One infant in each group required intubation for hemodynamic instability without associated apnea. Analysis of the groups anatomic subtypes (Table 1) with respect to single ventricle anatomy as a risk factor for apnea found no significant relationship.

DISCUSSION

We are aware of no prior reports of the use of aminophylline for the prevention of apnea in infants with congenital heart disease on PGE_1 therapy. We found that aminophylline reduced the incidence of apnea, and the need for intubation, associated with PGE_1 therapy. Although apnea was strictly defined for the purposes of this study, its determination is still somewhat subjective, based on the individual clinician's or nurse's judgment. During this study,

TABLE 2. Incidence of Apnea, Intubation for Apnea, and Relation to Sedation

	Aminophylline Group	Placebo Group	*P* Value
N	21	21	
Sedation used	7	6	NS
Apneic	0	4	.02
Intubated	0	3	NS
No sedation	14	15	NS
Apneic	2	7	NS
Intubated	0	3	NS
Total			
Apneic episodes	2	11	.006
Time since PGE	range: 0.5–26 h	range: 0.1–40 h	
Intubation for apnea	0	6	.02
Non-apnea intubation	1	1	NS

NS indicates not significant.
* Statistical *P* values > .05 are not significant.

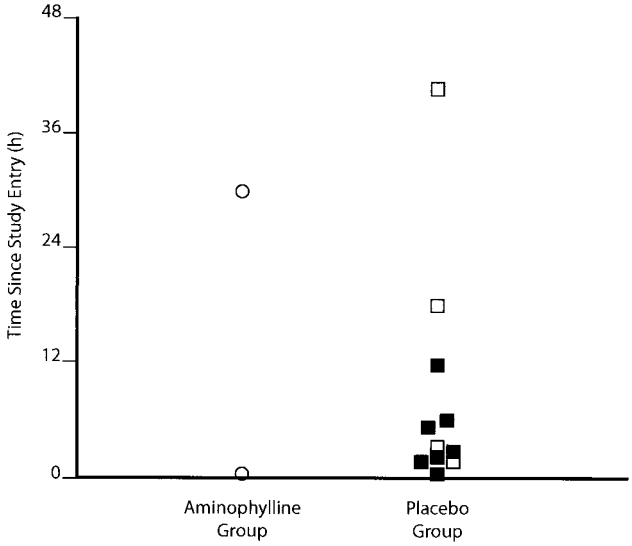

Fig 1. The time distribution of apneic events among infants in the 2 study groups is shown. The time to first apneic event is shown. Open circles represent apneic events without intubation in the aminophylline group. No infants in the aminophylline group required intubation for apnea. Open squares represent apneic events without intubation in the placebo group, and closed squares represent apneic events with subsequent intubation in the placebo group.

apnea was observed and recorded by either the attending cardiologist or the patient's nurse, and was based on the subjective determination of respiratory cessation. Therefore, the more clearly defined study endpoint of intubation for apnea was also used. Importantly, both study endpoints were significantly different between the 2 groups.

At the standard dose,[7] which was used in this study, aminophylline levels were within the desired range and no significant side effects were seen. Notably, 3 infants receiving aminophylline were noted by their nurses to be irritable, and this was not seen in any of the infants on placebo.

Apnea associated with PGE_1 is potentiated by concomitant use of sedatives.[8] In neonates with complex congenital heart disease, procedures necessitating sedation such as echocardiography or cardiac catheterization are frequent. In this study group, aminophylline reduced the incidence of apnea for those neonates receiving concomitant sedation. There was a trend for similar protection by aminophylline against intubation for apnea related to sedation.

Prospective evaluation for side effects of aminophylline therapy used in these study subjects revealed no incidence of seizures or arrhythmias or other significant side effects. Three infants in the aminophylline group were noted to have a minor side effect of increased irritability. This was neither a statistically significant difference from the placebo group, nor associated with elevated serum aminophylline levels. In contrast, the benefits of avoidance of intubation are substantial. Infants not needing intubation can be maintained in a lower intensity nursing unit at a lower cost, and are more accessible to parental interaction. Additionally, the potential complications related to intubation and mechanical ventilation are avoided.

CONCLUSIONS

This study demonstrated a protective benefit of aminophylline to prevent apnea and intubation for apnea associated with PGE_1 administration in neonates with ductal-dependent congenital heart disease.

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