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Cross-Over Trial of Treatment for Bradycardia Attributed to Gastroesophageal Reflux in Preterm Infants

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Abstract

Objective—To determine whether anti-reflux medications reduce bradycardia episodes attributed to clinically suspected gastroesophageal reflux (GER).

Study design—We conducted a masked trial comparing metoclopramide, 0.2 mg/kg/dose q 6 hours, and ranitidine, 2 mg/kg/dose q 8 hours, with saline placebo. Each infant served as his own control. Preterm infants having >3 bradycardia episodes per 2 days were eligible if the clinician intended to begin anti-reflux medications for bradycardia attributed to GER.

Results—The mean (SD) birth weight was 1238 (394) g and gestational age was 29 (3) weeks. Eighteen infants were enrolled at 35 (22) days of age. There were 4.6 (3.1) and 3.6 (2.7) bradycardia episodes per day in the drug and placebo periods, respectively. The mean difference (drug minus placebo) was 0.94 (95% CI, 0.04 to 1.95) ($P = .04$ by t test). There was a decrease in bradycardia episodes over time ($P < .001$ by nonparametric repeated-measures analysis of variance).

Conclusions—Anti-reflux medications did not reduce, and may have increased, bradycardia episodes in preterm infants with GER. Because there was an improvement of bradycardia episodes over time, unrelated to treatment, unmasked therapeutic trials of medications are likely to lead to misleading conclusions.

Gastroesophageal reflux (GER), commonly defined as the involuntary passage of gastric contents into the esophagus, has been reported to occur in more than 85% of preterm infants.¹ In some infants, GER can be severe enough to cause gastroesophageal reflux disease (GERD), which results in malnutrition, esophagitis, or respiratory disease.²

Claims have been made since the 1970s that apnea in preterm infants could be caused by GER.^{3,4} Apnea and bradycardia are very common in preterm infants; episodes frequently occur during and after feeding when GER is also frequent.⁵ Apnea and bradycardia occurring around feedings might be causally related to GER by the mechanism of refluxate traveling up the esophagus, blocking the airway, and causing an obstructive apnea and subsequent bradycardia. Another proposed mechanism to link these events is the laryngeal chemoreflex, which causes respiratory pauses and airway closure immediately after regurgitation to the upper airway.⁶ However, numerous observational studies have failed to demonstrate a temporal relationship between GER events and apnea.⁷

Common diagnostic approaches to GER include the upper gastrointestinal series (UGI) and the pH probe study. The UGI, which consists of radiographs taken after contrast material is infused or swallowed into the stomach, is neither sensitive nor specific for the diagnosis of GER.⁸ The pH probe study, which is the traditional gold standard for diagnosing GERD,

monitors the frequency and duration of acid reflux in the distal esophagus. However, the pH probe study has been criticized because preterm infants may have insufficient gastric acid to allow detection of acid reflux into the esophagus and because it may be performed in a brief time period (8 hours) in the neonatal intensive care unit (NICU). For these reasons, the North American Society of Pediatric Gastroenterology and Nutrition has recommended, for term infants, a “trial-limited medical therapy for GER... for determining if GER is causing a specific symptom.”⁸ However, a recent retrospective observational study by Kimball et al⁹ has shown that anti-reflux medications did not reduce the frequency of apnea in premature infants. A recent systematic review has determined that current literature is insufficient to either support or oppose the use of metoclopramide for GERD in infants.¹⁰ Despite the uncertainty in efficacy, adverse effects, and lack of evidence to support a causal relationship between GER and respiratory symptoms in preterm infants, prokinetic drugs (including metoclopramide) and H₂ receptor blocking agents (including ranitidine) are commonly used in preterm infants.¹¹ Approximately 25% of extremely low birth weight infants were discharged from the hospital with antireflux medications.¹²

There have been no prospective randomized trials of treatment for GERD in preterm infants with or without apnea and bradycardia. The purpose of our study was to determine whether anti-reflux medications reduce bradycardia attributed to the clinical diagnosis of GER.

Methods

Infants with bradycardia attributed to GER were prospectively recruited in the NICU at Children’s Memorial Hermann Hospital in Houston, Texas. The inclusion criteria were gestational age at birth <37 weeks and corrected gestational age at enrollment <44 weeks, a nasal clinical diagnosis of GER and bradycardia attributed to GER by clinicians, attending physician planning to begin anti-reflux medications, clinicians willing to maintain the same regimen for the 2-week study duration if the infant was on nasal continuous positive airway pressure (NCPAP) or methylxanthines, stable feeding regimen (per kilogram volume and feeding intervals), and at least 2 episodes of bradycardia in the past 3 days. Infants were excluded if they were receiving mechanical ventilation, had a history of congenital neurological defect, or if discharge was anticipated within 2 weeks. Approval for the study was obtained from the institutional review board at the University of Texas Health Science Center at Houston. Written informed parental or legal guardian consent was obtained for each patient before random assignment.

Intervention

A randomized, controlled, masked cross-over study was performed. Each infant was randomly assigned to 1 of 2 study groups. Study group assignment (order of medication and placebo administration) was determined by blocked random number generation. A research pharmacist assigned the study group for each patient at the time of enrollment. Investigators, clinicians, and parents were all blinded to the group assignment during the study period.

The “drug first” group received a 3-day course of anti-reflux medications followed by a 7-day course of placebo and then a 4-day course of anti-reflux medications. The “placebo first” group received a 3-day course of placebo followed by a 7-day course of anti-reflux medications and then a 4-day course of placebo. To allow for a period of washout between the drug regimens, outcomes were not assessed for the initial 24 hours of the second and third time periods.

Study medications were administered by nipple or orogastric tube. Metoclopramide was given as a dose of 0.2 mg/kg per dose every 6 hours. The first dose of metoclopramide was given with the first feeding after enrollment. Ranitidine was given as a dose of 2 mg/kg per dose every 8 hours. The first dose of ranitidine was given at the same time as the first dose of

metoclopramide. Intravenous preparations were used because they are clear and colorless. Saline placebos of the same volume and color were administered during the placebo periods.

At the end of the study period for each infant, after the study outcome data were summarized for the infant, the investigator contacted the pharmacist to ascertain the group assignment (order of medication and placebo administration) for the infant. The summary of bradycardia episodes during the drug and placebo periods was then reviewed with the infant's physician(s) so that the information about the infant could be used for subsequent clinical management. This approach for making therapeutic decisions in individual patients has been described as an "N of 1" trial.¹³

Outcomes

The primary study outcome was the number of bradycardia episodes per day during the drug and placebo periods for each infant. Bradycardia episodes were identified by telemetry and by nursing documentation. For the purposes of this study, a bradycardia event was defined as a heart rate (HR) <80 for >5 seconds. For each day of the study, 1 of the investigators reviewed the telemetry to identify and quantify bradycardia episodes that met the study definition. A heart rate ≤ 80 was identified by R-R intervals that averaged ≥ 0.75 seconds for a duration of 5 seconds. Any episode prompting intervention (stimulation or mask ventilation) by the nursing staff was included as a study bradycardia event, even if it did not meet the above telemetry criteria. Bradycardia events without intervention that were recorded in the nursing record but not verified by telemetry were not included as study bradycardia events.

Co-interventions

Clinicians were asked not to make changes in feeding regimens (continuous versus bolus, intragastric versus trans-pyloric) or in specific treatments for apnea/bradycardia (methylxanthines or NCPAP) during the 2-week study period. Increasing the volume of feedings and number of nipple feedings was allowed. Other aspects of medical management were left to the discretion of the clinicians managing the infants.

Sample Size

There were limited available published data from which to project the anticipated number of bradycardia episodes per day for infants enrolled in this study. A somewhat arbitrary original sample size of 34 was calculated to detect a mean decrease in bradycardia episodes of 2 per day between the placebo and drug periods with 80% power using a standard deviation of 4 for the difference.¹⁴ Because of slower than anticipated enrollment and a planned replacement of the NICU telemetry system, after 3½ years of enrollment, the study plan was revised to enroll as many infants as feasible before March 1, 2008.

Data Management and Statistical Analysis

Study data items were identified and defined in writing before enrollment began. Data were ascertained by chart and telemetry review by 1 of the investigators. For the primary comparison, a within-subject paired analysis (paired *t* test) was performed for the comparison of bradycardia episodes per day between the medication and placebo periods. The first and third observation periods for each infant were combined and compared with the second period. A nonparametric repeated-measures analysis of variance (ANOVA) was performed to evaluate the improvement of bradycardia episodes over time, independent of drug or placebo.

Results

Description of Study Participants

The study was conducted over 4 years, from May 2004 to February 2008. There were 56 infants who were eligible for the study. Eighteen infants were enrolled, and 17 infants completed the study, as detailed in Figure 1. The baseline characteristics of study infants are summarized in the Table. The reasons clinicians planned to start anti-reflux medications for study participants were as follows: bradycardia associated with feedings in 14 infants, bradycardia associated with emesis in 4 infants, and reflux behaviors in 4 infants. Five infants had a UGI study before enrollment, and all showed GER. Two infants had a pH probe before enrollment: 1 was mildly abnormal and 1 was normal. Fifteen infants had a head ultrasound before 1 month chronological age: 1 had a grade 1 intraventricular hemorrhage (IVH), 1 had a grade 2 IVH, and 13 had no IVH.

Outcomes

For the primary outcome, the mean number of bradycardia episodes per day in the combined drug periods was 4.6 (SD = 3.1), and the mean number of episodes per day in the combined placebo periods was 3.6 (SD = 2.7) (Figure 2). By paired *t* test, there was a statistically significant difference, with fewer episodes during the placebo periods. The mean difference (drug minus placebo) was 0.94 episodes per day, with a *P* value of .04. There was also a significant decrease in bradycardia episodes over time (*P* < .001) (Figure 3). There was a significant difference for each between-group comparison (*P* < .05). We also compared the episodes per day between drug and placebo using a more stringent definition of bradycardia (HR <80 for >10 seconds or prompting intervention). For this comparison, the mean difference (drug minus placebo) was 0.14 episodes per day, with a *P* value of .46. Although the difference was not statistically significant, the point estimate again favored the placebo periods.

The results of the individual subject assessments were as follows: 11 infants had fewer episodes during the placebo period(s). Two infants had the same number of bradycardic events during drug and placebo periods. Four infants had fewer episodes during the drug period(s) (Figure 4; available at www.jpeds.com). In each of these 4 cases, the assessment of the investigators and clinicians was that the effect of maturation (rather than drug effect) was the more likely explanation for the observed difference. There were no adverse effects attributed to the study drugs.

Discussion

In our study, the number of bradycardia episodes was lower in the placebo period(s) than during the drug period(s). This finding was unexpected; prior observational studies have not reported similar findings.^{7,8} Although this may represent a type 1 (false finding of difference) error, a potential explanation for a real effect could be a known side effect of ranitidine in adults: arrhythmias (tachycardia, bradycardia, atrioventricular block, premature ventricular beats).^{15,16}

Our study also shows that bradycardia events decreased over time, irrespective of anti-reflux medications or placebo. We chose to have 3 periods versus 2 so that the effect of the drugs would not be confounded by the effect of maturation in individual patients. The magnitude of this decrease over time (63% decrease within 2 weeks) was not anticipated. This finding makes it likely that any before-after comparison of treatment for bradycardia episodes in similar patients (35 weeks adjusted postmenstrual age on average) would lead to a false conclusion of efficacy.

We used a definition of bradycardia that was somewhat arbitrary but would be consistent for the purpose of the study. A heart rate of <80 is considered abnormal for a near-term infant. Choosing a duration of >5 seconds was somewhat arbitrary. There is no consensus in the literature regarding the duration that should be deemed abnormal and electronic monitors use different algorithms for averaging R-R intervals to calculate a heart rate. We included all bradycardia episodes that prompted nursing intervention because it seemed unlikely that these events would have resolved without intervention in <5 seconds.

The American Academy of Pediatrics Committee on Drugs state that “the off-label use of a drug should be based on sound scientific evidence, expert medical judgment, or published literature.”¹⁷ The scientific evidence supporting anti-reflux medication in preterm infants is lacking. Peter et al⁷ studied 19 infants with clinical evidence of apnea of prematurity (median birth gestational age of 30 weeks, median postmenstrual age at study of 33 weeks). A multiple intraluminal impedance technique was used to investigate whether there was a temporal relationship between GER and apnea of prematurity. The frequency of apnea occurring within 20 seconds of a reflux episode was not significantly different from that during reflux-free periods, and the same was true for bradycardias. Kimball et al⁹ retrospectively reviewed records of all infants <36 weeks’ gestational age at birth at 2 NICUs to determine whether medications commonly used in the management of GER (cisapride or metoclopramide) reduced the frequency of apnea in premature infants. Neither cisapride nor metoclopramide reduced the frequency of apnea, even in infants with documented GER. In patients who received cisapride, the frequency of apnea increased. Di Fiore et al¹⁸ retrospectively reviewed cardiorespiratory monitoring studies, using respiratory inductance plethysmography, heart rate, oxygen saturation, and esophageal pH, in 119 premature infants over a period of 5 years. Only 1% of GER episodes were associated with apnea, and there was no difference in rate of apnea before versus during GER. In another study addressing the effect of posture, Bhat et al¹⁹ found no association between acid reflux with obstructive or total apnea episodes. These observational studies provide no evidence of even a temporal relationship between acid or nonacid GER and apnea in preterm infants. These studies raise the question as to which infants, if any, warrant the use of anti-reflux medications.²⁰

Despite the lack of efficacy demonstrated in *clinical studies*, the use of anti-reflux medications remains widespread.¹¹ Even though metoclopramide and ranitidine are not approved by the Food and Drug Administration for use in neonates, metoclopramide and ranitidine are ranked first and fourth, respectively, among the medications most frequently used in the NICU (based on the number of doses dispensed).²¹ Anti-reflux medications may have important adverse effects in preterm infants. H₂-blocker therapy has been shown to cause bacterial translocation in animals.^{22,23} The acid environment of the stomach serves as an important defense against intestinal colonization by potentially pathogenic bacteria. The use of H₂-blockers has been associated with an increased risk of hospital-acquired sepsis²⁴ and with a higher incidence of necrotizing enterocolitis in very low birth weight infants.²⁵

Our study had several limitations. First, apnea was not used as an outcome because of the inability to detect episodes of obstructive apnea. If GER causes bradycardia by first causing apnea and then hypoxia, we may have missed brief episodes that did not lead to bradycardia. A second limitation was that there could have been residual effects from previous treatment periods. We used 24-hour washout periods at the beginning of the second and third time periods to minimize this problem. The pharmacokinetics of these 2 medications in infants are not well studied. Small studies have reported the half-life of metoclopramide to be approximately 5 to 6 hours in adults, 4 hours in infants, and up to 23 hours in neonates.^{26–28} The half-life of ranitidine is approximately 2 to 3 hours in neonates and infants, which is similar to that of adults.^{29,30} A third limitation was that we did not require diagnostic tests for GER, specifically a pH probe. Only 6 of the 17 infants enrolled had documented reflux, as shown by a UGI or

pH probe study, before enrollment. Because the pH probe study is not able to measure nonacid GER, which is common in infants, clinicians frequently rely on signs and symptoms of presumed GER for the initiation of GER treatment. Knowing that diagnostic studies for GER are problematic, clinicians frequently begin anti-reflux medications for clinical GER. Excluding infants that lacked diagnostic studies for GER would not have reflected common practice in the NICU. A new and promising diagnostic test for GER in infants, the combined pH-multichannel intraluminal impedance monitoring, should help to detect nonacid GER.³¹ A fourth limitation was that the mean postnatal age at enrollment was 35 weeks (± 22 days), a relatively mature population. These findings may not be generalizable to less mature infants or to mechanically ventilated infants. Finally, we enrolled a relatively small number of patients. With this number, we cannot exclude the possibility that some infants might benefit from anti-reflux medications for apnea. The 95% CI for 0 of 17 infants benefiting from treatment would be (0% to 18%).

When there is uncertainty about whether an individual patient will derive benefit from a treatment, an N of 1 trial can be helpful. An N of 1 trial is a type of cross-over study that was first described in 1986 as a method for objective evaluation of the short-term response to treatment in an individual patient. For each patient, study results can be used to decide whether or not to continue treatment after study completion. As described by Nikles et al,³² N of 1 trials have been used in pediatrics for management of attention-deficit/hyperactivity disorder. In this report, children with clinically diagnosed attention-deficit/hyperactivity disorder were selected because treatment effectiveness was uncertain. Management changed for 28 of the 64 children for whom information was available, and the authors concluded by highlighting the value of N of 1 trials in clarifying treatment effect when it is uncertain. In our study, a series of N of 1 trials was used to evaluate whether similar infants, as a group, would benefit from metoclopramide and ranitidine when GER is a suspected cause of bradycardia episodes.

In conclusion, this study has shown that anti-reflux medications did not reduce, and may have increased, bradycardia episodes in preterm infants with bradycardia attributed to GER by clinicians. The improvement of bradycardia over time raises a concern that an unmasked trial of therapy is likely to be biased toward unnecessary treatment in these infants. When the use of unproven therapies is considered, N of 1 trials may be useful in determining whether treatment should be continued in individual patients, provided that the intended benefit is a short-term outcome.

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Glossary

GER	Gastroesophageal reflux
GERD	Gastroesophageal reflux disease
HR	Heart rate
IVH	Intraventricular hemorrhage
NCPAP	Nasal continuous positive airway pressure
NICU	Neonatal intensive care unit
UGI	Upper gastrointestinal series

References

1. Gold BD. Outcomes of pediatric gastroesophageal reflux disease: in the first year of life, in childhood, and in adults... oh, and should we really leave *Helicobacter pylori* alone? *J Pediatr Gastroenterol Nutr* 2003;37(Suppl 1):S33–9. [PubMed: 14685076]
2. Orenstein SR. Gastroesophageal reflux. *Pediatr Rev* 1992;13:174–82. [PubMed: 1570247]
3. Herbst JJ, Minton SD, Book LS. Gastroesophageal reflux causing respiratory distress and apnea in newborn infants. *J Pediatr* 1979;95:763–8. [PubMed: 39984]
4. Spitzer AR, Boyle JT, Tuchman DN, Fox WW. Awake apnea associated with gastroesophageal reflux: a specific clinical syndrome. *J Pediatr* 1984;104:200–5. [PubMed: 6694012]
5. Poets CF. Gastroesophageal reflux: a critical review of its role in preterm infants. *Pediatrics* 2004;113:128–32.
6. Amin RS. Gastroesophageal reflux and infant apnea. *J Pediatr* 2000;137:298–300. [PubMed: 10969250]
7. Peter CS, Sprodowski N, Bohnhorst B, Silny J, Poets CF. Gastroesophageal reflux and apnea of prematurity: no temporal relationship. *Pediatrics* 2002;109:8–11. [PubMed: 11773535]
8. Rudolph CD, Mazur LJ, Liptak GS, Baker RD, Boyle JT, Colletti RB, et al. Guidelines for evaluation and treatment of gastroesophageal reflux in infants and children: recommendations of the North American Society for Pediatric Gastroenterology and Nutrition. *J Pediatr Gastroenterol Nutr* 2001;32(Suppl 2):S1–31. [PubMed: 11525610]
9. Kimball AL, Carlton DP. Gastroesophageal reflux medications in the treatment of apnea in premature infants. *J Pediatr* 2001;138:355–60. [PubMed: 11241042]
10. Hibbs AM, Lorch SA. Metoclopramide for the treatment of gastroesophageal reflux disease in infants: a systematic review. *Pediatrics* 2006;118:746–52. [PubMed: 16882832]
11. Clark RH, Bloom BT, Spitzer AR, Gerstmann DR. Reported medication use in the neonatal intensive care unit: data from a large national data set. *Pediatrics* 2006;117:1979–87. [PubMed: 16740839]
12. Malcolm WF, Gantz M, Martin RJ, Goldstein RF, Goldberg RN, Cotton CM. Use of medications for gastroesophageal reflux at discharge among extremely low birth weight infants. *Pediatrics* 2008;121:22–7. [PubMed: 18166553]
13. Guyatt G, Sackett D, Taylor DW, Chong J, Roberts R, Pugsley S. Determining optimal therapy-randomized trials in individual patients. *N Engl J Med* 1986;314:889–92. [PubMed: 2936958]
14. Suys B, De Wolf D, Hauser B, Blecker U, Vandenplas Y. Bradycardia and gastroesophageal reflux in term and preterm infants: is there any relation? *J Pediatr Gastroenterol Nutr* 1994;19:187–90.
15. Nault MA, Milne B, Parlow JL. Effects of the selective H1 and H2 histamine receptor antagonists loratadine and ranitidine on autonomic control of the heart. *Anesthesiology* 2002;96:336–41. [PubMed: 11818765]
16. Ooie T, Saikawa T, Hara M, Ona H, Seike M, Sakata T. H₂-blocker modulates heart rate variability. *Heart Vessels* 1999;14:137–42. [PubMed: 10776806]
17. American Academy of Pediatrics Committee on Drugs. Uses of drugs not described in the package insert (off-label uses). *Pediatrics* 2002;110:e52. [PubMed: 12415058]
18. Di Fiore JM, Arko M, Whitehouse M, Kimball A, Martin RJ. Apnea is not prolonged by acid gastroesophageal reflux in preterm infants. *Pediatrics* 2005;116:1059–62. [PubMed: 16263989]
19. Bhat RY, Fafferty GF, Hannam S, Greenough A. Acid gastroesophageal reflux in convalescent preterm infants: effect of posture and relationship to apnea. *Pediatr Res* 2007;62:620–3. [PubMed: 17805196]
20. Orenstein SR, McGowan JD. Efficacy of conservative therapy as taught in the primary care setting for symptoms suggesting infant gastroesophageal reflux. *J Pediatr* 2008;152:310–4. [PubMed: 18280832]
21. Kumar P, Walker JK, Hurt KM, Bennett KM, Grosshans N, Fotis MA. Medication use in the neonatal intensive care unit: current patterns and off-label use of parenteral medications. *J Pediatr* 2008;152:412–5. [PubMed: 18280851]
22. Basaran UN, Celayir S, Eray N, Ozturk R, Senyuz OF. The effect of an H₂-receptor antagonist on small-bowel colonization and bacterial translocation in newborn rats. *Pediatr Surg Int* 1998;13:118–20. [PubMed: 9563022]

23. Dinsmore JE, Jackson RJ, Smith SD. The protective role of gastric acidity in neonatal bacterial translocation. *J Pediatr Surg* 1997;32:1014–6. [PubMed: 9247224]
24. Stoll BJ, Marinella T, Tyson JE, Papile L, Wright LL, Bauer CR, et al. Dexamethasone therapy increases infection in very low birth weight infants. *Pediatrics* 1999;104:1–7. [PubMed: 10390252]
25. Guillet R, Stoll BJ, Cotton CM, Gantz M, McDonald S, Poole WK, et al. Association of H2-blocker therapy and higher incidence of necrotizing enterocolitis in very low birth weight infants. *Pediatrics* 2006;117:137–42.
26. Metoclopramide: Clinical Pharmacology. Drugs.com@drug database. May. 2008
<http://www.drugs.com>
27. Kearns GL, Butler HL, Lane JK, Carchman SH, Wright GJ. Metoclopramide pharmacokinetics and pharmacodynamics in infants with gastroesophageal reflux. *J Pediatr Gastroenterol Nutr* 1988;7:823–9. [PubMed: 3199269]
28. Kearns GL, van den Anker JN, Reed MD, Blumer JL. Pharmacokinetics of metoclopramide in neonates. *J Clin Pharmacol* 1998;38:122–8. [PubMed: 9549642]
29. Wiest DB, O'Neal W, Reigart JR, Brundage RC, Gillette PC, Yost RL. Pharmacokinetics of ranitidine in critically ill infants. *Dev Pharmacol Therapeutics* 1989;12:7–12.
30. Fontana M, Massironi E, Rossi A, Vaglia P, Gancia GP, Tagliabue P, et al. Ranitidine pharmacokinetics in newborn infants. *Arch Dis Child* 1993;68:602–3. [PubMed: 8323366]
31. Condino AA, Sondheimer J, Pan Z, Gralla J, Perry D, O'Connor JA. Evaluation of infantile acid and nonacid gastroesophageal reflux using combined pH monitoring and impedance measurement. *J Pediatr Gastroenterol Nutr* 2006;42:16–21. [PubMed: 16385248]
32. Nikles CJ, Mitchell GK, Del Mar CB, Clavarino A, McNairn N. An n-of-1 trial service in clinical practice: testing the effectiveness of stimulants for attention-deficit/hyperactivity disorder. *Pediatrics* 2006;117:2040–6. [PubMed: 16740846]

Figure 1.
Patient accrual.

Figure 2.
Bradycardia episodes per day for all study participants by treatment period.

Figure 3.
Bradycardia episodes per day for all study participants by time period.

Figure 4. Bradycardia episodes per day during the 3 time periods for each participant in whom there were fewer bradycardic episodes during the drug periods. The most striking pattern is the decrease in bradycardic episodes over time.

Table**Patient characteristics at enrollment**

Birth weight (g)	1238 ± 394
Birth gestational age (wk)	29 ± 3
Postnatal age at enrollment (d)	35 ± 22
Sex	
Male	5 (29.4%)
Female	12 (70.5%)
Race	
White	8 (47.0%)
Black	7 (41.2%)
Hispanic	2 (11.8%)
Supplemental oxygen	4 (23.5%)
NCPAP	1 (5.9%)