Simulation of an Epidural Test Dose with Intravenous Isoproterenol in Sevoflurane- and Halothane-Anesthetized Children

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Isoproterenol has been suggested as an alternative marker for epidural test dosing in children receiving halothane anesthesia. The purpose of this prospective, randomized, double-blind study was to determine the chronotropic response to IV isoproterenol in sevoflurane-anesthetized children. Thirty-six ASA physical status I children (0.5–8 yr) were anesthetized with either halothane or sevoflurane at 1 minimum alveolar anesthetic concentration adjusted for age in 70% nitrous oxide. Patients received incremental IV injections of isoproterenol until their heart rate increased ≥20 bpm above baseline. The minimal effective dose of isoproterenol required to produce an increase of ≥20 bpm was 55 ng/kg (42–72 ng/kg; 95% confidence interval) in sevoflurane-anesthetized children and 32 ng/kg (26–38 ng/kg; 95% confidence interval) in halothane-anesthetized children ($P < 0.05$). This dose-response study suggests that sevoflurane antagonizes β-adrenergic–mediated chronotropic responses to isoproterenol more than halothane. These observations also suggest that larger doses of isoproterenol will be necessary for epidural test dosing in children receiving sevoflurane rather than halothane anesthesia. **Implications:** Isoproterenol has been suggested as an alternative marker for epidural test dosing in children receiving halothane anesthesia. This isoproterenol dose-response study indicates that larger doses of isoproterenol will be necessary for epidural test dosing in children undergoing sevoflurane rather than halothane anesthesia.

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Inadvertent intravascular injection of local anesthetics intended for epidural anesthesia can result in serious cardiovascular and central nervous system toxicity (1). To avoid this adverse event of regional anesthesia in clinical practice, an epinephrine-containing epidural test dose that causes an increase in heart rate (HR) and blood pressure when injected intravascularly is administered before the fractionated administration of local anesthetics (2). In children, regional anesthetic techniques are usually performed during general anesthesia (3), and halothane has been shown to suppress the cardiovascular response to epinephrine (4). Isoproterenol, a pure β-adrenergic agonist, is a more reliable marker of intravascular injection than epinephrine in halothane-anesthetized children (5,6), laboring women (7), and isoflurane-anesthetized adults (8). Sevoflurane is a new volatile ether inhaled anesthetic that may be a suitable alternative to halothane in pediatric anesthesia (9). Sevoflurane has been found to suppress the cardiovascular response to epinephrine (10). The effects of sevoflurane in altering the chronotropic response to isoproterenol-containing test doses remain to be established. Accordingly, we attempted to characterize the chronotropic effects of IV isoproterenol in children under stable sevoflurane anesthesia in a prospective, randomized, double-blind study. Because halothane is the anesthetic most commonly used in pediatric patients, the chronotropic response to isoproterenol during halothane anesthesia was used as a reference.

Methods

Institutional review board approval was obtained before this study, and informed parental consent was obtained on each patient. Thirty-six ASA physical status I children aged 6 mo to 8 yr with normal sinus

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rhythm undergoing elective minor surgery were involved. Children fasted for 4–6 h and received premedication with 1 mg/kg rectal midazolam (≤15.0 mg) 30 min before the induction of anesthesia. Using computer-generated random tables, patients were assigned to be anesthetized with either halothane ($n = 19$) or sevoflurane ($n = 17$). Anesthesia was induced via a face mask using 70% nitrous oxide in oxygen and incremental dosing of anesthetics every three to five breaths. Halothane was begun at 0.5% and increased by increments of 0.5%–1%, whereas sevoflurane was begun at 1% and increased by increments of 1.5% until the patient was unconscious. The fresh gas flow exceeded 4 L/min. A standard anesthesia machine (Cicero; Draegerwerk AG, Luebeck, Germany) with a sevoflurane and halothane vaporizer (Draeger-Vapor 19.1; Draegerwerk AG) exclusively calibrated for each anesthesia drug was used to deliver anesthetics. Inhaled anesthesia via a face mask was continued using assisted or controlled ventilation while an IV catheter was inserted for infusion of 5 mL/kg lactated Ringer's solution, followed by a continuous infusion administered at the rate of 5 mL · kg−1 · h−1 throughout the study period. Neuromuscular blocking drugs were not administered. After inserting a laryngeal mask, ventilation was controlled to maintain an end-tidal carbon dioxide tension between 30 and 35 mm Hg and an end-tidal anesthetic concentration of 1 minimum alveolar anesthetic concentration (MAC) of inhaled anesthetic adjusted for age (11,12) in 70% nitrous oxide and oxygen. End-tidal gas concentrations were sampled at the proximal end of the laryngeal mask at a rate of 150 mL/min and were recorded continuously. Rectal temperature was maintained between 36 and 37°C. Electrocardiogram and pulse oximetry were monitored continuously throughout the study period. When hemodynamic variables and end-tidal gas concentrations had been stable for 5 min, each patient received test doses injected via a peripheral arm vein to simulate the intravascular administration of an epidural test dose. The volume of injection was standardized at 0.2 mL/kg. We administered incremental bolus injections consisting of isoproterenol 20, 30, 45, 65, and 100 ng/kg (Isuprel; Sanofi Winthrop Industrie, Gentilly, France) until the patient's HR increased ≥20 bpm above the baseline HR at the time of drug injection. Each incremental injection was administered either 5 min after the previous injection if there was no change in HR or 5 min after the patient's HR had returned to baseline in response to the previous injection. We estimated each patient's chronotropic dose (CD_{20}) by logarithmic interpolation between the two neighboring isoproterenol doses. Baseline HR for each test injection was defined as the measurement obtained before injection. Peak increase in HR was defined as the difference between the baseline values before injection and the greatest measured values after injection of each test solution. The data-collecting investigator was blinded to the anesthetic group. Measurements were performed before surgical incision.

A power analysis based on a pilot study revealed that a minimal study size of 34 individuals would provide a 90% power of detecting a difference of ≥5 bpm in peak increase in HR in response to IV isoproterenol at a dose of 50 ng/kg. Demographic data were compared between groups using an unpaired Student's t-test. Analysis of covariance was performed for each test dose with baseline HR as covariate. Peak increases in HR at each test dose were compared between groups using one-way analysis of variance followed by an unpaired Student's t-test. Changes in HR over time within each group were analyzed by using repeated-measures analysis of variance. Hemodynamic and demographic data are expressed as mean ± SD. Differences between the mean CD_{20} values of patients anesthetized with sevoflurane and halothane were analyzed by using an unpaired Student's t-test with logarithmic transformation. CD_{20} values are expressed as mean (95% confidence interval). Regression lines for anesthetic groups were calculated. $P < 0.05$ was considered statistically significant.

Results

There were no significant differences between the sevoflurane and halothane groups in terms of age (3.6 ± 2.0 vs 3.9 ± 1.8 yr), weight (15.6 ± 4.6 vs 17.5 ± 6.8 kg), height (102 ± 12 vs 108 ± 18 cm), or preinduction HR (117 ± 25 vs 118 ± 25 bpm). Compared with preinduction values, HR was unchanged at 1 MAC sevoflurane but was decreased at 1 MAC halothane. Baseline HR before each test injection remained constant in both groups throughout the study period (Table 1). The IV injection of isoproterenol increased HR during both sevoflurane and halothane anesthesia (Table 1). Neither a significant difference between within-group slopes of peak increase versus baseline HR nor a significant relation between baseline HR and peak increase could be found. Peak increases in HR in response to the IV injection of isoproterenol were significantly greater in children undergoing halothane versus sevoflurane anesthesia (Table 1). The mean CD_{20} was 55 (42–72) ng/kg in sevoflurane-anesthetized children and 32 (26–38) ng/kg in halothane-anesthetized children (Fig. 1). The difference in mean CD_{20} between the groups was statistically significant. The slopes of the regression lines of peak increase versus dose for the two anesthetic groups did not differ significantly.

Table 1. Heart Rate Response to Intravenous Isoproterenol

	Isoproterenol (ng/kg)				
	20	30	45	65	100
Baseline heart rate (bpm)					
Sevoflurane	117 ± 14	118 ± 17	122 ± 14	122 ± 10	122 ± 10
Halothane	106 ± 21	106 ± 20	110 ± 18	110 ± 2	
Peak increase in heart rate (bpm)					
Sevoflurane	13 ± 6	14 ± 5*	17 ± 3*	19 ± 2*	22 ± 1
Halothane	15 ± 5	19 ± 5	21 ± 5	25 ± 1	

Values are mean ± SD.
* $P < 0.05$ for sevoflurane versus halothane.

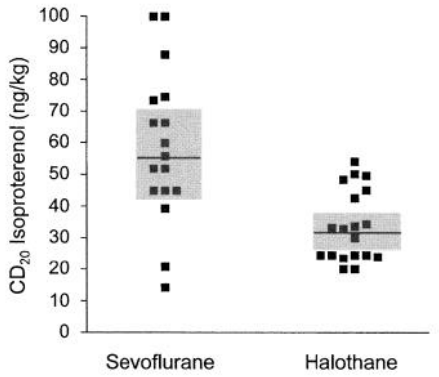

Figure 1. Chronotropic dose (CD_{20}) of isoproterenol in children anesthetized with sevoflurane and halothane at 1 minimum alveolar anesthetic concentration in 70% nitrous oxide. Data are expressed as mean and 95% confidence interval. *$P < 0.05$ for sevoflurane versus halothane.

Discussion

We found that a significantly larger dose of isoproterenol was required to produce a HR increase of ≥20 bpm in children undergoing sevoflurane than those undergoing halothane anesthesia at 1 MAC in 70% nitrous oxide. The mean CD_{20} of isoproterenol was 55 ng/kg in sevoflurane-anesthetized children and 32 ng/kg in halothane-anesthetized children. The slopes of the isoproterenol dose-response curves for the two anesthetic groups are comparable to that reported by DeSimone et al. (13). The baseline HR before each test dose injection was higher in the sevoflurane group than in the halothane group. This finding is in agreement with previous studies, which demonstrated that HR is maintained at preinduction values at 1 MAC sevoflurane but decreases at 1 MAC halothane (12,22). We found no significant relationship between baseline HR and peak increase in HR between or within groups. We therefore conclude that differences in baseline HR do not affect the responsiveness to isoproterenol.

Halothane has been proposed to affect the response to sympathomimetic amines by 1) suppressing the adrenoceptor responsiveness (14,15), 2) altering cardiac mechanical and electrophysiologic properties (16,17), 3) modifying the basal sympathetic and parasympathetic tone regulating HR (18), and 4) suppressing the baroreflex activity (19). Our study shows for the first time that the new inhaled anesthetic sevoflurane suppresses the chronotropic response to a β-adrenergic agonist more than halothane. Little is known about mechanisms of depressant effects of sevoflurane on β-adrenoceptor function. Sevoflurane has been reported to depress the β-adrenergic receptor signal transduction system (20) and to alter the action potential characteristics and cardiac impulse conduction velocity (17,21). Further studies are warranted to elucidate and to compare the mechanisms by which inhaled anesthetics antagonize β-adrenoceptor–mediated actions.

The greater reliability of isoproterenol over epinephrine for test dosing was confirmed in halothane-anesthetized children (5,6), laboring women (7), and isoflurane-anesthetized adults (8). Sevoflurane is being increasingly used in pediatric anesthesia. A study by Tanaka et al. (10) showed that epinephrine, with or without atropine pretreatment, is inadequate to guarantee sensitive identification of intravascular injection in children undergoing sevoflurane anesthesia based on the conventional HR criterion (positive if ≥20 bpm increase). The present study indicates that isoproterenol could be of value as an epidural test drug in children undergoing both halothane and sevoflurane anesthesia. However, the injection of isoproterenol into the human epidural space cannot be recommended until detailed studies have proven the safety of isoproterenol for epidural and intrathecal administration, as suggested in previous screening studies (24,25).

One limitation of our study is that the use of nitrous oxide or midazolam may have influenced the hemodynamic responsiveness. However, this study design represents common clinical practice and thereby augments the clinical usefulness of the present findings. Another potential objection to our study is that isoproterenol may accumulate with repeated injections, but isoproterenol is supposed to be readily adsorbed and metabolized after IV administration (23). The risk

of residual effects has also been minimized by using time intervals of at least 10 min between incremental injections.

In conclusion, we found a decreased chronotropic response to IV isoproterenol in sevoflurane-anesthetized children compared with halothane-anesthetized children at 1 MAC. Further studies are warranted to substantiate the difference between sevoflurane and halothane on the responsiveness to isoproterenol at varying MAC values in infants and children.

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