Simulation of an Epidural Test Dose with Intravenous Isoproterenol in Awake and in Halothane-anesthetized Children

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Background: An epidural test dose containing epinephrine does not reliably produce hemodynamic responses in children under halothane anesthesia. The purpose of this study was to determine hemodynamic responses to intravenous isoproterenol in both awake and halothane-anesthetized children.

Methods: After obtaining institutional review board approval and parental informed consent, 72 ASA physical status 1 or 2 children (2.8 ± 1.7 yr) undergoing elective minor surgery were studied before and during anesthesia with 1.2 minimum alveolar concentration halothane. A bolus containing 0.25 mg/kg bupivacaine and 0.05 μg/kg, 0.075 μg/kg, or 0.1 μg/kg isoproterenol, or bupivacaine and saline was injected *via* a peripheral arm vein to simulate intravascular injection of an epidural test dose.

Results: Before induction of anesthesia, all patients showed a positive test response after isoproterenol injection (heart rate increase ≥20 beats/min). During anesthesia, 79% of patients receiving 0.05 μg/kg, 89% of patients receiving 0.075 μg/kg, and 100% of patients receiving 0.1 μg/kg met the criterion of a positive test response. Among each treatment group, all infants showed a positive test response. Blood pressure did not differ among the groups at any time. Transient benign dysrhythmias occurred in only one patient under halothane anesthesia receiving 0.075 μg/kg isoproterenol.

Conclusion: Isoproterenol at a dose of 0.1 μg/kg is a sensitive indicator for intravascular injection of a test dose in children anesthetized with halothane and nitrous oxide. Isoproterenol at a dose of 0.05 μg/kg approximates a minimal effective dose in awake children and in infants. After detailed studies on neural toxicity, isoproterenol could be of value as an epidural test agent in children. (Key words: Anesthesia: pediatric. Anesthetics, local: bupivacaine. Anesthetics, volatile: halothane; isoproterenol.)

INADVERTENT intravascular injection of local anesthetics intended for epidural anesthesia can result in serious cardiovascular and central nervous system toxicity.[1] The incidence of intravascular placement or migration of an epidural catheter is not uncommon and appears to vary between 0.01% and 11% in adults.[2–4] Although no data on the incidence of epidural blood vessel puncture in pediatrics are available, children can be presumed to be at risk. An epidural test dose containing epinephrine and local anesthetics causes an increase in heart rate when injected intravascularly.[3,5] In children, regional anesthetic techniques are usually performed during general anesthesia.[6] Inhalational agents alter the cardiovascular response to epinephrine.[7] Epinephrine does not reliably produce hemodynamic responses in children under halothane anesthesia.[7–9] In addition, halothane sensitizes the myocardium to catecholamines and increases their dysrhythmogenic potential.[7] Because of the limitations of epinephrine as an epidural test agent, alternative markers are under investigation. Isoproterenol is the most potent pure nonselective β-adrenergic agonist.[10] Compared to a mixed α- and β-adrenergic agonist like epinephrine, isoproterenol induces no biphasic heart rate effect or bradycardia, occurring in response to α-adrenergic-mediated increase in systemic vascular resistance. In contrast to epinephrine, cardiac automaticity of isoproterenol is not enhanced in the presence of anesthetics.[11] The greater reliability of isoproterenol over epinephrine for test dosing was confirmed in laboring women[12] and in animals under general anesthesia.[9] In children under halothane anesthesia, the value of isoproterenol as a marker for epidural test dosing remains controversial.[13] The purpose of this study was to determine hemodynamic responses to intravenous isoproterenol in both awake and halothane-anesthetized children.

Materials and Methods

After institutional review board approval and parental informed consent were obtained, 72 ASA physical status

1 or 2 children aged 3 months to 8 yr with normal sinus rhythm undergoing elective minor surgery were studied. Patients received premedication with 1 mg/kg midazolam rectally (not more than 15.0 mg). Intravenous access was established under local anesthesia (Emla, Astra Pharmaceutical Production AB, Sodertalije, Sweden). Lactated Ringer's solution was administered at $5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ throughout the study period. Patients were randomized into four groups and received a test dose injected *via* a peripheral arm vein to simulate intravascular administration of an epidural test dose. The volume of the test injection was standardized at 0.2 ml/kg. The test solution contained 0.25 mg/kg bupivacaine (Carbostesin 0.25%, Astra Chemicals, Wedel, Germany) and 0.9% saline (control, n = 16), and isoproterenol (group I50, n = 18, Isuprel, Sanofi Winthrop Industries, Ambares, France), bupivacaine and isoproterenol $0.075 \ \mu\text{g} \cdot \text{kg}^{-1}$ (group I75, n = 19) or bupivacaine and isoproterenol $0.1 \ \mu\text{g} \cdot \text{kg}^{-1}$ (group I100, n = 19). The test injections were given in a double-blind manner. The first test injection was administered before induction of anesthesia. Anesthesia was induced with halothane and nitrous oxide in 30% inspired oxygen. The trachea was intubated and ventilation controlled to maintain an end-tidal carbon dioxide tension between 30 and 35 mmHg. Anesthesia was maintained with end-tidal halothane concentrations of 1.2 minimum alveolar concentration adjusted for age.[14] When hemodynamic variables and end-tidal concentrations were stable for 5 min, a second test injection of the same composition was administered. Electrocardiogram and pulse oximetry were monitored continuously before and for 10 min after each test injection. Automated noninvasive oscillometric blood pressure (Apollo Series 700, Merlin, Hewlett Packard, Böblingen, Germany) was recorded immediately before the test injection and for the first 5 minutes in 30-s intervals and for the next 4 min at 60-s intervals. Measurements were performed before surgical incision.

Baseline heart rate and blood pressure for each test injection were defined as the measurements obtained before each injection. Peak measured increases in heart rate and blood pressure were defined as the difference between the baseline values and the greatest measured values after injection of each test solution. Time to peak measured heart rate increase was the time after injection at which these measurements were obtained. The onset of an increase in heart rate of 10 beats/min greater than baseline was the time at which these measurements were obtained. In addition, time between test injection

and return of increased heart rate to baseline values was documented. Following Guinard *et al.*,[17] a positive response to intravascular injection of a test dose was defined as a heart rate increase ≥20 beats/min occurring within 2 min of injection. Sensitivity (number of true-positives divided by the number of true-positives plus false-negatives) and specificity (number of true-negatives divided by the number of true-negatives plus false-positives) were calculated.

Statistical analysis was performed by repeated-measures analysis of variance to compare intragroup and intergroup differences in changes in heart rate in awake *versus* anesthetized children. When significant, differences between the groups were identified with Scheffe's F test. Heart rate before and after induction of anesthesia were compared by paired *t* test. One-way analysis of variance determined the significance of demographic differences between the groups. Data are expressed as mean ± standard deviation (SD). A $P < 0.05$ was considered statistically significant.

Results

There were no significant differences among the groups with respect to age (2.8 ± 1.7 yr), weight (14.0 ± 4.9 kg), height (107 ± 19 cm), and baseline heart rate (table 1).

Injecting plain bupivacaine produced no hemodynamic changes (control group). In the treatment groups I50–I100, increases in heart rate were dose-dependent before and during halothane anesthesia (table 1). Halothane anesthesia alone produced a significant decrease in heart rate and an attenuation of isoproterenol-induced tachycardia (table 1).

Before induction of anesthesia, all patients of each treatment group showed a positive test response after each dose of isoproterenol (table 1). During anesthesia, a positive test response was achieved in 79% of patients in group I50, 89% of patients in group I75, and 100% of patients in group I100 (table 1). Within each treatment group, all infants (age <6 months) showed a positive test response.

Blood pressure did not differ among the groups at any time. Transient dysrhythmias occurred in only one patient of group I75 during halothane anesthesia. In a 3-month-old boy, three premature ventricular contractions were observed during the maximum heart rate of 145 beats/min.

Discussion

This study demonstrates that intravascular injection of a test dose containing local bupivacaine and isoproterenol produces a positive test response, defined as an increase in heart rate of ≥20 beats/min, in awake children and in children anesthetized with halothane and nitrous oxide. Controversy still exists about the use of epinephrine as an epidural test agent in children under halothane anesthesia. Halothane decreases the electromechanical activity of human atrial fibers, as well as the spontaneous sinoatrial nodal activity and reduces the responses to epinephrine in a noncompetitive manner.[15] In addition, by decreasing the ED50 of epinephrine, halothane increases the dysrhythmogenic potency.[11] Because of the limitations of epinephrine, alternative markers for epidural test dosing are under investigation.[8,12,13,16-18] Perillo et al.[13] investigated heart rate responses in halothane-anesthetized children after 0.05 and 0.075 μg/kg intravenous isoproterenol plus 1% lidocaine. The authors reported that the chosen doses of isoproterenol did not produce heart rate increases of at least 10 beats/min in all patients. The question of the efficacy and safety of larger doses of intravenous isoproterenol remained unanswered. We evaluated hemodynamic responses to 0.1 μg/kg intravenous isoproterenol. In addition, based on a pilot study of 15 patients that showed that a dose of 0.05 μg·kg⁻¹ produced marked tachycardia in awake children, doses of 0.05 and 0.075 μg/kg isoproterenol were investigated. To address the question of the effect of the anesthetic technique on hemodynamic responses to intravenous isoproterenol, the same test dose was administered before and during anesthesia. Before induction of anesthesia, we found a positive test response to intravascular injection defined as an increase in heart rate of at least 20 beats/min in all children. A dose of 0.05 μg/kg isoproterenol seems to be sufficient for detection of intravascular injection in awake children. During anesthesia, only 79% of patients in group I50, and 89% of patients in group I75 met hemodynamic criteria for detection of intravascular injection. A dose of 0.1 μg/kg isoproterenol produced a positive response in all children and seems to be adequate to guarantee sensitive identification of intravascular injection in halothane-anesthetized children.

Although there were no significant differences in mean age among the groups, we found an age-related difference in heart rate response to isoproterenol. Among each treatment group, all infants showed an

increase in heart rate of more than 20 beats/min. A dose of 0.05 μg/kg isoproterenol approximates a minimal effective dose in infants.

Although isoproterenol is a vasodilator, systemic blood pressure remained unchanged in all children throughout the study. An increase in myocardial contractility and cardiac output mediated by isoproterenol may compensate for its vasodilative effects. No dysrhythmias were seen before induction of anesthesia, although isoproterenol has a dysrhythmogenic potential.[10] During halothane anesthesia, in only one patient receiving 0.075 μg/kg isoproterenol, transient premature ventricular contractions were observed. Further

Table 1. Heart Rate Responses to Intravenous Isoproterenol

	Group I$_{50}$	Group I$_{75}$	Group I$_{100}$
No. of patients	18	19	19
Baseline heart rate (beats/min)			
Awake	121 ± 15	121 ± 12	120 ± 13
Anesthetized	104 ± 14*	103 ± 14*	104 ± 11*
Time (s) to measured heart rate increase of 10 beats/min greater than baseline			
Awake	14 ± 2†	12 ± 2‡	9 ± 2
Anesthetized	24 ± 2*·†	19 ± 2*·‡	13 ± 2*
Peak increase in heart rate (beats/min)			
Awake	52 ± 8†·§	59 ± 9‡	72 ± 7
Anesthetized	23 ± 8*·†	29 ± 9*	37 ± 6*
Time (s) to peak measured increase in heart rate			
Awake	46 ± 5†	43 ± 6‡	37 ± 4
Anesthetized	54 ± 6*·†	49 ± 6*·‡	44 ± 6*
Time (s) between test injection and return to baseline heart rate			
Awake	105 ± 4†·§	117 ± 5‡	125 ± 5
Anesthetized	88 ± 9*·†·§	111 ± 10‡	122 ± 9
Sensitivity of heart rate increase ≥ 20 beats/min (%)			
Awake	100	100	100
Anesthetized	79	89	100

Values are mean ± SD.

* $P < 0.05$, within group.

† $P < 0.05$, I$_{50}$ versus I$_{100}$.

‡ $P < 0.05$, I$_{75}$ versus I$_{100}$.

§ $P < 0.05$, I$_{50}$ versus I$_{75}$.

studies are warranted to evaluate the incidence of rare adverse events.

A limitation of our study is that the test doses have been injected *via* a peripheral arm vein to simulate an intravenously administered epidural test dose. Van Zundert *et al.*[18] reported a similar onset of tachycardia after intravenous injection of a test dose in an epidural vein compared to an intravenous injection in a peripheral arm vein. Nevertheless, extrapolations of hemodynamic responses to isoproterenol administered *via* a peripheral arm vein or leg vein to epidural injections should be made with care.

Neural toxicity of isoproterenol after epidural or subarachnoid administration has not been investigated in humans. Therefore, the use of isoproterenol as an epidural test agent cannot be recommended now. Further, the effect of an epidural test dose containing a β-adrenergic agonist on effectiveness and length of a regional block has to be determined.

In conclusion, this randomized, double-blind, placebo-controlled study shows that 0.1 μg/kg isoproterenol is a sensitive indicator for intravascular injection of a test dose in children anesthetized with halothane and nitrous oxide. Isoproterenol at a dose of 0.05 μg/kg seems to be adequate to guarantee sensitive identification of intravascular injection in awake children and in infants.

In addition, our results confirm and extend previous recommendations, that is, the brief increase in heart rate of small magnitude could be missed if heart rate is not monitored very closely using electrocardiography during and after injection for 2 min.

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