Epinephrine–Halothane Interactions in Children

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Cutaneous infiltration of dilute solutions of epinephrine for hemostasis during halothane anesthesia can result in ventricular dysrhythmias. Our clinical experience, published reports, and a study comparing piglets with adult swine suggest that children may be less susceptible than adults to dysrhythmias under these conditions. We therefore undertook a prospective survey of heart rate and rhythm in halothane-anesthetized children who received subcutaneous epinephrine for hemostasis. Mass spectrometry was used to quantitate end-tidal halothane and to avoid hypercarbia. In 83 children anesthetized with halothane, we continuously recorded ECG, heart rate (HR), end-tidal halothane (EThalo), and carbon dioxide (ETCO₂). The surgeons injected 0.4–15.7 µg/kg of epinephrine (in saline or 1% lidocaine) to provide hemostasis at a variety of sites. No child developed a ventricular dysrhythmia. One child had self-limited premature atrial contractions (PAC). Sixty-three children had some increase in heart rate after epinephrine injection, while seven increased their HR 15% or more above pre-injection levels. No relation between any increase in HR and epinephrine dosage, EThalo, ETCO₂, physical status, or age was found by multiple linear regression; however, HR was increased significantly in patients receiving epinephrine in head and neck sites other than the palate. The authors conclude that children tolerate higher doses of subcutaneous epinephrine than adults during halothane anesthesia. The arrhythmogenic dose of epinephrine in children receiving halothane has yet to be determined, but at least 10 µg/kg of epinephrine infiltration may be used safely in normocarbic and hypocarbic pediatric patients without congenital heart disease. The presence of PAC and tachycardia emphasize the need for continuous ECG monitoring and caution during halothane anesthesia with epinephrine injection. (Key words: Anesthesia; pediatric. Anesthetics, volatile; halothane. Heart: arrhythmias. Sympathetic nervous system: catecholamines, epinephrine.)

Twenty years ago, Katz et al. reported that cutaneous infiltration of dilute solutions of epinephrine for surgical hemostasis during halothane anesthesia can result in ventricular dysrhythmias.¹ Subsequent studies have shown that adult patients and animals often have such problems,²³ whereas children and young animals appear less susceptible.⁴–⁶

Many factors other than age may influence the incidence of epinephrine-associated dysrhythmias during halothane anesthesia. These include the perfusion of the site injected,¹ the speed of injection,¹ presence of hypercarbia,¹ presence of lidocaine in the injectate,¹,² other concomitant anesthetic drugs,⁵–⁷ as well as heart rate,¹⁰,¹¹ blood pressure,¹¹ electrolyte imbalance,¹² fasting,¹³ verapamil,¹⁴ and prostaglandins.¹⁵ Subjectively, the senior authors were impressed that they rarely observed such dysrhythmias in children. We then retrospectively reviewed the anesthetic records of 28 children undergoing craniofacial surgery at The Children’s Hospital of Philadelphia during 1979 and found no description of any dysrhythmias during halothane anesthesia with epinephrine doses up to 8.8 µg/kg.

The absence of this classical problem in our practice was gratifying, but surprising. To confirm this observation and possibly discover the reason for our low incidence, we undertook a prospective survey of heart rate and rhythm in halothane-anesthetized children who received subcutaneous epinephrine for hemostasis. Mass spectrometry was used to quantitate end-tidal halothane and to avoid hypercarbia.

Materials and Methods

After obtaining approval from the Hospital’s Committee for the Protection of Human Subjects, we studied 83 children, 3 months to 17 years old, scheduled for elective procedures in which epinephrine is commonly used for hemostasis. Twenty-two patients were less than 1 year old; 25 were 1 to 5 years; 19 were 6 to 10 years; and 17 were over 10 years. Their weights ranged from 5 to 68 kg. The majority were classified ASA Physical Status I(63) and II(19), but seven were judged to be Physical Status III, usually because of severe mental retardation and chronic seizure disorders. Children with congenital heart disease or those receiving hypotensive anesthesia were excluded.

Sixty-seven of the children were premedicated as follows: patients 0–6 months of age received 0.02 mg/kg atropine; those between 6 and 12 months received 4 mg/kg pentobarbital as well as the atropine; and for children over 12 months, 0.1 mg/kg morphine was added to the atropine and pentobarbital. Four older patients received atropine only, two received 0.01 mg/kg glycopyrrolate, and six patients were premedicated but received no anticholinergic. Four children were not premedicated.

Seventy-four patients then underwent inhalation induction with 70% nitrous oxide (N₂O), 30% oxygen (O₂), and halothane delivered through a Mapleson D circuit; nine children received intravenous thiopental.
for induction. Routine measurements of precordial heart tones, ECG (the limb lead which showed the clear-
est P wave and QRS complex), rectal temperature, and
systemic arterial pressure (doppler method) were made.
Pancuronium, 0.1 mg/kg, was added to N₂O, O₂, and
halothane during maintenance of anesthesia. End-
tidal N₂O, halothane, O₂, and CO₂ were sampled immedi-
ately proximal to the endotracheal tube with a coaxial
airway adapter, and analyzed with a mass spectrometer
(Chemetron Medspec II). Ventilation was controlled
manually. The anesthetist was allowed to determine the
clinically indicated inspired halothane concentration
and to adjust ventilation to keep ET_{CO₂} below 5.6% (40
mmHg). ECG, heart rate, and end-tidal concentrations
of CO₂ and halothane were recorded continuously on
a strip chart recorder.

The surgeon injected a volume and concentration of
epinephrine in saline or 1% lidocaine sufficient to pro-
vide hemostasis. The most commonly used epinephrine
preparation was 10 μg/ml (1:100,000) epinephrine in
1% lidocaine (72 patients). Eleven patients received 1–
10 μg/ml epinephrine in saline. Injection sites included
the palate, lips, external nares, ears, back, scalp, and
several other peripheral regions; all injections were
completed within eight minutes. We limited the dose
to 10 μg/kg in the first 57 patients, and then, with the
concurance of the Committee for the Protection of
Human Subjects, we removed the dose limit.

Correlations between changes in HR and many other
variables were made using multiple linear regression or
chi-square analysis as appropriate; P < 0.05 was consid-
ered statistically significant.

Results

No patient developed premature ventricular con-
tractions (PVC) or other ventricular dysrhythmia de-
spite the large number of children (73) receiving doses of
epinephrine exceeding the recommended adult dos-
age (1.7 μg/kg).¹

One patient developed premature atrial contractions
(PAC) following injection. This 15-year-old, 50-kg
healthy girl, received a nasal submucosal injection of 10
μg/ml (1:100,000) epinephrine in 1% lidocaine. Im-
mediately prior to injection, HR was 140 beats per
minute, ET_{CO₂} was 4% (29 mmHg), and ET_{Halo} was
0.6%. Within 3 minutes of injection of 3 μg/kg epi-

epinephrine, HR reached 175 beats per minute and
supraventricular ectopic beats with aberrant conduction
occurred. No further epinephrine was injected, and the
dysrhythmia resolved spontaneously over the next
minute.

All but five children had higher heart rates imme-
diately prior to the injection of epinephrine than those
recorded before anesthesia induction (fig. 1). Within ten
minutes post-injection, sixty-three children had some
increase in heart rate, while seven increased HR 15% or
more above the pre-injection level. Maximum HR
was reached 2 to 7 minutes after the beginning of
injection. Of these seven tachycardic patients, two re-
ceived 2.5 and 15.7 μg/kg epinephrine in saline, and
five received 0.8–11.3 μg/kg epinephrine in 1% lidio-
caine. Techniques of blood pressure measurement var-
ied too much to permit inclusion of this variable.

Figure 2 illustrates the distribution of ET_{Halo} and to-
tal dosage of epinephrine injected in the 83 children
studied. The dosage of epinephrine ranged from 0.4 to
15.7 μg/kg with a mean value of 5.4 and standard de-
vation of 3.5. ET\textsubscript{Halo} concentrations ranged from 0.2 to 1.8% with a mean value of 0.66 and standard deviation of 0.33. ET\textsubscript{CO\textsubscript{2}} values ranged from 2.8 to 5.6% with a mean value of 4.3 and standard deviation of 0.72. No significant relation between any increase in HR and epinephrine dosage, ET\textsubscript{Halo}, ET\textsubscript{CO\textsubscript{2}}, physical status, or age could be found by stepwise multiple linear regression\textsuperscript{16,17}; however, increased HR was significantly higher (\(P < 0.05\)) in those patients who received epinephrine in head and neck sites other than the palate. Chi-square analysis of a 2 × 2 contingency table\textsuperscript{18} failed to demonstrate that the presence of nonstandard pre-anesthetic medication, thiopental induction, or lidocaine in the injectate influenced the incidence of clinically significant tachycardia (an increase in HR 15% or more above pre-injection level).

**Discussion**

With maintenance halothane levels and hyperventilation, large subcutaneous and submucosal doses of epinephrine were given safely to children without the development of ventricular dysrhythmias. Our findings and those of Wallbank\textsuperscript{5} differ considerably from those of Johnston et al.\textsuperscript{2} who observed ventricular irritability in eight of 15 adult patients undergoing transphenoidal pituitary surgery with halothane-oxygen anesthesia. These patients received 2.0 to 4.1 \(\mu\text{g/kg}\) of epinephrine in saline or 0.5% lidocaine. The dose producing 3 PVC at any time during or immediately following epinephrine injection in 50% of patients (ED\textsubscript{50}) was lower in patients given epinephrine in saline (2.11 \(\mu\text{g/kg}\)) than the ED\textsubscript{50} for those receiving epinephrine in 0.5% lidocaine (3.69 \(\mu\text{g/kg}\)). If children in our study had an 8/15 chance of developing PVC with halothane and epinephrine as in the report of Johnston et al.,\textsuperscript{2} the chances of 83 consecutive patients having no PVC can be calculated as a Bemoulli trial\textsuperscript{19} and is vanishingly small (<10\textsuperscript{-28}). Obviously, our incidence is much lower.

Puerto et al. and Atlee and Malkinson\textsuperscript{7} demonstrated a lower threshold for atrial than for ventricular dysrhythmias in adult dogs receiving halothane and epinephrine infusion. Perhaps more frequent atrial and even ventricular dysrhythmias will occur if higher epinephrine doses than we used are injected in children undergoing halothane anesthesia. Wallbank\textsuperscript{5} noted tachycardia in the majority of his patients as well, and took this as "evidence of rapid systemic absorption." The nearly universal occurrence of some tachycardia in our patients confirms this, though there is no quantitative relationship between the dose of epinephrine administered and the change in heart rate.

While our results confirm the clinical impression that children are less susceptible than adults to dysrhythmias when epinephrine is infiltrated during halothane anesthesia, the reasons for this difference remain unclear. Further laboratory and clinical studies are needed to determine whether the absence of significant atherosclerotic cardiovascular disease in pediatric patients, or perhaps their higher heart rates, or the presence of hypocarbia are factors in protecting children from dysrhythmias caused by the halothane–epinephrine com-
bination. Using this anesthetic regimen, at least 10 μg/kg of epinephrine may be safely used to achieve hemostasis by infiltration in pediatric patients without congenital heart disease.

In conclusion, a wide range of end-tidal halothane concentrations and doses of epinephrine by infiltration as employed in a variety of operative procedures has been shown to be free of dysrhythmias in normocarbic and hypocarbic pediatric patients. The arrhythmogenic dose of subcutaneous or submucosal epinephrine during halothane anesthesia in children remains to be determined. The occasional presence of premature atrial contractions and tachycardia emphasizes the need for continuous ECG monitoring and caution during halothane anesthesia with epinephrine injection.

The authors acknowledge the assistance of Dr. M. Gewitz, Cardiology, who reviewed the electrocardiograms, Dr. M. Snider, Department of Anesthesia, The Pennsylvania State University, who provided statistical advice, and of Ms. S. Crammer who helped to collect the data. They also thank the residents and staff of the Department of Anesthesia and the Divisions of Orthopedic and Plastic Surgery of The Children's Hospital of Philadelphia for their cooperation.

References