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# Clinical Characteristics of Sevoflurane in Children

## A Comparison with Halothane

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***Background:*** **For pediatric patients, sevoflurane may be an alternative to halothane, the anesthetic agent used most commonly for inhalational induction. The induction, maintenance, and emergence characteristics were studied in 120 unpremedicated children 1–12 yr of age randomly assigned to receive one of three anesthesia regimens: sevoflurane with oxygen (group S), sevoflurane with nitrous oxide and oxygen (group SN), or halothane with nitrous oxide and oxygen (group HN).**

***Methods:*** **Anesthetic was administered (*via* a Mapleson D, F or Bain circuit) beginning with face mask application in incremental doses to deliver maximum inspired concentrations of 4.5% halothane or 7% sevoflurane. End-tidal concentrations of anesthetic agents and vocal cord position were noted at the time of intubation. Elapsed time intervals from face mask application to loss of the eyelash reflex, intubation, surgical incision, and discontinuation of the anesthetic were measured. Heart rate, systolic, diastolic, and mean blood pressures, and end-tidal anesthetic concentrations were measured at fixed intervals. Anesthetic MAC-hour durations were calculated. The end-tidal concentration of anesthetic was adjusted to 1 MAC (0.9% halothane, 2.5% sevoflurane) for at least the last 10 min of surgery. Intervals from discontinuation of anesthetic to hip flexion or bucking, extubation, administration of first postoperative analgesic, and attaining discharge criteria from recovery room were measured. Venous blood was sampled at anesthetic induction, at the end of anesthesia, and 1, 4, 6, 12, and 18–24 h after discontinuation of the anesthetic for determination of plasma inorganic fluoride content.**

***Results:*** **Induction of anesthesia was satisfactory in groups SN and HN. Induction in group S was associated with a significantly greater incidence of excitement (35%) than in the other groups (5%), resulting in a longer time to intubation. The end-tidal minimum alveolar concentration multiple of potent inhalational anesthetic at the time of intubation was significantly greater in patients receiving halothane than in patients receiving sevoflurane. Induction time, vocal cord position at intubation, time to incision, duration of anesthesia, and MAC-hour duration were similar in the three groups. During emergence, the time to hip flexion was similar among the three groups, whereas the time to extubation, time to first analgesic, and time to attaining discharge criteria were significantly greater in group HN than in groups S and SN. Mean heart rate and systolic blood pressure decreased during induction in group HN but not in groups S and SN. The maximum serum fluoride concentration among all patients was 28 μM.**

***Conclusions:*** **Sevoflurane with nitrous oxide provides satisfactory anesthetic induction and intubating conditions; however, induction using sevoflurane without nitrous oxide is associated with a high incidence of patient excitement and prolonged time to intubation. There were greater decreases in heart rate and systolic blood pressure during induction with halothane than with sevoflurane; however, these differences may be dose-related. The more rapid emergence with sevoflurane when compared with halothane is consistent with the low solubility of sevoflurane in blood and tissues. Children receiving sevoflurane for up to 9.6 MAC-hours did not develop high serum fluoride concentrations. (Key words: Anesthesia: pediatric. Anesthetics, gases: nitrous oxide. Anesthetics, volatile: halothane; sevoflurane.)**

SEVOFLURANE (fluoromethyl 2,2,2-trifluoro-1-[trifluoromethyl] ethyl ether), an inhalational anesthetic agent, has a low blood-gas partition coefficient (0.6–0.7) and a pleasant, nonpungent odor and provides a rapid, smooth induction and a rapid emergence from anesthesia in adults.[1–3]

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In the pediatric age group, sevoflurane may offer several advantages over halothane, the anesthetic agent used most commonly for inhalational induction. The cardiovascular effects of sevoflurane appear to be similar to those observed with isoflurane anesthesia, with heart rate either increasing or remaining unchanged.[4] Sevoflurane is also intermediate between enflurane and isoflurane and significantly less than halothane in the degree to which it sensitizes the myocardium to the arrhythmogenic effects of catecholamines.[5,6] The potential for maintaining heart rate combined with lack of airway irritation and rapid emergence[7] suggests that sevoflurane may be an excellent alternative to halothane for use during induction and maintenance of anesthesia in pediatric patients. This study was undertaken to evaluate the clinical characteristics of sevoflurane (with and without nitrous oxide) compared with halothane with nitrous oxide in children requiring general anesthesia.

## Methods and Materials

This randomized, prospective, partially blinded study was conducted at Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania, and The Hospital for Sick Children, Toronto, Ontario, and was approved by the Institutional Review Boards at both institutions. Informed consent was obtained from parents. One hundred twenty patients (ASA physical status 1–2) 1–12 yr of age having low- to moderate-risk elective surgical procedures were studied. Inclusion criteria were an expected surgery time of 1–5 h, tracheal intubation, and overnight hospitalization.

Patients were randomized to one of three study groups: sevoflurane with oxygen (group S, n = 40), sevoflurane with nitrous oxide (66%) and oxygen (group SN, n = 40), and halothane with nitrous oxide (66%) and oxygen (group HN, n = 40). None of the children received preanesthetic medication. Inhalation induction of anesthesia was accomplished in all patients using a Mapleson D, F (Jackson-Rees modification of the Ayre's T-piece) or Bain (CPRAM$^{R}$) breathing system and an unscented face mask. Designated Ohmeda Modulus II Plus anesthesia machines equipped with halothane Tec 5 and sevoflurane Tec 3 vaporizers were used exclusively for patients in this study. For children in group HN, anesthesia was induced with halothane with nitrous oxide (66%) and oxygen. For children in group SN, anesthesia was induced with sevoflurane with nitrous oxide (66%) and oxygen. For children in group S, induction of anesthesia was identical to that for group SN patients except that nitrous oxide was omitted. Nitrous oxide and halothane or sevoflurane were initiated simultaneously in group HN and group SN, respectively. Anesthetic induction began with face mask application and was achieved using incremental dosing of anesthetic every three to five breaths. Halothane was begun at 0.5% and increased by increments of 0.5–1% (up to 4.5% maximum inspired concentration); sevoflurane was begun at 1% and increased by increments of 1.5% (up to 7% maximum inspired concentration). Spontaneous ventilation was maintained until loss of the ciliary (eyelash) reflex occurred.

Inhalational anesthesia *via* mask was continued using assisted or controlled ventilation, while an intravenous catheter was inserted for the infusion of 5% dextrose in lactated Ringer's or plain lactated Ringer's solution. Blood pressure and heart rate were recorded by automated sphygmomanometry; electrocardiogram and blood oxygen saturation by pulse oximetry were continuously monitored. End-tidal concentrations of halothane, sevoflurane, and carbon dioxide were measured using a calibrated Datex Capnomac Ultima monitor (Helsinki, Finland). Before intubation, end-tidal concentrations were monitored from gas samples obtained at the elbow connector of the face mask. After intubation, end-tidal concentrations were monitored from gas samples obtained using a 16-G intravenous catheter inserted into the lumen of the endotracheal tube through the right-angle elbow. Vagolytic agents, muscle relaxants, and other anesthetic adjuvants were avoided before tracheal intubation. Patients in groups HN and SN had no adjustment of the inspired nitrous oxide concentration before tracheal intubation. The end-tidal concentration of halothane or sevoflurane and the position of the vocal cords (open, midline, or closed) were noted at the time of tracheal intubation. After tracheal intubation, the end-tidal anesthetic concentration was adjusted to 1.3 MAC (1.2% halothane, 3.2% sevoflurane); nitrous oxide and oxygen were continued at the same concentrations used before intubation. End-tidal carbon dioxide tension was maintained between 30 and 40 mmHg using controlled ventilation. Body temperature was maintained within normal limits. Patients received vecuronium (up to 70 μg/kg) after intubation when neuromuscular blockade was clinically indicated. At one institution, neuromuscular blockade was monitored using a conventional nerve stimulator. At the other institution, neuromuscular blockade was monitored using a Puritan Bennett Datex NMT to assess

the evoked electromyogram response obtained from train-of-four stimulation of the adductor pollicis muscle at 10-s intervals.

Heart rate, systolic, diastolic, and mean arterial blood pressure, end-tidal carbon dioxide, respiratory rate, temperature, and inspired and end-tidal anesthetic concentrations were recorded every 2 min before surgical incision, at 1-min intervals for 5 min after incision, and then every 5 min until the end of surgery. The depth of anesthesia was assessed clinically by evaluation of changes in heart rate and blood pressure during surgery, and these were maintained within 20% of baseline values by adjustment of the inspired concentration of halothane or sevoflurane. At the discretion of the investigators, intraoperative opioids or regional nerve blocks could be administered.

During the last 10 min of surgery, the end-tidal concentration of inhaled anesthetic was adjusted to 1 MAC (0.9% halothane, 2.5% sevoflurane). The concentration of nitrous oxide was not adjusted. If necessary, residual neuromuscular blockade was completely antagonized using neostigmine (50–60 μg/kg) and glycopyrrolate (10 μg/kg) or atropine (25 μg/kg) before emergence from anesthesia. At the end of surgery, all anesthetic agents were discontinued simultaneously. The trachea was extubated when the gag reflex had returned and the patients were breathing spontaneously and making purposeful movements.

Airway-related complications, including breathholding (>15 s), laryngospasm (inability to ventilate effectively in the presence of a patent pharyngeal airway associated with an $Sp_{O_2}$ less than 90%), and excitement (nonpurposeful movement requiring restraint), were noted during induction. The time from initiation of anesthetic agent to loss of the eyelash reflex (induction time) was recorded. The intervals from mask application to intubation, surgical incision, and discontinuation of the anesthetic (duration of anesthesia) were measured. The intervals from discontinuation of the anesthetic to patient response by hip flexion or bucking (time to hip flexion), extubation (time to extubation), administration of first postoperative analgesic (time to first analgesic), and attaining discharge criteria from the recovery room were recorded by an observer blinded to the anesthetic agents administered to each patient.

For each patient, the MAC-hour exposure to halothane and sevoflurane was determined using a time-weighted (to compensate for variable data collection intervals) average end-tidal anesthetic concentration and age-specific minimum alveolar concentration values.[4]

The occurrence of all perioperative adverse experiences was documented. Urine for routine urinalysis and blood for measurement of complete blood count and serum sodium, potassium, chloride, uric acid, glucose, urea nitrogen, creatinine, albumin, total bilirubin, aspartate aminotransferase, alanine aminotransferase, total protein, calcium, phosphorus, lactic dehydrogenase, and alkaline phosphatase were obtained at induction of anesthesia and approximately 18–24 h postoperatively. In addition, plasma samples were obtained for fluoride analysis at induction of anesthesia, at the end of anesthesia, and at 1, 4, 6, 12, and 18–24 h after discontinuation of the anesthetic.

All data are reported as mean ± SD unless otherwise noted. Data between institutions were compared using an unpaired *t* test. Between-group comparison of parametric data was analyzed using one-way ANOVA and Scheffé's F test. Between-group comparison of nonparametric data was analyzed using Kruskal-Wallis test. Between-group comparison of vocal cord position at intubation and the incidence of adverse experiences were compared using Fisher's exact test. Between-group comparison of serial measurements of heart rate, blood pressures, and end-tidal carbon dioxide were determined using repeated measures ANOVA and Scheffé's F test to assess the following time periods: (1) 1 min preinduction until 6 min postinduction (induction period), (2) 1 min preintubation until 6 min postintubation (intubation period), and (3) 1 min preincision until 5 min postincision (incision period). Times to hip flexion and extubation were compared with duration of anesthesia using Spearman's rank correlation and Pearson's correlation, respectively. Differences were considered statistically significant when $P < 0.05$.

## Results

Fifty-nine patients were enrolled in Pittsburgh (group S, n = 20; group SN, n = 19; group HN, n = 20), and 61 patients were enrolled in Toronto (group S, n = 20; group SN, n = 21; group HN, n = 20).

Age did not differ between institutions, but children studied in group S in Pittsburgh (28.7 ± 8.0 kg, n = 20) were significantly heavier than children studied in group S in Toronto (23.0 ± 6.8 kg, n = 20). Because no significant difference between institutions was found in the induction or emergence data, hemodynamic data,

and adverse experience data, the Pittsburgh and Toronto data were combined for comparisons between groups S, SN, and HN.

The grand mean age was 6.2 ± 2.9 yr. The grand mean weight was 23.8 ± 9.7 kg. Age, weight, times to loss of eyelash reflex, times to incision and hip flexion, duration of anesthesia, and MAC-hours (table 1) were similar among patients in groups S, SN, and HN. The maximum anesthetic doses received by a patient in each group were 9.6 MAC-hours (group S), 7.0 MAC-hours (group SN), and 4.5 MAC-hours (group HN).

One patient (group HN) received glycopyrrolate (3 μg/kg) to treat copious oral secretions, one patient (group S) received vecuronium (100 μg/kg) because of emesis during induction, three patients (one in group S and two in group HN) received succinylcholine to treat laryngospasm, and two patients (group S) received succinylcholine because of emesis or excitement during induction. An additional two patients (group S) received succinylcholine after intubation because of excessive movement. An additional 22 patients (4 in group S, 10 in group SN, and 8 in group HN) received vecuronium (up to 70 μg/kg) after intubation to facilitate the surgical procedure. Of the 23 patients who received vecuronium, 11 patients had their residual neuromuscular blockade completely antagonized with neostigmine (50–60 μg/kg) and glycopyrrolate (10 μg/kg) or atropine (25 μg/kg) before emergence from anesthesia. In the remaining 12 patients, complete spontaneous electromyogram recovery occurred before anesthetic emergence, and consequently, these patients received no neuromuscular reversal agents.

Six patients (four in group S and two in group HN) who received muscle relaxant before intubation were excluded from the calculations of time to intubation, vocal cord position, and end-tidal anesthetic concentration at intubation. Time to intubation was significantly greater in group S when compared with groups SN and HN (table 1). The distribution of vocal cord positions at intubation was similar between group S (30 open, 5 midline, 1 closed), group SN (31 open, 8 midline, 1 closed), and group HN (34 open, 4 midline, 0 closed). End-tidal carbon dioxide immediately before intubation did not differ among the three groups. The end-tidal anesthetic concentrations at intubation in groups S, SN, and H were 5.3 ± 0.6% sevoflurane, 4.9 ± 0.7% sevoflurane, and 3.1 ± 0.6% halothane, respectively. However, the end-tidal minimum alveolar concentration multiple of potent inhalational anesthetic at the time of intubation was significantly greater in patients receiving halothane than in patients receiving sevoflurane (table 1).

Times to extubation and attaining discharge criteria from recovery room were significantly less in groups S and SN than in group HN (table 1). Because exclusion of patients receiving intraoperative analgesics from the comparisons of time to extubation and time to hip flexion did not significantly change the results, these patients are included in table 1. There was no correlation between time to extubation or time to hip flexion and duration of anesthesia.

Two of 59 patients at one institution received regional nerve block using bupivacaine (0.25%) at the end of surgery for caudal (one in group HN) and intercostal (one in group S) nerve block. At the other institution, 15 of 61 patients (eight in group S, six in group SN, and one in group HN) received intravenous fentanyl (1–8 μg/kg) intraoperatively, and an additional 26 patients (7 in group S, 8 in group SN, and 11 in group HN) received regional nerve block after intubation. Because a large number of patients (67%) studied at this institution received intraoperative analgesics (opioid or nerve block), only patients at the other institution who did not receive intraoperative analgesics were included in the analysis of time to first analgesic. Time to first analgesic in patients who received no intraoperative analgesics was significantly less in group S and group SN than in group HN (table 1).

The analysis of heart rate and blood pressure trends during the induction, intubation, and incision periods excluded patients who received succinylcholine or glycopyrrolate. No patient developed hypotension, hypertension, bradycardia, or tachycardia requiring treatment other than adjustment of the anesthetic concentration delivered. During induction, patients in groups S and SN maintained significantly higher average heart rates and systolic blood pressures than patients in group HN (table 2). Mean and diastolic blood pressures did not differ between groups during the induction period. No significant difference was found between groups in heart rate or systolic, mean, or diastolic blood pressures during the intubation or incision periods.

The incidence of excitement during induction of anesthesia and movement during maintenance of anesthesia was significantly greater in group S than in groups SN and HN. There was no other significant difference in the incidence of adverse experiences between the three groups (table 3).

**Table 1. Induction and Emergence Data**

| | Group S | Group SN | Group HN |
|---|---|---|---|
| Duration of anesthesia (min) | 132 ± 73 | 124 ± 64 | 112 ± 47 |
| MAC-hours (% h) | 2.8 ± 1.6 | 2.6 ± 1.5 (n = 38) | 2.5 ± 1.1 |
| Time to loss of eyelash reflex (min) | 1.9 ± 0.9 | 1.6 ± 0.7 | 1.7 ± 0.6 (n = 39) |
| Time to intubation (min) | 6.2 ± 1.8† (n = 36) | 5.1 ± 1.9 | 5.2 ± 1.4 (n = 38) |
| End-tidal MAC multiple at intubation | 2.1 ± 0.2 (n = 33) | 2.0 ± 0.3 (n = 39) | 3.4 ± 0.7† (n = 36) |
| Time to incision (min) | 37.3 ± 17.8 | 32.4 ± 15.5 | 31.9 ± 11.8 |
| Time to hip flexion (min) | 6.8 ± 9.9‡ (n = 39) | 5.9 ± 2.6 (n = 36) | 6.8 ± 2.8 (n = 39) |
| Time to extubation (min) | 7.7 ± 2.5 | 8.3 ± 2.5 | 11.4 ± 4.0† |
| Time to first postoperative analgesic (min)* | 18.0 ± 9.0 (n = 16) | 14.2 ± 6.5 (n = 13) | 36.8 ± 25.3 (n = 9) |
| Time to attaining discharge criteria (min) | 46.2 ± 2.9 | 50.0 ± 2.9 | 60.2 ± 2.9† |

Values are mean ± SD (n = 40) unless otherwise noted.

* Excludes all patients studied at one institution where intraoperative opioids or regional nerve blocks were routinely used; also excludes two patients at the other institution who received regional nerve blocks and 19 patients who required no analgesics prior to discharge from the recovery room.

† Significantly different from the other two groups ($P < 0.05$).

‡ Median value is 5.0.

There were no clinically significant differences between groups with regard to changes in urinalysis, hematology, or chemistry values between initial and final evaluation.

Inorganic fluoride concentrations in groups S and SN were significantly greater than those in group HN from initial to final evaluation. The maximum mean concentrations of inorganic fluoride were 15.5 μM in group S

**Table 2. Systolic Blood Pressure, Diastolic Blood Pressure, Mean Blood Pressure, and Heart Rate Trends during Induction of Anesthesia**

| | Group S (n = 35) | Group SN (n = 40) | Group HN* (n = 38) |
|---|---|---|---|
| **Systolic blood pressure (mmHg)** | | | |
| 1 min before | 113 ± 14 | 114 ± 14 | 111 ± 14 |
| Baseline† | 120 ± 16 | 114 ± 15 | 118 ± 17 |
| 2 min after | 117 ± 22 | 105 ± 23 | 102 ± 19 |
| 4 min after | 113 ± 21 | 106 ± 19 | 95 ± 16 |
| 6 min after | 110 ± 20 | 104 ± 20 | 92 ± 21 |
| **Heart rate (beats/min)** | | | |
| 1 min before | 102 ± 19 | 103 ± 27 | 99 ± 21 |
| Baseline† | 107 ± 21 | 107 ± 26 | 106 ± 26 |
| 2 min after | 115 ± 21 | 110 ± 24 | 98 ± 25 |
| 4 min after | 120 ± 23 | 120 ± 28 | 96 ± 21 |
| 6 min after | 116 ± 22 | 105 ± 22 | 89 ± 18 |
| **Mean blood pressure (mmHg)** | | | |
| | 79 ± 10 | 78 ± 13 | 76 ± 14 |
| | 85 ± 13 | 82 ± 17 | 82 ± 17 |
| | 84 ± 22 | 77 ± 19 | 70 ± 14 |
| | 78 ± 20 | 74 ± 17 | 67 ± 15 |
| | 76 ± 16 | 69 ± 18 | 63 ± 16 |
| **Diastolic blood pressure (mmHg)** | | | |
| | 60 ± 10 | 62 ± 13 | 57 ± 14 |
| | 66 ± 14 | 63 ± 13 | 64 ± 17 |
| | 60 ± 16 | 59 ± 20 | 55 ± 13 |
| | 59 ± 19 | 56 ± 17 | 51 ± 14 |
| | 56 ± 16 | 50 ± 16 | 48 ± 17 |

Values are mean ± SD.

* Significantly different from group S and group SN over time ($P < 0.05$).

† Baseline measurements were made at the time of simultaneous face mask application and beginning of anesthetic administration.

**Table 3. Combined Data for Adverse Experiences in Patients from Pittsburgh and Toronto**

| | Group S (n = 40) (%) | Group SN (n = 40) (%) | Group HN (n = 40) (%) |
|---|---|---|---|
| Induction | | | |
| Coughing | 15.0 | 10.0 | 17.5 |
| Breath holding | 2.5 | 0.0 | 10.0 |
| Laryngospasm | 2.5 | 0.0 | 5.0 |
| Bronchospasm | 2.5 | 0.0 | 0.0 |
| Excitement | 35.0* | 5.0 | 5.0 |
| Emesis | 10.0 | 7.5 | 2.5 |
| Maintenance | | | |
| Movement at skin incision | 12.5* | 0.0 | 0.0 |
| Extrasystoles | 0.0 | 2.5 | 2.5 |
| Emergence | | | |
| Emesis | 5.0 | 0.0 | 5.0 |
| Postoperative | | | |
| Nausea | 15.0 | 17.5 | 12.5 |
| Emesis | 60.0 | 45.0 | 65.0 |

* Significantly different from other two groups ($P < 0.05$).

14.7 μM in group SN, and 1.8 μM in group HN. In all patients except three who were anesthetized with sevoflurane, the maximum serum fluoride concentration occurred either at the end of anesthesia or 1 h after discontinuation of the anesthetic agent. Among the three patients with late peak fluoride values occurring at 6 h after discontinuation of the anesthetic agent, peak fluoride values were all less than 11 μM. The highest serum fluoride level measured during the study was 28 μM, and this was in a patient in group SN after 7.0 MAC-hours of anesthesia.

## Discussion

Halothane remains the anesthetic used most frequently for inhalational induction in children because it produces less airway irritation than enflurane,[8] isoflurane,[8,9] or desflurane.[10] Despite its efficacy and frequency of use, however, halothane is not an ideal induction agent because of its potential to cause bradycardia, hypotension, and ventricular ectopy.[11–14] Although the use of halothane in adults has diminished markedly, a suitable replacement is needed before halothane is supplanted in the practice of pediatric anesthesia. The pleasant, nonpungent odor of sevoflurane and its low blood-gas partition coefficient suggest that it may be a suitable alternative to halothane for use in pediatric anesthesia.

Our study demonstrates that inhalational induction of anesthesia with sevoflurane and nitrous oxide is similar to that with halothane and nitrous oxide in that neither stimulates airway reflexes and both appear to be equally well tolerated when administered with nitrous oxide.

The speed of inhalational induction is determined not only by an anesthetic's airway irritation but also by its solubility, the maximum inspired concentration, and the rate at which the maximum inspired concentration is achieved. Although the blood-gas partition coefficients predict that induction should be more rapid with sevoflurane than with halothane, we observed no difference in induction times. The rate at which the maximum inspired concentration was achieved by incremental dosing was comparable for halothane and sevoflurane in our study. However, the degree of anesthetic "overpressure" (high inspired concentrations provided for initial wash-in) with halothane (4.5% maximum inspired = 5.0 MAC) was greater than that with sevoflurane (7% maximum inspired = 2.8 MAC) and may have accelerated the halothane induction times. The maximum concentration that can be delivered by the Sevotec 3 vaporizer is 7%; this suggests that the limitation of induction time for sevoflurane may be a function of the vaporizer.

We used a conventional incremental dosing technique to establish the maximum inspired anesthetic concentration. Yurino and Kimura[15] recently compared conventional inhalation induction to vital capacity rapid inhalation induction using 4.5% sevoflurane and nitrous oxide (66%) in unpremedicated adult patients. Vital capacity rapid inhalation induction was better tolerated than conventional inhalation induction, and induction time was 50% faster, decreasing from 108 s to 54 s. Although the Sevotec 3 vaporizer used in our study delivers up to 7% sevoflurane, the study protocol did not permit a rapid induction technique. Future studies are needed to determine the applicability of rapid sevoflurane induction in children and its ability to further accelerate anesthetic induction.

Our initial hypothesis was that the low blood-gas partition coefficient of sevoflurane (0.6–0.7) might make superfluous the use of nitrous oxide (blood-gas partition coefficient = 0.47) during inhalational induction. Although avoiding nitrous oxide theoretically provides a greater safety margin for the patient in the event of an airway complication during anesthetic induction, we found the omission of nitrous oxide during induction with sevoflurane to be unsatisfactory. Excitement

occurred in 35% of patients and prolonged the time required to achieve safe intubating conditions. Once adequate anesthetic depth was achieved, intubation was accomplished easily, and the degree of vocal cord relaxation at intubation was similar for our three study groups. It remains to be demonstrated in children whether a "single-breath induction" dosing technique[15–19] might improve the quality of induction with sevoflurane with oxygen.

Another explanation for the beneficial effect of nitrous oxide during induction is its additive effect on minimum alveolar concentration. The administration of nitrous oxide permitted delivery of a higher minimum alveolar concentration multiple to patients in group SN than in group S and thus conveyed an advantage during anesthetic overpressure. However, the additive effects of nitrous oxide minimum alveolar concentration and sevoflurane minimum alveolar concentration vary in different age groups. Whereas, in adults, the addition of 64% nitrous oxide decreased sevoflurane minimum alveolar concentration by 61%,[20,21] in children, 60% nitrous oxide decreased sevoflurane minimum alveolar concentration by only 20%.[4,22]

Group S and group SN patients both received the same end-tidal sevoflurane concentrations before skin incision (3.2%) and before emergence (2.5%). This small discrepancy in potency (minimum alveolar concentration) with the addition of nitrous oxide made no significant difference between groups S and SN in the time to emergence. However, it may account for the greater incidence of movement at the time of skin incision observed in patients receiving sevoflurane with oxygen (group S). Movement occurred at the time of skin incision in group S patients who had received no opioid or regional anesthetic. Sevoflurane (3.2% end-tidal) without nitrous oxide or other supplementation did not reliably prevent movement at the time of skin incision as it did when delivered with nitrous oxide. Although the potentiation of sevoflurane minimum alveolar concentration by nitrous oxide in children is reported to be minimal, it appears to be clinically important. However, we cannot exclude the possibility that the movement observed with some group S patients was related to an end-tidal anesthetic concentration too close to its minimum alveolar concentration value.

Emergence from anesthesia was significantly faster in patients receiving sevoflurane (with or without nitrous oxide) than in patients receiving halothane and nitrous oxide (more than 3 min difference). Time to attaining discharge criteria from the recovery room with patients receiving sevoflurane occurred significantly earlier than with patients receiving halothane (10 min difference). Among the patients who did not receive intraoperative analgesics, those who received sevoflurane also required postoperative analgesics earlier than those who received halothane. The earlier times for extubation, requiring pain medication, and discharge readiness suggest that sevoflurane provided more rapid emergence and earlier awakening than halothane.

The majority of patients who did receive intraoperative analgesics at one institution were in group S or SN (14 of 41), and not in group HN (1 of 20). The investigators at this institution were concerned that the rapid emergence from sevoflurane anesthesia might be associated with pain-related delirium. Whether there is a difference between the analgesic properties of sevoflurane and halothane remains to be demonstrated.

Hemodynamic changes during anesthesia were evaluated. In our study, children receiving halothane tended to have a decrease in heart rate during the anesthetic induction period, whereas children receiving sevoflurane maintained or increased heart rate. The decrease in systolic blood pressure during induction was greater in patients receiving halothane than in those receiving sevoflurane. While it is possible that these differences are related to different properties of the two anesthetics, they may have resulted from differences in delivered anesthetic dose. During induction, halothane was administered in a higher dose (3.4 MAC) than sevoflurane (2.0 MAC).

Metabolism of anesthetic agents is a major concern with respect to potential toxicities. Although sevoflurane was reported as a new anesthetic in the 1970s, initial studies raised concerns about its metabolism to organic and inorganic fluoride as well as the formation of toxic compounds in the presence of soda lime.[23–26] Because our protocol required the use of a Mapleson breathing apparatus and did not include the measurement of sevoflurane degradation byproducts, we could draw no conclusions about the significance of soda lime or other degradation byproducts of sevoflurane in children. Further studies may be necessary to determine the compatibility and toxicity of sevoflurane with various breathing circuits.

Metabolism of sevoflurane *in vivo* occurs to a similar extent as with enflurane,[3,27–29] producing inorganic fluoride ion and hexafluoroisopropanol. Although hexafluoroisopropanol is not associated with known toxicity, fluoride ion-induced nephrotoxicity has been reported after administration of methoxyflurane.[30–32] In-

terestingly, nephrotoxicity from sevoflurane has not been reported, although serum fluoride concentrations in excess of 50 μM have been documented in some adult patients.[33,‖] It has been suggested that sevoflurane exposures up to 15 MAC-hours in adults are safe.‖ Although the risk of sevoflurane toxicity in children remains unknown, the evidence indicates that children may metabolize inhalational anesthetics less than do adults. Specifically, peak serum fluoride concentrations obtained in children exposed to methoxyflurane are much lower than those obtained in adults.‖ None of the patients in our study had a high serum fluoride concentration.

In conclusion, sevoflurane with nitrous oxide is effective for inhalational induction and maintenance of and emergence from anesthesia. Because of the limitations of anesthetic delivery (7% maximum sevoflurane), the low solubility in blood of sevoflurane does not provide more rapid anesthetic induction than halothane when each is administered incrementally. However, emergence from anesthesia appears to be more rapid in children anesthetized with sevoflurane (with or without nitrous oxide) for up to 9.6 MAC-hours compared with halothane and nitrous oxide. Hemodynamic stability and a low incidence of airway-related complications provided during inhalational induction coupled with rapid emergence suggest that sevoflurane may be a reasonable alternative to halothane in children.

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