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Desflurane and Isoflurane in Surgical Patients: Comparison of Emergence Time

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In order to examine the clinical potential of desflurane (difluoromethyl-1-fluoro-2,2,2-trifluoroethyl ether) in humans, a randomized, controlled study was designed to compare time of emergence from anesthesia in patients undergoing elective surgery under desflurane anesthesia to that of patients under isoflurane anesthesia. Twenty-eight patients were randomly divided into four groups. Group 1 received isoflurane 0.65 MAC; group 2, desflurane 0.65 MAC; group 3, isoflurane 1.25 MAC; and group 4, desflurane 1.25 MAC. Anesthesia was induced with sodium thiopental, and N_2O 60% was added to the volatile agent. Mean anesthetic exposure times (min [mean ± SD]) were 108 ± 49 in group 1, 132 ± 46 in group 2, 147 ± 74 in group 3, and 166 ± 71 in group 4, with no significant differences between groups. The times from discontinuation of anesthetic gases until patients opened their eyes and squeezed the investigator's hand in response to a command were averaged and recorded as "emergence time." Emergence time was significantly less with desflurane than with isoflurane given at the same MAC. Patients receiving isoflurane 0.65 MAC responded to commands 15.6 ± 4.3 min after discontinuation of the anesthetic; patients in the desflurane 0.65 MAC group responded in 8.8 ± 2.7 min ($P < 0.01$). Emergence time for isoflurane 1.25 MAC was 30.0 ± 11.0 min; for desflurane 1.25 MAC it was 16.1 ± 6.0 min ($P < 0.05$). Our results confirm that emergence from desflurane anesthesia is more rapid than from isoflurane. (Key words: Anesthetics, volatile: desflurane; isoflurane.)

Desflurane (difluoromethyl-1-fluoro-2,2,2-trifluoroethyl ether) is a new volatile anesthetic currently under clinical investigation. A potential major advantage over currently available agents is that the blood/gas partition coefficient of desflurane is 0.42, significantly lower than that of all clinically used halogenated agents, and even lower than that of N_2O (0.46).[1,2] This property predicts more rapid induction of and emergence from anesthesia with desflurane relative to other potent volatile agents; this has been confirmed in animal experiments and preliminary human studies.[3–7] In order to examine the clinical potential of desflurane in humans, a randomized, controlled study was designed to compare emergence times in patients undergoing elective surgery with desflurane or isoflurane anesthesia.

Materials and Methods

Subjects

The study had the approval of the Institutional Review Board of the Columbia–Presbyterian Medical Center, and written informed consent was obtained from all subjects. Twenty-eight patients (8 women, 20 men), aged 18–64 yr, weight 50–100 kg, were studied during elective surgery. None of the operations was intraabdominal, intrathoracic, or intracranial, and all were expected to last at least 60 min. The patients all were ASA Physical Status 1 or 2, and had not taken medications known to affect anesthetic depth or MAC for at least 7 days. No women of childbearing potential were studied. Baseline laboratory values, including serum electrolytes, BUN, creatinine, complete blood count, liver function tests, and ECG were all within normal limits.

Conduct of Anesthesia

According to a randomly generated table of assignments, patients were assigned to one of four groups, each to receive a specific concentration (0.65 or 1.25 MAC) of isoflurane or desflurane with 60% N_2O in O_2 for maintenance of anesthesia. Group 1 received isoflurane 0.65 MAC; group 2 received desflurane 0.65 MAC; group 3 received isoflurane 1.25 MAC; and group 4 received desflurane 1.25 MAC. The percentage equivalents of MAC were taken to be 1.28% for isoflurane and 7.25% for desflurane.[1,2] For desflurane, this resulted in end-tidal concentrations of 4.7% (0.65 MAC) and 9.1% (1.25 MAC); for isoflurane the relevant concentrations were 0.8 and 1.6%. The subjects received no preanesthetic medication until after they arrived in the operating suite. After insertion of an intravenous (iv) catheter, midazolam 0.03 mg/kg was administered iv 5–15 min before anesthetic induction.

All patients were monitored by continuous electrocardiogram (lead II), automated blood pressure cuff, pulse oximeter, and a temperature probe (axillary before intubation, esophageal after intubation). End-tidal CO_2,

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TABLE 1. Patient Data

Group	Anesthetic MAC	M	F	Age (yr)	Weight (kg)
1	ISO 0.65	4	3	44.9 ± 16.2	72.9 ± 11.0
2	DES 0.65	5	2	42.9 ± 16.2	76.2 ± 8.9
3	ISO 1.25	6	1	43.6 ± 14.6	79.5 ± 12.8
4	DES 1.25	5	2	47.1 ± 16.5	70.1 ± 13.1

Values are mean ± SD.
ISO = isoflurane; DES = desflurane.
No significant differences among groups.

N_2O, O_2, and isoflurane or desflurane were measured with a modified Datex 254 Airway Gas Analyzer (Puritan-Bennett). Patients receiving isoflurane were anesthetized with the standard anesthesia machine in the operating room. The anesthesia machine used for patients in the desflurane groups was a modified Ohmeda (Madison, WI) DM5000 machine equipped with a temperature-controlled vaporizer and pressurized to approximately 1,520 mmHg to allow controlled delivery of desflurane, a compound with a boiling point of 23.5° C at atmospheric pressure.

While the patients breathed 100% O_2, anesthesia was induced with sodium thiopental (5 mg/kg). Ventilation *via* mask (controlled or assisted, as necessary) was instituted with slowly increasing concentrations of isoflurane or desflurane in 60% N_2O/40% O_2. No muscle relaxants were given during induction. Occasionally, an additional dose of thiopental (0.5–2 mg/kg) was administered to facilitate increasing the concentration of the inspired anesthetic and to avoid or treat excitement or airway irritability. Tracheal intubation was performed after satisfactory anesthetic depth was achieved, as determined by the attending anesthesiologist. During laryngoscopy, the trachea was sprayed with lidocaine (160 mg in 4 ml) and then intubated. The time from induction to intubation was typically 8–12 min, with the expired concentration of isoflurane or desflurane at approximately 1–1.5 MAC. After intubation, the anesthetic concentration was adjusted to the appropriate end-tidal concentration and maintained constant until near the end of surgery. If clinically indicated, ephedrine (5–10 mg) or phenylephrine (40–160 μg) was administered to maintain systemic blood pressure at acceptable levels. Similarly, labetalol was given in doses of 5–10 mg to control hypertension or tachycardia. End-tidal CO_2 concentration ($P_{ET_{CO_2}}$) was maintained at 30–35 mm Hg with controlled ventilation.

All anesthetic gases were discontinued approximately 5 min prior to the anticipated end of surgery in groups 1 and 2 (0.65 MAC), and 10 min prior to the anticipated end of surgery in groups 3 and 4 (1.25 MAC). The lungs were ventilated with 100% O_2 at a fresh gas flow of 5 l/min, maintaining $P_{ET_{CO_2}}$ at 30–35 mm Hg. When spontaneous ventilation resumed at this CO_2 level, the patients were allowed to breathe spontaneously. At least once every minute after the anesthetic was discontinued, the patient was asked to open his or her eyes and to squeeze the investigator's hand. The time from discontinuation of the anesthetic until a positive response to each of these requests was recorded; the two times were averaged and the average recorded as "emergence time." Typically, the time of eye opening and hand squeezing differed by 0–2 min.

DATA ANALYSIS

Patient variables (age and weight), emergence times, anesthetic exposure times, and thiopental doses for each group were compared to the other groups by one-way analysis of variance (ANOVA). Scheffe's F-test was used to demonstrate the statistical significance of any differences at the $P < 0.05$ level. P values of < 0.05 were considered statistically significant.

Results

SUBJECTS

There were no significant differences between the groups with regard to age, weight, sex distribution, amount of thiopental required during induction, or anesthetic exposure time, although desflurane exposures tended to be longer (tables 1 and 2). Several patients in each group exhibited some airway irritation or laryngospasm during the induction; this was minimized by increasing the concentration of agent slowly. One patient in a desflurane group received succinylcholine (60 mg) because of laryngospasm during induction. This patient was the second patient studied with desflurane, and the administered concentration of desflurane had been increased to 10% in the first 30 s after thiopental induction. A total of eight patients received ephedrine or phenylephrine arterial blood pressure support (two patients in

TABLE 2. Emergence Times

Group	Anesthetic MAC	Exposure Time (min)	Thiopental Dose (mg/kg)	Emergence Time (min)
1	ISO 0.65	108 ± 49	5.8 ± 1.0	15.6 ± 4.3*†
2	DES 0.65	132 ± 46	5.6 ± 0.5	8.8 ± 2.7†‡
3	ISO 1.25	147 ± 74	5.8 ± 1.0	30.0 ± 11.0*‡§
4	DES 1.25	166 ± 71	6.0 ± 0.9	16.1 ± 6.0*†

Values are mean ± SD.
ISO = isoflurane; DES = desflurane.
* $P < 0.05$ *versus* DES 0.65.
† $P < 0.05$ *versus* ISO 1.25.
‡ $P < 0.05$ *versus* DES 1.25.
§ $P < 0.05$ *versus* ISO 0.65.

group 2, four in group 3, and two in group 4), and one patient (group 4) received labetalol 10 mg, during surgery. There were no significant adverse reactions in any subject.

Emergence Time

Patients awoke more rapidly from desflurane than from isoflurane. In groups 1 and 2 (0.65 MAC), the emergence times (mean ± SD) were 15.6 ± 4.3 min for isoflurane and 8.8 ± 2.7 min for desflurane ($P < 0.01$). In groups 3 and 4, receiving 1.25 MAC, the times were 30.0 ± 11.0 min and 16.1 ± 6.0 min, for isoflurane and desflurane, respectively ($P < 0.05$) (fig. 1, table 2). When the data were analyzed with either of the emergence criteria alone (eye opening or hand grip in response to command), none of the emergence times changed by more than 1.5 min, and the relative times of emergence were unchanged. Emergence time did not correlate significantly with exposure time (min) of either anesthetic.

Discussion

We have demonstrated that anesthesia with desflurane is associated with significantly more rapid emergence than is that with isoflurane, at two different doses, when each is administered with N_2O. At both doses, 1.25 and 0.65 MAC, patients awoke from desflurane/N_2O in approximately half the time of awakening from isoflurane/N_2O. Clearly, this emergence time—which we defined as the time from discontinuation of the anesthetic agents from a constant end-tidal concentration until patients obeyed simple commands (eye opening and hand squeeze)—does not represent the end of all anesthetic effect, nor does it define an "awake" state. However, it is a relatively objective measure of increasing consciousness, and one might expect other measurements of awareness, memory, and "street readiness" or "ward readiness" to follow the same pattern. We did not assess these parameters, although this will certainly be a important area for further investigation.

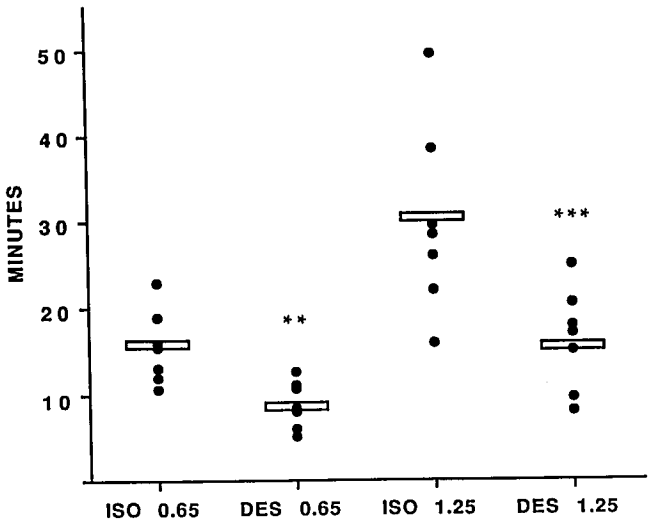

FIG. 1. Individual emergence times for the 28 subjects (n = 7 per group) (filled circles). Rectangles = means for each group. $**P < 0.01$ *versus* ISO 0.65. $***P < 0.05$ *versus* ISO 1.25.

All of the study patients received a dose of midazolam several minutes before anesthetic induction, and anesthesia was induced with sodium thiopental; some patients received additional small doses of thiopental during the induction period. Lidocaine was administered intratracheally to all patients before intubation. All of these drugs may prolong emergence from desflurane and isoflurane, relative to either anesthetic given without adjuvants. Because most of the operations were greater than 2 h in duration, the effect of the iv induction agents is likely to have been small. In addition, similar prolongation would be expected in each group, and thus the significance of our results is unlikely to be affected by our use of these iv agents. The use of iv induction adds clinical relevance to these results, since in most cases potent volatile agents, including desflurane, will be administered after iv induction.

Another effect of the use of iv agents for induction may be a slightly prolonged emergence for patients undergoing shorter operations, since more of the thiopental and midazolam remains present during emergence. This factor may partially explain the lack of correlation of anesthetic exposure time with emergence time in our patients: the effect of the thiopental and midazolam may be more significant at the end of the shorter operations, such that these emergence times were relatively prolonged compared with those after longer cases. It is possible that more sophisticated tests of neurologic recovery might have detected a correlation between recovery time and duration of exposure. A correlation between anesthetic exposure time and anesthetic recovery has been reported for both isoflurane and desflurane in rats; the recovery time from isoflurane increased more than that from desflurane as the length of anesthetic exposure increased.[3]

The variable time from the discontinuation of the anesthetic gases to the end of surgery may be a confounding factor in the analysis of the emergence times in this study. In patients receiving 1.25 MAC, anesthetic gases were discontinued approximately 10 min before the anticipated end of surgery, as compared to 5 min in the 0.65 MAC groups. We could have waited until all surgical stimulation had ceased before discontinuation of the anesthetics, in order to prevent surgical stimulation from causing an earlier awakening than might be expected in the absence of stimulation; however, we opted to administer the anesthetics in a manner similar to that in which they are and will be used clinically.

All of our patients were anesthetized with 60% N_2O in addition to the assigned concentration of volatile agent. N_2O appeared to "wash out" significantly more quickly than either volatile agent, as indicated by its end-tidal concentrations of essentially zero at emergence, and is unlikely to have had much effect on the difference between the two agents. Although N_2O has a slightly higher blood solubility than does desflurane, its tissue solubility (fat and muscle) is lower; therefore its alveolar concentration decreases at a greater rate upon discontinuation of the anesthetic.

The values of MAC used for isoflurane and desflurane are the MAC values for young patients (21–30 yr old); no correction was used for age.[8] Various aspects of desflurane were being studied in related protocols at several institutions, and the decision was made after preliminary experiments to standardize studies with one dose for all age groups.§ Because there is limited clinical experience with desflurane, there still is some controversy over the appropriate MAC value, especially since most of the published values have been determined in volunteers and with a nonclassical stimulus (tetanic stimulation of the ulnar nerve). Reported values in humans have ranged from 5.0 to 7.25%.[6,8] MAC values decrease with age, but the ages of the four groups in the current study were so similar (table 1) that it appears unlikely that any significant bias could have been introduced by keeping the concentrations of anesthetic identical in all age groups.

Many of our patients underwent orthopedic and other painful operations, and most received an opioid (fentanyl or morphine) immediately after awakening in the operating room, or in the recovery room. We did not compare the groups with respect to their need for opioids, or for the effect of opioid administration on the progress of anesthetic recovery.

In conclusion, we have demonstrated that desflurane leads to a more rapid emergence than does isoflurane when given with N_2O to surgical patients under clinical conditions and in a controlled, randomized manner. Our data suggest that desflurane may have significant clinical potential in a wide range of surgical and anesthetic settings in which rapid, clear emergence and ability to alter anesthetic depth quickly is desired.

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