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Clinical Characteristics of Desflurane in Surgical Patients: Minimum Alveolar Concentration

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Desflurane (formerly I-653) is a new inhalational anesthetic with a promising pharmacokinetic profile that includes low solubility in blood and tissue, including fat. Since its lipid solubility is less than that of other volatile agents, it may have lower potency. Low solubility would be expected to increase the rate at which alveolar concentration approaches inspired concentration during induction as well as to increase the rate of elimination of desflurane from blood at emergence. We determined the minimum alveolar concentration (MAC) of desflurane in 44 unpremedicated ASA physical status 1 or 2 patients undergoing elective surgery. We prospectively studied four patient groups distinguished by age and anesthetic regimen: 18–30 *versus* 31–65 yr and desflurane in 60% N_2O/40% O_2 *versus* desflurane in O_2. Anesthesia was induced with desflurane or desflurane in 60% N_2O/40% O_2. MAC was determined by a modification of Dixon's up-and-down method with increments of 0.5% desflurane. The MAC of desflurane in O_2 was 7.25 ± 0.0 (mean ± SD) in the 18–30-yr age group, and 6.0 ± 0.29 in the 31–65-yr group; the addition of 60% N_2O reduced the MAC to 4.0 ± 0.29 and 2.83 ± 0.58, respectively. The median time from discontinuation of desflurane to an appropriate response to commands was 5.25 min. Desflurane appears to be a mild airway irritant but was well tolerated by all patients. (Key words: Anesthesia, requirements: MAC. Anesthetics, gaseous: nitrous oxide. Anesthetics, volatile: desflurane. Potency, anesthetic: MAC.)

A CLEAR TREND in the development of new anesthetic pharmaceuticals is the formulation of drugs that act more rapidly and are eliminated more quickly. This trend is accentuated by the current interest in ambulatory surgery and its emphasis on short postanesthetic recovery times.

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Desflurane is a new inhalational anesthetic with a promising pharmacokinetic profile and is now undergoing clinical evaluation.

Desflurane (CF_2H-O-CFH-CF_3, formerly I-653) is a substituted (fluorine-for-chlorine) derivative of isoflurane having several physical properties that distinguish it from other potent inhalation agents. Foremost are desflurane's low solubilities in human blood and tissue. Its blood–gas partition coefficient is 0.42,[1,2] which is comparable to that of N_2O or cyclopropane and one third that of isoflurane. Therefore, changes in the inspired concentration of desflurane produce more rapid changes in alveolar concentration than do changes in other volatile anesthetics. Its oil solubility (18.7) also predicts diminished potency compared to that of halothane or isoflurane, according to the Meyer-Overton hypothesis.

The rapid kinetics of desflurane already have been demonstrated in animals.[3] Desflurane also appears to resist biodegradation[4–6] and does not sensitize the myocardium to epinephrine-induced dysrhythmias.[7] In swine, its hemodynamic[8] and electroencephalographic effects[9] are similar to those observed during equipotent doses of isoflurane. Assessment of the clinical effects of desflurane relative to other agents requires first the determination of its minimum alveolar concentration (MAC). The current study reports the determination of MAC for desflurane in surgical patients and presents observations on its use as a clinical anesthetic.

Materials and Methods

We enrolled 46 patients after obtaining approval of the protocol from the University of California, San Francisco Committee on Human Research and after obtaining the patients' informed consent. Our patients were 18–65 yr of age and ASA physical status 1 or 2 and were scheduled for an elective operation requiring a skin incision. Exclusion criteria were a history or laboratory evidence of hepatic, renal, cardiac, or central nervous system disease; alcohol or recreational drug abuse; chronic use of a drug that would alter MAC; general anesthesia in the 30 days prior to the scheduled surgery; or current childbearing potential.

Patients were divided into two groups according to age (18–30 *vs.* 31–65 yr), and these were further divided into groups to receive desflurane in O_2 or desflurane in N_2O (60%) and O_2 (table 1).

TABLE 1. Description of Experimental Groups

	18-30/O_2	31-65/O_2	18-30/N_2O	31-65/N_2O
n	9	11	8	16
Age (yr)	25.6 ± 3.8	48 ± 8.73	24.6 ± 3.5	42.4 ± 9.6
Weight (kg)	79 ± 9	86 ± 19	75 ± 11	76 ± 16
Height (cm)	178 ± 4	171 ± 8	179 ± 9	172 ± 16
MAC (%)	7.25 ± 0.00	6.00 ± 0.29	4.00 ± 0.29	2.83 ± 0.58
Female (%)	45	44	0	13
Duration of surgery (min)	157 ± 76	259 ± 97	214 ± 120	185 ± 130

Values are expressed as means ± SD.

All patients were monitored by continuous electrocardiography and pulse oximetry. Patients received no preanesthetic medication. Anesthesia was induced by inhalation of desflurane in O_2 or O_2/N_2O *via* face mask. Desflurane was vaporized and delivered by a modified Ohmeda DM-5000 vaporizer. Airway gases were monitored continuously with an infrared absorption spectrometer (Datex PB-254) calibrated to desflurane. During induction, total gas flow rates were approximately 6 l/min, and the inspired concentration of desflurane was increased slowly (approximately 1% per min) until the patient was judged ready for laryngoscopy and tracheal intubation (final range: 10–18%) without the use of muscle relaxants. Eight patients required succinylcholine 1 $mg \cdot kg^{-1}$ iv to facilitate intubation. These eight patients were evenly distributed among the four groups, and the relaxant effects had resolved prior to surgical incision. Endotracheal tube cuffs were coated with a thin layer of lidocaine ointment prior to intubation. Signs of airway irritation during induction were assessed by the responsible anesthesiologist with the predefined criteria listed in table 2.

After tracheal intubation, fresh gas flow rates were reduced to 0.5–3 l/min, and the inspired concentration of desflurane was adjusted to maintain a stable end-tidal concentration for at least 10 min at the test concentration selected for the individual patient. End-tidal CO_2 concentrations were maintained in the range 30–35 mmHg with mechanical ventilation. Normothermia was maintained with passive measures.

The test concentration of desflurane for each patient was determined using a modification of Dixon's up-and-down method.[10] In each group the first patient was tested at a best guess (for MAC) concentration, and subsequent patients were tested at a concentration defined by the previous patient's response to incision. If the previous patient had moved, the test concentration was increased by 0.5% desflurane; in the absence of movement, the desflurane concentration was decreased by 0.5%. A positive response to incision required purposeful movement of an extremity or the head within 1 min after incision. Coughing was not considered a positive response.

Values for MAC were obtained by calculating the midpoint concentration of all independent pairs of patients that involved a crossover (*i.e.*, movement to no movement). Patients were tested until each group had four to five crossovers. MAC was defined as the average of the crossover midpoints in each subgroup. Two patients were excluded from the analysis: one acknowledged a history of chronic, high-dose opioid use only after surgery, and in the other, limited head and neck mobility flexibility precluded timely tracheal intubation.

After assessment of the response to incision, adjuvant drugs, such as opioid or relaxants, were administered when clinically indicated. Intraoperatively, desflurane concentration was adjusted to maintain clinically acceptable anesthesia. Before the anticipated completion of surgery, spontaneous ventilation was initiated, and morphine sulfate or fentanyl was given in doses (approximately 5 mg for morphine sulfate and 50 μg for fentanyl) that did not decrease the respiratory rate to less than 8 breaths per min. Desflurane and N_2O were continued at concentrations that maintained immobility until surgery was complete. Administration of anesthesia then was discontinued and the gas flow set to 10 l/min O_2. The time to

TABLE 2. Prevalence of Signs of Airway Irritation

Symptom	Threshold	18-30/O_2	31-65/O_2	18-30/N_2O	31-65/N_2O
Apnea	>15 s	0	0	0	0
Bronchospasm	Wheezing	0	0	0	0
Cough	Any	56	55	38	50
Laryngospasm	>10 s	0	0	0	12
Secretions	Suction required	45	45	25	38

Values are expressed as percentages.

awakening was measured as the interval between the discontinuation of anesthesia and the patient's acknowledgement of or response to two commands ("open your eyes," and "squeeze my fingers"). We interviewed the patients in the postanesthesia care unit (PACU) and on the 1st and 3rd postoperative days (if possible) to determine the incidence of subjective side effects.

The recorded signs of airway irritation and the patient interview data were analyzed with Kruskal-Wallis analysis of variance (ANOVA) for nonparametric data (with correction for tied ranks). Significance was accepted at $P < 0.05$.

Results

The MAC of desflurane for each group is listed in table 1. As with other anesthetics, the MAC of 18–30-yr-old patients was significantly greater than the MAC of the patients aged 31–65 yr, and MAC decreased by approximately 50% in both age groups with the use of 60% N_2O.

Induction of anesthesia in the groups given desflurane in O_2 frequently was associated with mild excitement phenomena, such as struggling. Two patients exhibited rapid, rhythmic movement of extremities that appeared to be related to clonus, because the activity increased with rapid limb extension; movement rapidly subsided as the end-tidal concentration of desflurane was increased to achieve the second stage of anesthesia. The incidence and intensity of excitement phenomena were lower in the N_2O groups.

Signs of minor, self-limited airway irritation were apparent in all groups during induction, but clinically significant airway irritation was limited to two patients in the 31–65-yr, N_2O group; these two patients required succinylcholine for laryngospasm (table 2). Secretions and coughing were the most common manifestations of irritation; apnea and bronchospasm did not occur. There were no differences in these symptoms between the groups. Most of the episodes of coughing occurred during induction at a time when the end-tidal desflurane concentration was increasing through the range of 6–7%.

Overall, 64% of patients remembered the start of induction and a strong odor (table 3). Some (43%) had found the smell disagreeable. The most common descriptions of the odor were "burning" or "soap" in the nose. Administration of N_2O significantly reduced the incidence of memory of induction and the incidence of nausea in older patients. Overall, 20 patients complained of nausea: 17 noted this symptom in the PACU, 7 on the 1st postoperative day, and only 1 on the 3rd postoperative day. Twenty-three percent of all younger patients, with comparable incidence in the presence or absence of N_2O, described some degree of postoperative headache. The mean incidence of emesis was 18%, with no difference between groups. Of the 15 patients who noted impaired concentration, all reported this effect only during the first interview in the PACU.

Emergence from anesthesia was rapid, as indicated in figure 1. For all patients, the median time to awakening was 5.25 min. It is likely that the administration of small doses of opioid slowed emergence both by its sedative effect and by its reduction of alveolar ventilation. This confounding factor could not be avoided since very rapid emergence without analgesia was considered inappropriate patient care.

Discussion

The Meyer-Overton relationship implies an inverse relationship between a drug's anesthetic potency and its lipophilicity. Desflurane fulfills this relationship in its low tissue solubilities and proportional decrease in potency (fig. 2). Simultaneous administration of 60% (approximately 51–57% of MAC[11,12]) N_2O reduced MAC by 45% in the 18–30-yr-old patients and by 53% in older patients. This additive effect on the potency of desflurane is comparable to the effect of N_2O on other volatile agents.[12]

Advancing age is associated with decreasing anesthetic requirements for cyclopropane,[13] halothane,[14] and isoflurane.[12] In our study, for those between the 3rd and the 5th decades, the desflurane anesthetic requirement declined to 83% of 3rd-decade MAC (and to 71% with

TABLE 3. Prevalence of Subjective Symptoms in the 3 Days after Administration of Desflurane

Symptom	18-30/O_2	31-65/O_2	18-30/N_2O	31-65/N_2O	P
Memory of induction	78	82	88	31	<0.02
Pungent	78	45	25	31	
Headache	22	0	25	0	<0.02
Impaired concentration	33	64	38	13	
Vertigo	22	18	38	6	
Nausea	44	82	25	31	<0.04
Vomiting	11	27	13	19	
Myalgia	0	0	13	6	
Sore throat	44	27	25	13	

Values are expressed as percentages.

Indicated differences reflect inhomogeneity among groups.

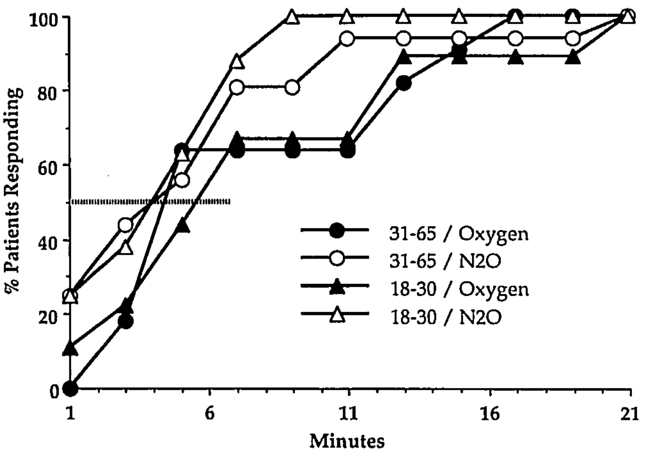

FIG. 1. Recovery from desflurane was rapid despite agent clearance *via* spontaneous ventilation and small doses of opioids. Desflurane was maintained at approximately 1 MAC until the surgical dressing was in place. The intersection of the dashed line with the group data curves represents the point at which 50% of each group was awake and responding to commands.

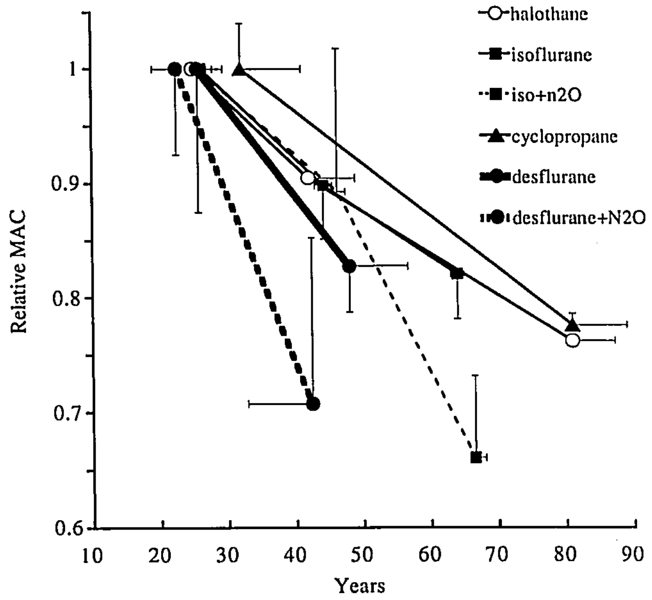

FIG. 3. The anesthetic requirement for desflurane (as well as other volatile agents) declines with age. In this graph, each agent's MAC in the third decade of life is normalized to 1. The presence of nitrous oxide appears to accentuate the relative increase in potency of both desflurane and isoflurane with increasing age. Data for agents other than desflurane taken from reference 10 (isoflurane), reference 11 (cyclopropane), and reference 12 (halothane).

60% N_2O), a decrease comparable to those of other volatile agents (fig. 3). Simultaneously, the potency of N_2O appeared to increase with increasing age in our patients: its presence increased (in a negative direction) the slope of the change in MAC with age.

Jones *et al.*[15] reported the MAC of desflurane in young (average age 25.6 yr), healthy, male volunteers to be 4.58%, which is 63% of the value we report in surgical patients of similar age. The differences in protocol between these studies probably account for the difference in the observed MAC. Jones *et al.* applied 50-Hz tetanic electrical stimulation to the ulnar nerve for a maximum of 30 s (in contrast to our 1-min-duration observations for movement) and took repeated measurements in each subject while monotonically increasing or decreasing the inspired concentration of desflurane until a change in the subject's response to the stimulus changed. However, the determination of MAC is sensitive to the type and intensity of stimulation used,[16] and electrical tetany evidently is less than a supramaximal stimulus.

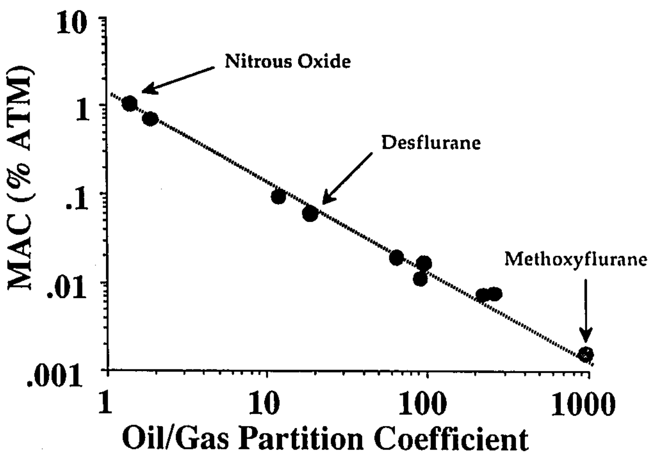

FIG. 2. The Meyer-Overton hypothesis implies that the product of an anesthetic vapor's oil–gas partition coefficient and its potency (as expressed by MAC) should be constant. The measured data from desflurane falls on the straight line described by other anesthetic gases, demonstrating that desflurane conforms to the Meyer-Overton hypothesis.

In summary, desflurane provides satisfactory surgical anesthesia when used alone or in combination with N_2O or morphine sulfate or both. Rapid elimination of desflurane may result in more rapid full return to alertness and may consequently reduce the stay in the PACU and allow accelerated return to street fitness. This agent is modestly irritating to the airway in unpremedicated patients, but in our study, bronchospasm, laryngospasm, or copious secretions were either absent or mild. Intravenous administration of short-acting agents such as thiopental, propofol, or alfentanil would accelerate induction, and in combination with desflurane might provide an optimal anesthetic regimen for patients undergoing outpatient surgery.

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