Anesthesiology
76:373–378, 1992

Induction and Maintenance Characteristics of Anesthesia with Desflurane and Nitrous Oxide in Infants and Children

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To determine the induction and maintenance characteristics of desflurane in pediatric patients, the authors anesthetized 206 infants and children aged 1 month to 12 yr with nitrous oxide plus desflurane and/or halothane in oxygen. Patients were assigned to one of four groups: anesthesia was 1) induced and maintained with desflurane after premedication with an oral combination of meperidine, diazepam, and atropine; 2) induced and maintained with desflurane; 3) induced with halothane and maintained with desflurane; or 4) induced and maintained with halothane. An unblinded observer recorded time to loss of consciousness (lid reflex), time to intubation, and clinical characteristics of the induction and maintenance of anesthesia. Moderate-to-severe laryngospasm (49%) and moderate-to-severe coughing (58%) occurred frequently during induction of anesthesia with desflurane; the incidence of these was not altered by premedication. In contrast, laryngospasm and coughing were rare during induction of anesthesia with halothane. In unpremedicated patients, time to loss of lid reflex (mean ± SD) was similar for desflurane (2.4 ± 1.2 min) and halothane (2.1 ± 0.8 min). During induction of anesthesia, before laryngoscopy and intubation, mean arterial pressure < 80% of baseline was more common with halothane; heart rate and mean arterial pressure > 120% of baseline were more common with desflurane. Intraoperatively, heart rate > 120% of baseline was more common with desflurane; blood pressures were similar for the two anesthetics. The authors conclude that the high incidence of airway complications during induction of anesthesia with desflurane limits its utility for inhalation induction in pediatric patients. Anesthesia can be safely maintained with desflurane if induced with a different anesthetic. (Key words: Anesthesia, pediatric: desflurane; halothane. Anesthetics: nitrous oxide. Anesthetics, volatile: desflurane; halothane. Complications: hypoxemia; laryngospasm.)

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DESFLURANE'S low blood–gas partition coefficient, similar to that of nitrous oxide (N_2O),[1] should result in rapid induction of anesthesia. However, desflurane's pungency may limit the rate at which its inspired concentration can be increased, thereby slowing the rate at which anesthesia can be induced. Although preliminary trials have demonstrated that anesthesia can be induced with N_2O and desflurane in unpremedicated young adults without significant laryngospasm,[2] similar trials have not been conducted in children. To evaluate whether desflurane, administered with N_2O, is a desirable anesthetic for induction and maintenance of anesthesia in children, we compared the clinical characteristics of desflurane and halothane, including whether anesthetic premedication altered the incidence of desflurane-induced airway complications.

Materials and Methods

After obtaining approval from the Institutional Review Board of each of the participating institutions (University of California, San Francisco; Children's National Medical Center, Washington, D.C.; Massachusetts General Hospital, Boston; Children's Hospital of Pittsburgh; and New York Hospital, New York City), we obtained informed written consent from the parents of 206 ASA physical status 1 or 2 children undergoing a variety of elective minor surgical procedures (table 1). Exclusion criteria included age less than one month or more than than 12 yr; history of premature birth; preexisting pulmonary, cardiac, renal, central nervous, metabolic or neuromuscular disease; gastroesophageal reflux; or concurrent treatment with opioid, sedative, or anticonvulsant agents.

Initially, patients were randomized to one of four groups (table 1). Patients in the first group received an

TABLE 1. Demographic Data for Patients Undergoing Anesthesia with Desflurane, Halothane, or Induction of Anesthesia with Halothane and Maintenance with Desflurane (Crossover)

	Desflurane, Premedication	Desflurane, No Premedication	Crossover	Halothane
Premedication	Yes	No	No	No
Induction anesthetic agent	Desflurane	Desflurane	Halothane	Halothane
Maintenance anesthetic agent	Desflurane	Desflurane	Desflurane	Halothane
n	23	22	80	81
Age (months, mean ± SD)	59 ± 41	48 ± 40	43 ± 41	43 ± 35
Weight (kg, mean ± SD)	19.8 ± 9.7	17.2 ± 9.0	17.6 ± 15.5	17.9 ± 15.3
Patients aged <1 yr (%)	13	18	30	20
Outpatients (%)	84	82	74	79
Duration of anesthesia (min, mean ± SD)	79 ± 51	67 ± 44	70 ± 59	73 ± 54
Surgical procedures (%)				
General surgical	43	27	38	43
Genitourologic	30	14	26	12
Plastic	13	36	10	12
Other	13	23	26	26
Regional analgesia (%)				
None	14	32	29	30
Ilioinguinal block	18	14	11	9
Local infiltration	18	27	29	30
Caudal or epidural block	45	23	28	28
Other	5	5	1	1

There were no differences between groups. Percentage values may not total 100% because of rounding.

oral combination of meperidine 1.5 mg/kg, diazepam 0.15 mg/kg, and atropine 20 μg/kg, in a total volume of 0.25 ml/kg, 20–40 min prior to induction of anesthesia.[3] Anesthesia was induced with desflurane vaporized in 60% N_2O and 40% oxygen (O_2) using flows of 5–10 l/min through a circle system or a Mapleson D circuit; desflurane was vaporized by a modified Ohmeda DM-5000 vaporizer (Ohmeda, Madison, WI). In the second group, patients received no premedication, and anesthesia was induced with desflurane in N_2O and O_2 as for the first group. Patients in the third and fourth groups were not premedicated and underwent induction of anesthesia with halothane in N_2O (60%) and O_2 at flows of 5–10 l/min.

For all groups, the inspired concentration of the potent anesthetic was increased at a rate of approximately 1.5% desflurane or 0.5% halothane per three breaths. All patients underwent tracheal intubation without the use of muscle relaxants (except patients who required succinylcholine to treat laryngospasm). After tracheal intubation, anesthesia was maintained with N_2O and the same potent agent was used for induction in all but the third group, which underwent induction with N_2O/halothane followed by maintenance with N_2O/desflurane (crossover). When the 85 initial studies (45 with desflurane) demonstrated an unacceptably high incidence of laryngospasm and other airway-related difficulties during induction of anesthesia with desflurane (both with and without premedication), no additional patients were enrolled in the first two groups; *i.e.*, all remaining patients were unpremedicated and underwent induction with halothane and N_2O and maintenance with either halothane or desflurane and N_2O.

During surgery, patient's lungs were mechanically or manually ventilated to maintain end-tidal CO_2 tension between 35 and 45 mmHg. Temperature was kept at >35° C. Vecuronium was administered for muscle relaxation when surgically indicated. Prior to incision, the inspired concentration of desflurane or halothane was adjusted to prevent movement (based on values for MAC in O_2[4,5]). Following incision, inspired concentrations of desflurane or halothane were adjusted as clinically indicated to maintain heart rate and arterial blood pressure within 30% of baseline values; N_2O concentrations were maintained at 60%. No additional intravenous or inhaled anesthetics or analgesics were administered during surgery. Atropine was administered at the discretion of the attending anesthesiologist to increase heart rate or to dry secretions. Prior to completion of surgery, if appropriate, a regional block was performed to provide postoperative analgesia (table 1). At completion of surgery, residual neuromuscular blockade was antagonized with neostigmine and atropine, and administration of inhaled anesthetic drugs was discontinued.

Arterial blood pressure and heart rate were noted preoperatively (baseline). These parameters, O_2 saturation by pulse oximetry (Sp_{O_2}), and end-tidal concentrations of potent inhalational agent and CO_2 were recorded every two min prior to incision, every min during the first ten min following incision, then every five min throughout surgery. Concentrations of desflurane or halothane, CO_2, and N_2O, sampled at the connection between the circuit

and the mask or at the proximal end of the endotracheal tube, were measured using infrared absorption spectroscopy (Datex PB254, Puritan-Bennett, Tewksbury, MA for desflurane; and RGM 5250, Ohmeda for halothane). The time intervals between placement of the face mask and loss of lash reflex (loss of consciousness) and mask placement and tracheal intubation were noted. The incidence of excitement was recorded and airway-related complications such as laryngospasm, breathholding, coughing, and secretions were graded. Laryngospasm was graded as none, mild (no decrease in Sp_{O_2}), moderate (decreasing Sp_{O_2}), or severe ($Sp_{O_2} < 90\%$ or succinylcholine administered). Breathholding was graded as none, mild (< 10 s), moderate (> 10 s), or severe (decreasing Sp_{O_2}). Coughing was graded as none, mild (fewer than three coughs), moderate (three or more coughs), or severe (decreasing Sp_{O_2}). Secretions were graded as none, mild, moderate (requiring suctioning), or copious (compromising ventilation). Also recorded were the use of succinylcholine to treat laryngospasm, incidence of $Sp_{O_2} < 90\%$, and discontinuation of N_2O during induction of anesthesia due to airway-related complications. During emergence and recovery from anesthesia, the end-tidal anesthetic concentration at discontinuation of anesthetic gases (F_{last}), duration of anesthesia, and the time from discontinuation of anesthetic drugs to eye-opening (at which time the trachea was extubated) were recorded. In the postanesthesia recovery room, we recorded heart rate and arterial blood pressure at 15-min intervals, the incidence of vomiting, the time to satisfy discharge criteria (modified Aldrete score), and whether the patient exhibited or complained of pain and was administered an opioid. All observations were made by an unblinded observer.

The effects of premedication on the incidence of airway complications was evaluated using chi-square analysis. For unpremedicated patients, differences between crossover, desflurane, and halothane groups were determined, as appropriate, using chi-square or parametric or nonparametric analysis of variance with the Student-Newman-Keuls test. Because F_{last} represented a greater fraction of MAC for the halothane group than for the crossover and desflurane groups, emergence and recovery times were not compared. In addition, values for emergence and recovery times do not include data from one institution that deviated from that portion of the protocol. For all statistical comparisons, $P < 0.05$ was considered significant.

Results

The four groups were comparable in age, weight, type of surgical procedures, and percentage of patients undergoing procedures as outpatients (table 1). As noted above, fewer patients were enrolled in the groups undergoing induction of anesthesia with desflurane because of the high incidence of airway-related complications noted in the initial studies.

Induction of anesthesia with desflurane with or without premedication resulted in an incidence of moderate or severe coughing of 58%, moderate or severe laryngospasm of 49%, moderate or severe breathholding of 29%, moderate or copious secretions of 36%, and excitement of 51% (table 2). As a result of these airway complications, Sp_{O_2} decreased to < 90% in 22% of patients; N_2O was discontinued in 21%; and succinylcholine was required to treat severe laryngospasm in 29%. Premedication did not alter the severity or incidence of airway-related complications. In contrast, the incidence of airway-related complications was low during induction of anesthesia with halothane: only 2% of patients required discontinuation of N_2O and/or administration of succinylcholine.

In unpremedicated patients, loss of consciousness and tracheal intubation occurred at similar times for the crossover, desflurane, and halothane groups (table 3) and were not influenced by the administration of succinylcholine. During induction of anesthesia, inspired anesthetic concentrations were comparable for the crossover and halothane groups (table 4); during maintenance of anesthesia and at discontinuation of anesthesia (at which times the crossover group was receiving desflurane), end-tidal anesthetic concentrations were similar for the crossover and desflurane groups.

During the first 4 min of anesthesia, heart rate and mean blood pressure > 120% of baseline were more common with desflurane (table 5). Mean blood pressure < 80% of baseline was more common with crossover and halothane. During maintenance of anesthesia, heart rate > 120% of baseline was more common with desflurane and crossover; the incidence of dysrhythmias was similar for the three groups, and blood pressures did not differ. During recovery from anesthesia, there were no differences between groups in heart rate or blood pressure. During recovery from anesthesia, more patients who received desflurane required supplemental opioids (table 6). The incidence of vomiting was greater with halothane than with desflurane or crossover despite the lesser use of opioids.

In several patients, desflurane concentrations were increased progressively to as high as 15–25% end-tidal in response to clinical signs interpreted as light anesthesia (tachycardia and hypertension but not movement). In two instances, these high inspired desflurane concentrations resulted in mild arterial desaturation, necessitating a decrease in the inspired N_2O concentration.

Discussion

Desflurane's low blood solubility, similar to that of N_2O and less than that of other commonly used potent inhaled

TABLE 2. The Percentage of Patients Experiencing Airway-related Complications during Induction of Anesthesia with Desflurane with or without Premedication or Induction of Anesthesia with Halothane

	Desflurane			Halothane (Includes Crossover) (n = 161)
	All Patients (n = 45)	Premedication (n = 23)	No Premedication (n = 22)	
Coughing				
None	16	9	22	89
Mild	27	26	27	7
Moderate	20	17	23	3
Severe	38	35	41	1
Laryngospasm				
None	33	30	36	97
Mild	18	30	5	1
Moderate	13	9	18	2
Severe	36	30	41	1
Breathholding				
None	49	48	50	96
Mild	22	30	14	4
Moderate	18	13	23	0
Severe	11	9	14	1
Secretions				
None	36	48	23	94
Mild	29	22	36	4
Moderate	31	22	41	2
Copious	4	9	0	0
Excitement				
Absent	49	57	41	89
Present	51	43	59	11
$Sp_{O_2} < 90\%$				
No	78	91	64	99
Yes	22	9	36	1
Nitrous oxide discontinued secondary to airway-related complications				
No	80	87	71	98
Yes	20	13	29	2
Succinylcholine administered to treat laryngospasm				
No	71	74	68	98
Yes	29	26	32	2

Data for patients in the desflurane groups are displayed twice, first for all patients and then separated by whether a premedication was administered.

There was no difference between the two desflurane groups. For all variables, halothane differed from the desflurane, no-premedication group ($P < 0.05$ by chi-square analysis); no comparisons were made between the halothane group and the desflurane, premedication group. Percentage values may not total 100% due to rounding.

anesthetics, should permit a rapid increase in the rate at which alveolar concentration approaches the inspired concentration, thereby facilitating induction of anesthesia. However, induction of anesthesia with desflurane and N_2O in pediatric patients produced many airway-related complications, including coughing and laryngospasm, frequently necessitating administration of succinylcholine. Desflurane's pungency also limits the rate at which its

TABLE 3. Duration of Induction, Maintenance, and Emergence from Anesthesia (minutes) for Unpremedicated Patients

	Crossover	Desflurane	Halothane
n	80	22	81
Induction of anesthesia to loss of consciousness	2.2 ± 0.7	2.4 ± 1.2	2.1 ± 0.8
Induction of anesthesia to tracheal intubation	8.4 ± 2.8	7.6 ± 4.3	8.9 ± 3.6
Induction of anesthesia to tracheal extubation	70 ± 59	67 ± 44	73 ± 54
Discontinuation of anesthesia to eye-opening and tracheal extubation	5.4 ± 3.3	4.0 ± 2.0	7.5 ± 3.4
Entry into recovery room to satisfying criteria for discharge from recovery room	52 ± 55	32 ± 32	55 ± 33

Mean ± SD.

There were no differences between groups; data for emergence and recovery from anesthesia were not compared because of differences in the end-tidal anesthetic concentration at discontinuation of anesthetic gases (see text).

TABLE 4. Inspired or End-Tidal Anesthetic Concentrations (%)

	Crossover	Desflurane	Halothane
n	80	22	81
Loss of consciousness (inspired)	3.1 ± 1.1 (halothane)	10.5 ± 3.7	3.1 ± 1.1
Tracheal intubation (inspired)	3.3 ± 1.3 (halothane)	13.4 ± 2.8	3.1 ± 1.0
Maintenance of anesthesia (end-tidal)	6.9 ± 1.6 (desflurane)	7.5 ± 2.0	1.2 ± 0.3
Discontinuation of anesthesia (F_{last})	4.1 ± 2.6 (desflurane)	3.8 ± 2.6	0.7 ± 0.4

Mean ± SD.
F_{last} = the end-tidal anesthetic concentration at discontinuation of anesthetic gases.

inspired concentration can be increased, thereby offsetting the advantages conferred by its low blood solubility. The incidence of these airway complications was similar whether or not a premedication was administered. This disproved our hypothesis that an opioid premedication would ameliorate coughing[6] and that atropine would decrease secretions, further improving airway conditions. Although the high incidence of airway-related complications during induction of anesthesia with desflurane may, in part, reflect our inexperience with this anesthetic, we speculate that desflurane's pungency will result in airway irritation even when anesthesia is induced by clinicians skilled in its administration. The high incidence of airway complications with desflurane in pediatric patients is analogous to the findings with isoflurane[7] (the molecular structure of which differs minimally from that of desflurane), reaffirming the usefulness of halothane as an induction agent for pediatric patients.

The rate at which the inspired desflurane concentration was increased was slower (in MAC fractions) than that of halothane. This may have slowed induction of anesthesia with desflurane, leaving the patient in a semiconscious state for a longer period, and thereby increasing the likelihood of airway-related complications. The rate at which we increased the inspired desflurane concentration was based on preliminary trials in adults in whom more rapid increases produced airway irritation. It is possible that more rapid increases in the inspired desflurane concentration in pediatric patients might result in a more rapid loss of consciousness with fewer airway complications.

Desflurane's low blood solubility should result in rapid emergence from anesthesia. However, the design of the present study does not permit comparison of emergence from anesthesia with desflurane *vs.* halothane: the end-tidal anesthetic concentration at discontinuation of anesthetic gases was lower for desflurane, thereby confounding any potential benefits of desflurane's low blood solubility. We note that emergence from desflurane anesthesia was rapid, consistent with its low blood solubility. In addition, emergence times for crossover patients were similar to those for desflurane, suggesting that the crossover technique provides halothane's advantages during

TABLE 5. Percentage of Patients Experiencing Cardiovascular Changes during Induction, Maintenance, or Recovery from Anesthesia in the Three Unpremedicated Groups

	Crossover (n = 80)	Desflurane (n = 22)	Halothane (n = 81)
Heart rate during the first four min of anesthesia			
>120 (% of baseline)	12	43*	18
<80 (% of baseline)	26	10	30
Blood pressure during the first four min of anesthesia			
>120 (% of baseline)	13	59*	18
<80 (% of baseline)	23	0*	18
Heart rate during maintenance of anesthesia			
>120 (% of baseline)	25	33	8*
<80 (% of baseline)	15	11	5
Blood pressure during maintenance of anesthesia			
>120 (% of baseline)	15	5	4
<80 (% of baseline)	23	14	18
Dysrhythmias during maintenance of anesthesia	2	9	1
Heart rate during recovery from anesthesia			
>120 (% of baseline)	42	50	34
<80 (% of baseline)	14	15	6
Blood pressure during recovery from anesthesia			
>120 (% of baseline)	37	50	25
<80 (% of baseline)	3	5	10

* Different ($P < 0.05$) from other groups by chi-square analysis.

TABLE 6. The Percentage of Patients Who Required Opioids for Pain or Vomited during Recovery from Anesthesia in the Three Unpremedicated Groups

	Crossover (n = 80)	Desflurane (n = 22)	Halothane (n = 81)
Required opioids	29	50*	22
Vomited	8	5	21*

* Differs from other groups ($P < 0.05$) by chi-square analysis.

induction of anesthesia and desflurane's clinical characteristics during maintenance and emergence from anesthesia. Whether maintenance of anesthesia with desflurane results in more rapid discharge from the recovery room compared to halothane remains to be seen in future clinical studies.

During recovery, more patients anesthetized with desflurane required opioids compared to the halothane and crossover groups, despite similar distributions of surgical procedures and regional anesthetic techniques in the three groups. Because patients in the crossover group received desflurane for the majority of their anesthetic, we are unable to explain this observation. In contrast, Ghouri *et al.*[8] observed that adults given desflurane required fewer doses of opioids than adults anesthetized with isoflurane. Whether anesthesia with desflurane is associated with a greater postoperative analgesic requirement in pediatric patients remains to be determined. We also observed that vomiting was less common in the desflurane and crossover groups than in the halothane group. If this observation is confirmed in larger clinical trials, it suggests a potentially desirable feature of desflurane anesthesia.

Desflurane's cardiovascular effects differ from those of halothane. Whereas halothane minimally affects heart rate,[9] desflurane frequently causes tachycardia (table 5). In unparalyzed patients, desflurane-induced tachycardia in the absence of movement probably does not indicate inadequate anesthesia; however, the present study does not address whether tachycardia (or hypertension) in a paralyzed child necessitates administration of either an opioid or greater concentrations of desflurane.

N_2O may be less useful as an adjunct to desflurane compared to halothane in pediatric patients because high desflurane concentrations are occasionally required during induction of anesthesia or in response to hypertension or tachycardia: these high desflurane concentrations necessitate decreasing the inspired N_2O concentration to maintain a constant F_IO_2. In addition, Fisher and Zwass[10] demonstrated that 60% N_2O decreases desflurane's MAC by only 25% in infants and children.

The intention of the investigators participating in this multicenter study was to examine induction, maintenance, and emergence from anesthesia with desflurane. However, differences between institutions in the management of emergence from anesthesia (*e.g.*, several investigators maintained lighter planes of anesthesia with desflurane than with halothane, thereby favoring rapid emergence and recovery from desflurane anesthesia) prevented us from comparing desflurane to halothane. Despite these differences between institutions, certain aspects of desflurane anesthesia were consistent. Most important of these was the high incidence of airway-related complications during induction of anesthesia. Although institutional differences may limit the utility of multicenter studies, some aspects of desflurane anesthesia were consistent among institutions, suggesting that these problems would occur in clinical practice.

In summary, our findings of a high incidence of airway-related complications during induction of anesthesia with desflurane will probably limit its role as an induction agent in pediatric patients. However, once anesthesia has been successfully induced with another agent, such as halothane (or possibly thiopental or other intravenous anesthetics), desflurane appears to be a satisfactory agent for the maintenance and emergence from anesthesia.

The authors wish to thank the many individuals—anesthesia residents, surgeons, nurses, other colleagues, and Winifred Von Ehrenburg—without whose assistance and support this study would not have been possible.

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