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Desflurane Controls the Hemodynamic Response to Surgical Stimulation More Rapidly Than Isoflurane

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Study Objective: *To compare the control of hemodynamic response to surgical stimulus of desflurane to that of isoflurane.*
Design: *Prospective randomized study.*
Setting: *Operating room of a major U.S. teaching hospital.*
Patients: *59 ASA status I, II, and III patients 18 to 80 years of age and were undergoing orthopedic or intra-abdominal surgical procedures of 1 or more hours in duration.*
Interventions: *Group 1 (n = 29) received desflurane in oxygen (O_2) for their surgical procedure. Group 2 (n = 30) received isoflurane in O_2 for their surgical procedure. Thiopental sodium 4 mg/kg and fentanyl 3 μg/kg provided induction; vecuronium 0.1 mg/kg facilitated intubation. Prior to incision the volatile anesthetic drug was titrated to maintain systolic blood pressure (SBP) within 20% of preinduction (baseline) values. Any time after incision, an SBP increase greater than 20% of baseline was treated with a 30% increase in inspired anesthetic concentration for 3 minutes, or until SBP was within 10% of baseline. Another three 30% increases were allowed at 3 minute intervals to return SBP to 10% of baseline. If four 30% increases did not return SBP to 10% of baseline, additional fentanyl up to 5 μg/kg or labetalol in 5 mg increments was given.*
Measurements and Main Results: *Measurement of hemodynamics and anesthetic concentration occurred every 2 minutes prior to skin incision and every 5 minutes thereafter. Measurement of hemodynamics and anesthetic concentration occurred every minute during treatment of blood pressure (BP) response to surgical stimulus. Desflurane allowed for more rapid control of BP response to surgical stimulus median 2 minutes (range 1 to 12 minutes) for desflurane* versus *6 minutes (range 1 to 12 minutes, p = 0.011). The desflurane group required fewer 30% incremental anesthetic increases than the isoflurane group (1.8* versus *2.5, p = 0.016) to control increased SBP. End tidal/inspired drug concentration ratios were closer to unity in the desflurane patients both before (0.94* versus *0.80) and after (0.86* versus *0.70) changes in drug concentration to treat increased SBP.*
Conclusion: *Anesthetic depth can be more rapidly titrated with desflurane compared to isoflurane. Alveolar/inspired concentration ratio approaches unity more rapidly with desflurane anesthesia.*

Keywords: Desflurane; hemodynamics; isoflurane; surgical stimulation.

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Introduction

The unique properties of desflurane owe to its very low blood gas partition coefficient of 0.42.[1] The low solubility provides a more rapid emergence[2] and a shorter stay in the postanesthesia care unit.[3] Yasuda *et al.*[4] compared kinetics of desflurane halothane and isoflurane to nitrous oxide (N_2O). They found that the alveolar/inspired (FA/FI) concentration of desflurane closely matched that of N_2O and more rapidly approached unity than did the other drugs. Desflurane's low blood gas solubility should allow for rapid changes in anesthetic depth.[4,5] Does this property allow the clinician to control intraoperative hemodynamics more rapidly? This study compared the abilities of desflurane and isoflurane to control the hemodynamic response, such as an increase in systolic blood pressure (SBP) resulting from surgical stimulation.

Materials and Methods

With Hahnemann University Human Studies Committee approval, 59 patients aged 18 years or more, ASA physical status I, II, and III, gave informed consent to participate in this prospective, randomized trial. All patients underwent orthopedic or intra-abdominal procedures of 1 or more hours duration. No patient with a recent myocardial infarction (less than 6 months), unstable angina, or an ECG with new ischemic changes participated. Patients with a history of alcohol or drug abuse, those receiving medications such as opioids or clonidine, which could alter volatile anesthetic potency [minimum alveolar concentration (MAC)], and those with a personal or family history of malignant hyperthermia were excluded. Patients were instructed to continue their antihypertensive medications prior to surgery and were asked to take their morning medications with a small sip of water.

After establishing routine monitoring, all patients received intravenous (IV) Plasmalyte-A (Baxter Healthcare, Deerfield, IL) 5 ml/kg. Prior to induction, patients with medical conditions that required further invasive monitoring had those monitoring catheters placed with local anesthesia. Fentanyl 3 μg/kg followed by thiopental sodium 4 mg/kg provided anesthetic induction. Vecuronium 0.1 mg/kg provided muscle relaxation. Patients received randomly, via a computer generated randomization table provided by Anaquest, either desflurane or isoflurane in 100% oxygen (O_2) with a 3 L/min fresh gas flow through a semi-closed circle system. Initial anesthetic concentrations were set at the MAC for each drug (6% desflurane, 1.2% isoflurane).[6,7] The volatile anesthetic was titrated to maintain SBP within 20% of its preinduction value. Intubation occurred upon ablation of the response to a train-of-four (TOF) stimulus. Incremental doses of vecuronium titrated to a single-twitch response to the TOF stimulus maintained muscle relaxation. A modified Datex infrared gas analyzer (Datex Instrumentarium, Helsinki, Finland) measured the inspired and end-tidal concentrations of the inhaled anesthetic as well as the end-tidal carbon dioxide concentration. Body temperature and oxygen saturation (SpO_2) were measured in all patients using an esophageal thermistor probe and pulse oximeter, respectively. Normothermia was maintained with the use of a Bair Hugger warm air blanket system (Augustine Medical Inc., Eden Prairie, MN). Hemodynamics and volatile drug concentrations were measured every 2 minutes prior to skin incision and every 5 minutes thereafter.

Any time after incision, an increase in SBP that exceeded 20% of the preinduction (baseline) value triggered treatment. The inspired drug concentration was increased 30% from its value at the time of the hemodynamic response. Blood pressure (BP), heart rate (HR), and inspired/expired drug concentrations were measured every minute during the treatment of a hemodynamic response. The new inspired drug concentration was maintained for 3 minutes or until SBP was within 10% of the baseline value. If after 3 minutes, SBP had not returned to within 10% of baseline, another 30% increase over the current inspired drug concentration was administered. This treatment protocol continued until SBP returned to within 10% of baseline or a total of 4 30% increases of inspired drug concentration occurred. Patients whose SBP did not return to within 10% of their baseline after four increases in drug concentration failed the treatment regimen. Patients who failed treatment then received additional fentanyl to a total of 5 μg/kg or labetalol in 5 mg increments at the discretion of the investigator. After hemodynamics were controlled all measurements continued at 5-minute intervals. Subsequent hemodynamic responses to surgical stimulation were identically treated, as described above.

At the conclusion of surgery, patients received glycopyrrolate 5 μg/kg and neostigmine 50 μg/kg IV. Following the return of spontaneous ventilation and the completion of wound dressing, inhaled drug administration was terminated, and the O_2 flow increased to 10 L/min. Extubation occurred when the T1/T4 ratio was greater than 70% and the patient exhibited an appropriate level of consciousness.

The two-tailed Student's unpaired *t*-test compared normally distributed data, which are reported as means ± SD. ASA physical status, gender, number of patients under medical treatment of hypertension, and surgical sites were compared with likelihood ratio chi-square statistics. The Mann-Whitney U test compared time to control of BP. A p-value less than 0.05 was considered statistically significant.

Results

All 59 patients received an anesthetic for at least one hour in duration. *Table 1* displays summary statistics for age, gender, ASA physical status, diagnosis of hypertension, weight, surgical site, and antihypertensive medications. The groups did not differ with respect to these parameters. *Table 2* shows the results of the treatment of hemodynamic responses to surgical stimulation. The

Table 1. Demographics

	Desflurane	Isoflurane	p-value
N (M/F)	29 (11/18)	30 (9/21)	0.52
Age (yr)	47 ± 18	46 ± 14	0.87
ASA 1 (N)	5	7	
ASA 2 (N)	24	22	
ASA 3 (N)	0	1	0.49
No. of patients under treatment for hypertension	9	9	0.93
Drugs used for treatment of hypertension			
Diuretic	6	4	
ACE inhibitor	2	3	
Beta blocker	1	1	
Ca^{++} channel blocker	2	3	
Weight (kg)	77 ± 17	74 ± 11	0.31
Anesthetic time (min)	216 ± 85	225 ± 109	0.73
Surgical site			
Orthopedic (N)	19	12	
Abdomen—gyn (N)	6	12	
Abdomen—other (N)	4	6	0.14

Note: Entries are mean ± SD or number of patients.

ACE = angiotensin converting enzyme; Ca^{++} = calcium.

time to control the hemodynamic response to surgical stimulus was analyzed in two groups. For patients who were controlled by inhaled drug alone (*i.e.*, those who did not fail the treatment protocol) the desflurane patients responded significantly faster (2 *versus* 6 minutes, $p = 0.011$ by Mann-Whitney U test). Comparison of all patients (responders plus patients requiring additional medication) also showed more rapid control with desflurane (3 *versus* 7 minutes, $p = 0.009$ by Mann-Whitney U test). The desflurane patients required fewer 30% incremental increases in inspired drug concentration (1.8 *versus* 2.5, $p = 0.02$). The desflurane group demonstrated a closer matching of end-tidal to inspired drug concentration both before (ratio of 0.94 *versus* 0.80, $p = 0.013$) and after (0.86 *versus* 0.70, $p = 0.0001$) an increase in drug concentration. The table displays a summary of the additional medications needed to control hypertension by group. The results of the treatment of patients under medical management for hypertension are also displayed. *Table 3* shows hemodynamic data at baseline, intubation, incision, and the beginning and end of the treatment for intraoperative hypertension. The groups did not differ with respect to these parameters.

Discussion

These data show that desflurane controls the hemodynamic alterations induced by surgical stimulation more rapidly than isoflurane. This finding holds both for the group that required only an increase in inhaled drug concentration as well as for the group that required the addition of opioid or antihypertensive medication. In this setting of a moderately low fresh gas flow (3 L/min) the low blood gas solubility of desflurane allowed it to more closely approach MAC before an intervention to control an elevated SBP was needed. This is reflected in the closer match of end-tidal/inspired concentration (0.94 *versus* 0.80, $p = 0.013$), and in the end-tidal MAC equivalent reached in each group before treatment (0.65 *versus* 0.50, $p = 0.008$). This initial difference may account for the smaller number of desflurane patients, who required treatment (23 *versus* 26, NS). Despite this initial disparity, the two groups achieved comparable increases in end-tidal concentrations by the end of treatment (30% *versus* 36%); however, it took the isoflurane group twice as long to achieve this increase.

Hypertensive patients tend to have more labile hemodynamic responses to surgical stimulation than the normotensive population.[8] The ability to rapidly control hemodynamic responses with desflurane may give this

Table 2. Results

	Desflurane	Isoflurane	p-value
Time to BP control in successful treatments only (min)	2 (1 to 12)	6 (1 to 12)	0.011
Total time to BP control all patients (min)	3 (1 to 15)	7 (1 to 30)	0.009
Number of 30% increments administered	1.8 ± 1.20	2.5 ± 1.2	0.02
ET con % before treatment	3.9	0.6	NA
ET/INS before treatment	0.94 ± 0.3	0.80 ± 0.15	0.013
MAC equivalent before treatment	0.65 ± 0.31	0.50 ± 0.15	0.008
ET con % after treatment	5.6	0.94	NA
MAC equivalent after treatment	0.93 ± 0.34	0.82 ± 0.39	0.19
ET/INS after treatment	0.86 ± 0.07	0.70 ± 0.15	0.0001
Patients treated (N)	23 of 29	26 of 30	0.45
Failed treatments (N)	4 of 38	9 of 35	0.09
HTN patients not needing treatment (N)	2	2	
HTN patients successfully treated (N)	5	6	
HTN patients failed treatment (N)	2	1	
Medications for failed treatments			
Fentanyl (50 μg to 250 μg)	4	7	
Labetalol (5 to 15 mg)	1	3	

Note: Values are means ± SD or median (range) or number of patients.

BP = blood pressure; ET = end tidal; con = concentration; NA = not applicable; INS = inspired; MAC = minimum alveolar concentration; HTN = patients under treatment for hypertension.

Table 3. Results

	Desflurane	Isoflurane	p-value
Baseline SBP	127 ± 18	129 ± 18	0.74
Baseline DBP	77 ± 12	79 ± 10	0.62
Baseline HR	77 ± 10	78 ± 13	0.61
Intubation SBP	120 ± 23	123 ± 26	0.65
Intubation DBP	70 ± 11	73 ± 19	0.45
Intubation HR	86 ± 16	86 ± 16	0.99
Incision SBP	112 ± 19	115 ± 15	0.49
Incision DBP	64 ± 13	70 ± 12	0.09
Incision HR	79 ± 19	79 ± 13	0.95
SBP at start of treatment	151 ± 16	151 ± 19	0.92
DBP at start of treatment	87 ± 12	91 ± 18	0.27
HR at start of treatment	94 ± 18	90 ± 15	0.30
SBP at end of treatment	127 ± 17	129 ± 19	0.74
DBP at end of treatment	73 ± 11	75 ± 15	0.61
HR at end of treatment	85 ± 17	82 ± 15	0.34

Note: Values are means ± SD.

SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate.

drug a decided advantage in this population. Desflurane may be more successful in controlling hypertensive responses than isoflurane. Despite reaching comparable MAC equivalents at the end of treatment numerically (0.93 *versus* 0.82, NS), about twice the number of failed treatments occurred in the isoflurane group than the desflurane group: 4 of 38 treatments in the desflurane group, versus 9 of 35 in the isoflurane group. This did not reach statistical significance ($p = 0.09$) due to the modest sample size in this study. Further investigation is required to reach any firm conclusions on these indeterminate data.

Some readers may object to the rigid protocol of anesthetic titration used in this study, thinking that if we had used overpressure techniques with isoflurane, we may not have seen a difference between drugs. While this may be true, administration of very high inspired concentrations of a volatile drug carries inherent dangers, most notably the possibility of a forgotten high vaporizer setting, which can cause unwanted hypotension and, if left long enough, iatrogenic cardiovascular collapse. The protocol used balances a controlled comparison of the two drugs with a commonly used clinical setting.

The results of a recent study indicate that large increases in inspired desflurane concentration may cause an increase in sympathetic tone, resulting in tachycardia and hypertension.[9] We demonstrated that small incremental increases in inspired desflurane concentration can rapidly control hemodynamic responses, obviating the need for large inspired concentrations in an overpressure technique. Desflurane offers an advantage over isoflurane in the control of hemodynamic responses to surgical stimulation. This, in combination with more rapid emergence and a shorter stay in the postanesthesia care unit in some populations, make desflurane a useful drug.[3,10,11]

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