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Fentanyl Augments the Blockade of the Sympathetic Response to Incision (MAC-BAR) Produced by Desflurane and Isoflurane

Desflurane and Isoflurane MAC-BAR without and with Fentanyl

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Background: **Heart rate (HR) or mean arterial blood pressure (MAP) may increase in response to incision despite the absence of a motor response. The authors hypothesized that the MAC-BAR (minimum alveolar concentration of an anesthetic that blocks adrenergic response to incision) for isoflurane would exceed that for desflurane, and that fentanyl would decrease the MAC-BAR for each anesthetic in a dose-dependent manner.**

Methods: **Seventy-one patients were randomly allocated to one of six groups: desflurane or isoflurane without fentanyl or with 1.5 or 3 μg/kg fentanyl given intravenously 5 min before surgical incision. Anesthesia was induced with 2 mg/kg propofol given intravenously, and tracheal intubation facilitated with 0.1 mg/kg given intravenously. The first patient in each group received 1 MAC (end-tidal) of the inhaled anesthetic in 60% nitrous oxide (0.55 MAC), balance oxygen, maintained for at least 10 min before incision. The response was considered positive if the HR or MAP increased 15% or more. If the response was positive, the end-tidal concentration given to the next patient was 0.3 MAC greater; if the response was negative, the end-tidal concentration was 0.3 MAC less. The MAC-BAR level was calculated as the mean of four independent cross-over responses in each group.**

Results: **Desflurane and isoflurane anesthesia with 60% nitrous oxide did not change HR ($P > 0.05$) and decreased MAP ($P < 0.05$) before incision. Plasma epinephrine and norepinephrine concentrations after anesthesia and before incision were normal in all groups. The MAC-BAR level, without fentanyl, did not differ ($P > 0.05$) between desflurane (1.30 ± 0.34 MAC [mean ± SD]) and isoflurane (1.30 ± 0.18 MAC). Fentanyl given at 1.5 μg/kg intravenously equivalently ($P > 0.05$) reduced the MAC-BAR for desflurane (to 0.40 ± 0.18 MAC; $P < 0.05$) and isoflurane (to 0.55 ± 0.00 MAC; $P < 0.05$), but a further increase in fentanyl to 3 μg/kg caused no greater decrease in the MAC-BAR for desflurane (0.48 ± 0.16 MAC) and isoflurane (0.40 ± 0.30 MAC).**

Conclusions: **Clinically attainable doses of desflurane and isoflurane, in 60% nitrous oxide (0.55 MAC), block the cardiovascular response to surgical incision at 1.3 MAC. Fentanyl given at 1.5 μg/kg decreases the MAC-BAR for each agent with no further decrease produced by 3 μg/kg fentanyl. (Key words: Inhaled anesthetics; sympathetic nervous system.)**

THE minimum alveolar concentration (MAC) that prevents movement in response to a noxious stimulus in 50% of a population[1] for halothane and enflurane is less than that which blocks the adrenergic response to that stimulus (MAC-BAR).[2] In the United States, isoflurane and desflurane have largely replaced these anesthetics. The possibility that these newer anesthetics differ from each other or from older anesthetics in their capacity to block the hemodynamic responses to a surgical stimulus is clinically important because increases of heart rate (HR), mean arterial blood pressure (MAP), or both are associated with intraoperative and postoperative myocardial ischemia in patients with coronary artery disease.[3–9] Zbinden *et al.*[10] found concentrations of isoflurane up to 1.8 MAC did not block the hemodynamic response to various noxious stimuli, including skin incision. In contrast, Yasuda *et al.*[11] found that 1.7 MAC desflurane with and without nitrous oxide in volunteers blocked hemodynamic responses to electrical stimulation. The capacity of opioids to decrease

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MAC-BAR has not been studied for any potent inhaled anesthetic. A decrease would be anticipated because fentanyl is commonly used to attenuate cardiovascular responses in patients with coronary artery disease. Fentanyl decreases HR during anesthesia with halothane, enflurane, and isoflurane,[12] and morphine (with nitrous oxide) has a MAC-BAR of 1.1 mg/kg.[2]

We tested two hypotheses: (1) that the MAC-BAR for isoflurane would exceed that for desflurane; and (2) that fentanyl would produce a dose-dependent decrease in the MAC-BAR of desflurane.

Methods

With approval of the UCSF Committee on Human Research, and with informed consent, we studied 71 unpremedicated adult patients, aged 18–59 yr, who were classified as American Society of Anesthesiologists physical status 1 or 2. Patients with a history of cardiovascular or nervous system disease, those taking drugs with cardiovascular or central nervous system effects, or drugs that alter MAC, and patients with a history of drug or alcohol abuse were excluded.

Patients were not premedicated. Patients were randomly allocated (except for three to replace unusable data of three previous patients) to one of six groups: desflurane or isoflurane, in 60% nitrous oxide (0.55 MAC),[13] balance oxygen, either without fentanyl or with 1.5 or 3 μg/kg fentanyl given intravenously 5 min before surgical incision. Anesthesia was induced with 2 mg/kg propofol given intravenously, and tracheal intubation was facilitated with 0.1 mg/kg vecuronium given intravenously. The first patient assigned to each group received 1 MAC of the inhaled anesthetic, adjusted for age based on published data for desflurane[14] and isoflurane.[15] All patients also received 60% end-tidal nitrous oxide, balance oxygen. The target end-tidal concentrations of the inhaled anesthetics were maintained for at least 10 min before surgical incision. Inspired and end-tidal oxygen, carbon dioxide, nitrous oxide, and desflurane or isoflurane concentrations were measured continuously by an infrared spectrometer (Datex AS3, Helsinki, Finland), calibrated just before and after each anesthetic with a secondary (tank) standard, which had been calibrated by gas chromatography against a primary (gravimetric) standard. Gases were sampled at the orifice of the endotracheal tube, and a 40-ml deadspace protected the end-tidal gas from contamination by inflow of fresh gas. Mechanical ventilation maintained end-tidal partial pressure of carbon dioxide ($P_{ET}CO_2$ at 35 mmHg. Heart rate and MAP determined by oscillometry were recorded before induction of anesthesia, 5 min and 1 min before incision, at incision, and at 1-min intervals for 10 min thereafter.

The "up and down" method was used to determine MAC-BAR.[1] The response of the preceding patient determined the concentration of the inhalational agent given to succeeding patients in each group. If the response of the preceding patient in that group was positive (an increase of either HR or MAP $\geq$ 15% above the value 1 min before incision), the end-tidal concentration given to the next patient was increased by 0.3 MAC. If the response was negative (neither HR nor MAP increased by $\geq$ 15%), the end-tidal concentration given to the next patient was decreased by 0.3 MAC. The mean of four independent cross-overs of response provided the MAC-BAR for each group. The maximum end-tidal concentration required was 1.9 MAC plus 60% nitrous oxide, and the minimum end-tidal concentration required was 0.1 MAC plus 60% nitrous oxide. Data for MAC are expressed without the contribution of 60% nitrous oxide (0.55 MAC).

Arterialized venous blood was sampled 1 min before and 2 min after incision to measure plasma epinephrine and norepinephrine concentrations. Plasma was stored at −20°C until it was thawed for analysis. Plasma catecholamine concentrations were determined by high-performance liquid chromatography,[16] with lower limits of detection of 14 pg/ml for epinephrine and 25 pg/ml for norepinephrine. Coefficients of variation for within-run were epinephrine, 2–7% and norepinephrine, 1–2%; and for between-runs they were epinephrine, 7% and norepinephrine, 3%. Sample values less than the limit of detection were considered to have a concentration just less than the limit of detection.

Data are expressed as means ± SD. Data among groups were analyzed by analysis of variance or *t* test, with correction for multiple comparisons, when appropriate. Probability values < 0.05 were considered statistically significant.

Results

The groups did not differ significantly in age, preoperative HR or MAP, time between induction of anesthesia and incision, or mean MAP 1 min before incision (table 1). When administered without fentanyl, both desflurane and isoflurane with 60% ni-

Table 1. Age, Preoperative and Preincisional Heart Rate and Mean Arterial Pressure, and Time Between Induction and Incision

	Fentanyl Dose (μg/kg)	N	Age (yr)	Preoperative		1 min before Incision		Time from Induction of Anesthesia to Incision (min)
				HR (bpm)	MAP (mmHg)	HR (bpm)	MAP (mmHg)	
Desflurane	0	15	35 ± 11	72 ± 11	88 ± 8	76 ± 16	71 ± 13†	38 ± 14
Desflurane	1.5	13	43 ± 9	75 ± 14	86 ± 10	59 ± 15*†	73 ± 10†	40 ± 19
Desflurane	3.0	12	34 ± 8	74 ± 11	88 ± 9	52 ± 6*†	73 ± 12†	42 ± 13
Isoflurane	0	9	40 ± 8	73 ± 10	87 ± 11	70 ± 17	66 ± 10†	50 ± 10
Isoflurane	1.5	9	41 ± 10	70 ± 12	89 ± 10	60 ± 12†	70 ± 7†	32 ± 8
Isoflurane	3.0	12	38 ± 13	72 ± 12	90 ± 9	56 ± 12†	75 ± 13†	36 ± 14

Values are mean ± SD. Variables did not differ among the groups before anesthesia. Before incision there were no significant differences among the groups, except for a lesser HR with both doses of fentanyl (*vs.* no fentanyl) with desflurane (* $P < 0.05$), but not isoflurane. Anesthesia in all groups includes 60% N_2O.

HR = heart rate; MAP = mean arterial pressure.

† Significantly different ($P < 0.05$) from preanesthetic value.

trous oxide decreased MAP ($P < 0.05$) but did not change HR ($P > 0.05$; table 1). The groups given fentanyl plus desflurane had a lower HR before incision than did the group given desflurane alone (table 1); however, this effect was not significant in the isoflurane groups ($P > 0.05$; power to detect a difference with a P value $< 0.05 = 0.3$-0.5). Groups did not differ in plasma concentrations of epinephrine or norepinephrine before incision. Because fentanyl did not affect the catecholamine concentrations before incision, to compare the effects of desflurane with those of isoflurane the three groups for each anesthetic were combined, and the data were compared by unpaired *t*-tests. The desflurane and isoflurane groups did not differ in their plasma epinephrine (40 ± 25 pg/ml *vs.* 28 ± 26 pg/ml; $P > 0.05$) or norepinephrine (435 ± 208 pg/ml *vs.* 375 ± 198 pg/ml; $P > 0.05$) concentrations before incision, nor were they outside the normal limits (normal reference ranges: epinephrine, < 50 pg/ml; norepinephrine, 110-658 pg/ml).

The MAC-BAR for desflurane (1.30 ± 0.34 MAC [mean ± SD] plus 60% nitrous oxide) did not differ from that for isoflurane (1.30 ± 0.18 MAC plus 60% nitrous oxide [fig. 1; $P > 0.05$]). Fentanyl significantly decreased MAC-BAR for both volatile anesthetics. Fentanyl (1.5 μg/kg) given intravenously 5 min before surgical incision significantly ($P < 0.05$) and similarly ($P > 0.05$) reduced the MAC-BAR for desflurane and isoflurane to 0.40 ± 0.18 MAC plus 60% nitrous oxide, and 0.55 ± 0.00 MAC plus 60% nitrous oxide, respectively (fig. 1). Similarly, 3 μg/kg fentanyl given 5 min before surgical incision significantly ($P < 0.05$) decreased MAC-BAR for desflurane and isoflurane, to 0.48 ± 0.16 MAC plus 60% nitrous oxide, and 0.40 ± 0.30 MAC plus 60% nitrous oxide, respectively (fig. 1). These values did not differ significantly from each other or from those found with 1.5 μg/kg fentanyl ($P > 0.05$).

Plasma epinephrine or norepinephrine concentrations did not change with incision in any group, nor did groups differ in plasma catecholamine concentrations after incision. Changes in plasma catecholamine concentrations did not correlate with changes in heart rate or MAP with incision (range of r^2, 0.00005-0.02).

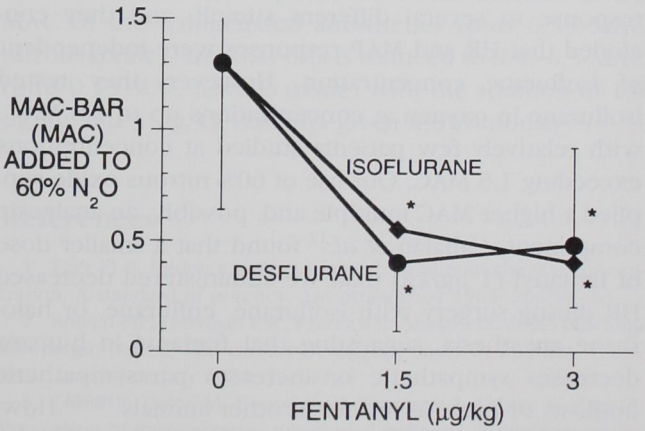

Fig. 1. The anesthetic dose of desflurane (●) and isoflurane (♦) required to block the adrenergic response (MAC-BAR) to incision in 50% of patients, without and with fentanyl. The MAC values do not include the 0.55 MAC contribution of nitrous oxide. There was no significant difference between desflurane and isoflurane at any fentanyl dose. Both doses of fentanyl significantly reduced the MAC-BAR of desflurane and isoflurane (*$P < 0.05$), but there was no significant difference between effects of the two fentanyl doses. Data are means ± SD. See table 1 for group sizes.

Discussion

Our results indicate that (1) desflurane and isoflurane administered with 60% nitrous oxide block adrenergic responses to a noxious stimulus (skin incision) at equivalent, clinically attainable concentrations; (2) 1.5 μg/kg fentanyl given intravenously and 3 μg/kg given intravenously 5 min before the stimulus equivalently decrease by 60–70% the concentration of desflurane and isoflurane required to block cardiovascular response to a skin incision; (3) in these healthy patients desflurane and isoflurane administered in a usual clinical manner did not produce evidence of sympathetic stimulation; and (4) changes in plasma catecholamine concentrations did not correlate with changes in HR or MAP in response to a surgical stimulus.

The MAC-BAR for desflurane is somewhat greater than that suggested by Yasuda *et al.*[11] They used a supramaximal electrical stimulus of the ulnar nerve of healthy volunteers, aged 24 ± 2 yr (mean ± SD), and found that a total of 1.66 MAC of desflurane in oxygen or nitrous oxide prevented a 15% increase in HR and MAP, whereas 1.24 MAC did not. An electrical stimulus may provide less-intense stimulation than does an incision.[14,17] However, Zbinden *et al.*[10] found no differences in the hemodynamic responses to electrical stimulation and skin incision.

Zbinden *et al.*[10] did not find a concentration of isoflurane that blocked an increase in HR or MAP in response to several different stimuli, and they concluded that HR and MAP responses were independent of isoflurane concentration. However, they tested isoflurane in oxygen at concentrations up to 1.8 MAC, with relatively few patients studied at concentrations exceeding 1.5 MAC. Our use of 60% nitrous oxide supplied a higher MAC multiple and, possibly, an analgesic component. Cahalan *et al.*[12] found that a smaller dose of fentanyl (1 μg/kg) than we administered decreased HR during surgery with isoflurane, enflurane, or halothane anesthesia, suggesting that fentanyl in humans decreases sympathetic or increases parasympathetic outflow, or both, as it does in other animals.[18–20] However, they did not test the response to incision.[12]

The MAC-BAR we obtained for desflurane and isoflurane may appear to be greater than those for halothane (0.88 ± 0.08 MAC) and enflurane (1.03 ± 0.13 MAC) plus 60% nitrous oxide,[2] but the differences in methods between the present study and that of the earlier one preclude us from reaching this conclusion. Roizen *et al.*[2] induced anesthesia with either thiopental (approximately 40% of cases) or the inhaled anesthetic. We do not believe that their use of thiopental or our use of propofol for induction of anesthesia or vecuronium for neuromuscular blockade affected the results because of the substantial time between the administration of these drugs and the surgical incision, and the absence of cardiovascular effects of vecuronium.[21–23] The plasma concentration of propofol 40 min after its intravenous administration is less than 5% of its peak value.[24] Although propofol decreases sympathetic activity in the unstimulated state,[25] it does not attenuate the cardiovascular response to a sympathetic stimulus 5 min after its administration,[26] when its blood concentration is considerably higher than 40 min after its administration (the mean time to incision in this study). Both we and Roizen *et al.*[2] used similar concentrations of nitrous oxide. More important, is the difference between the two studies in the conditions and criteria used for the determination of MAC-BAR. Roizen *et al.*[2] considered a "positive" response as one of an increase of more than 10% in plasma norepinephrine concentration from the mean value before incision to the mean of values 3 and 10 min after incision. Analysis of our catecholamine data suggests that application of Roizen *et al.*'s criterion to our single samples before and after incision would likely have produced lesser MAC-BAR values for both desflurane and isoflurane than they found for halothane and enflurane. Interestingly, Roizen *et al.* could not find a good correlation between changes in HR, MAP, pupil size, or rate-pressure product and the concentration of enflurane. Thus it would appear likely, that if they had used the same criteria as we did, they would have found a MAC-BAR for halothane, but not for enflurane.

Sympathetic outflow does not necessarily increase uniformly to all tissues. Stimuli producing increased sympathetic neural traffic to muscle and skin (generally resulting in increased plasma norepinephrine concentration), may not be associated with increased HR or MAP.[27] This may have confounded our attempt to correlate changes in plasma catecholamine concentrations and changes in HR or MAP in response to an incision. Our findings confirm those by Philbin *et al.*[28] in patients given large doses of fentanyl or sufentanil for coronary artery bypass surgery that changes in plasma catecholamine concentrations do not correlate with changes in HR or MAP. This also provides the basis for our preference for using markers of adrenergic response (*i.e.*, HR and MAP) that are associated with an important clinical adverse marker, myocardial ischemia,[4–6,29] rather than

laboratory determinations that have not been shown to have such clinical importance.

Our finding that small doses of fentanyl decrease the inhaled concentration of desflurane or isoflurane that blocks the HR and MAP response to incision is new, but not surprising. Clinicians routinely use opioids for this purpose, in doses and timing before incision as we did. Similar doses of fentanyl attenuate the cardiovascular response to a stimulus.[30] Fentanyl decreases MAC for these anesthetics,[31-33] and our finding is consistent with a "ceiling" effect (no difference between the effect of 1.5 and 3 μg/kg fentanyl) for the reduction of enflurane MAC by fentanyl,[34] sufentanil,[35] and alfentanil[36] in the dog, and the reduction of MAC for desflurane[32] and isoflurane[33] by fentanyl in humans. However, Ghouri and White[31] found a dose-dependent reduction of desflurane MAC by fentanyl in humans. Large doses of opioids used for patients undergoing coronary artery bypass graft surgery, including fentanyl to doses as much as 100 μg/kg, do not reliably prevent an increase of heart rate or blood pressure in response to tracheal intubation or sternotomy.[28,37] Commonly an inhaled anesthetic is added to blunt the cardiovascular response, especially that of MAP and systemic vascular resistance. For example, Parsons *et al.*[38] found that up to 1 MAC of desflurane added to 10 μg/kg fentanyl given to patients undergoing myocardial revascularization decreased the cardiovascular response to sternotomy and tracheal intubation and the need for treatment with vasodilators, more than did the administration of 50 μg/kg fentanyl without an inhaled anesthetic.

We did not find that administration of either desflurane or isoflurane when given in a usual clinical manner produces sympathetic stimulation, despite administration of concentrations up to 1.9 MAC. This is in contrast to findings in patients and volunteers that rapid increases in concentration of these anesthetics transiently increases HR and MAP.[39-42] In the present study, values for HR and MAP before incision were not higher than those when the patients were awake. In addition, our limited data for plasma norepinephrine concentrations 1 min before and 2 min after incision in patients given desflurane or isoflurane without fentanyl do not appear to differ from those obtained by Roizen *et al.*[2] in patients given similarly potent concentrations of halothane, an anesthetic that not only blocks adrenergic responses but also decreases adrenergic transmission in the unstimulated state.[43] Desflurane and isoflurane also decrease adrenergic transmission: They equivalently suppress sympathetic ganglionic transmission in dogs, probably as a result of reduced postganglionic neuronal sensitivity to neurotransmitters.[44]

There is an additional implication of our findings. Inhaled anesthetics frequently are added to an opioid-based anesthetic during coronary artery bypass surgery, because the opioids do not reliably suppress "learning," whereas the inhaled anesthetics do.[45] The concentrations of isoflurane and desflurane that suppress learning approximate MAC-awake (the anesthetic alveolar concentration that just prevents [or allows] response to command) of 0.4 MAC.[46-49] Clinicians commonly use the lack of movement or lack of increase in HR or MAP in response to a noxious stimulus as an indication that the anesthetic concentration is sufficient to prevent memory of intraoperative events. This problem has been discussed in conjunction with the use of large doses of opioids.[50] However, because even small doses of fentanyl decrease MAC and now also have been shown to decrease MAC-BAR, but may not have a similar effect on "learning," the clinician should be alerted to the possibility that the signs of "adequate" anesthesia used in the absence of opioid may not pertain when even small doses of opioid are administered.

In conclusion, we find that steady-state concentrations of desflurane and isoflurane of up to 1.7 MAC with 60% nitrous oxide (0.55 MAC) do not produce sympathetic stimulation. We also find that desflurane and isoflurane with 60% nitrous oxide block increases in HR and MAP in response to a skin incision at 1.3 MAC of the halogenated anesthetics (plus 0.55 MAC nitrous oxide), and that this is reduced to 0.4-0.5 MAC (plus 0.55 MAC nitrous oxide) with the addition of 1.5 μg/kg and 3 μg/kg fentanyl given intravenously.

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