

Fentanyl and Sufentanil Anesthesia Revisited: How Much is Enough?

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This study was undertaken to determine if fentanyl and sufentanil could produce dose-related suppression of hemodynamic and hormonal responses to surgical stimulation. Eighty patients scheduled for elective CABG were studied in two consecutive protocols: protocol I was a randomized double-blind study of 40 patients who received a single dose of fentanyl (50 or 100 $\mu\text{g}/\text{kg}$) or sufentanil (10, 20, or 30 $\mu\text{g}/\text{kg}$). Hemodynamic measurements and hormonal concentrations (renin, aldosterone, cortisol, and catecholamines) were determined before and after induction and after intubation and sternotomy. Protocol II was an open randomized study of 40 patients who received sufentanil in one of four doses: 30 $\mu\text{g}/\text{kg}$ as a single dose, 10 $\mu\text{g}/\text{kg}$ plus infusion 0.05 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, 20 $\mu\text{g}/\text{kg}$ plus infusion 0.1 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, or 40 $\mu\text{g}/\text{kg}$ plus infusion 0.2 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. Hemodynamic measurements and plasma sufentanil and catecholamine concentrations were determined before and after induction and after intubation, sternotomy, and aortic cannulation. Both protocols defined a hemodynamic response as a 15% or more increase in systolic blood pressure (SBP) from control and a hormonal response 50% or more increase over control. During protocol I, 18 patients had a hemodynamic response (average increase in SBP 22.6 \pm 2%) and 35 patients had a total of 59 hormonal responses. During protocol II, 24 patients had a hemodynamic response (average increase in SBP - 31 \pm 3%) and there were 15 catecholamine responses. There were no differences between dose groups in either protocol. It was concluded that in these dose ranges, suppression of hemodynamic or hormonal stress responses is not related to opioid dose. Furthermore, the maintenance of high plasma opioid concentrations by opioid infusions does not decrease the incidence of these responses. (Key words: Anesthesia: cardiac. Anesthetics, intravenous: fentanyl; sufentanil. Hormones: aldosterone; cortisol; renin. Opioids, intravenous: fentanyl; sufentanil. Sympathetic nervous system: catecholamines.)

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SINCE THEIR INTRODUCTION, the synthetic opioids fentanyl and sufentanil have become the most popular induction and maintenance agents in patients with coronary artery disease undergoing coronary artery bypass surgery. High doses of these drugs greatly reduce the hemodynamic and hormonal responses to surgical stimulation (the "stress response") while producing minimal cardiovascular depression.¹⁻⁴

Fentanyl was approved by the Food and Drug Administration for use in cardiac surgical procedures in a dose range of 50-150 $\mu\text{g}/\text{kg}$, an amount over ten times that needed to produce apnea and profound analgesia in most individuals. Sufentanil was subsequently approved for the same indication in doses of 10-30 $\mu\text{g}/\text{kg}$. What is the rationale for using such large amounts of opioid? When fentanyl or sufentanil is used alone with oxygen, a high dose is required to induce and maintain unconsciousness.⁴ It is much less clear what dose or concentration is necessary to block the hemodynamic response to stimulation. When fentanyl is given with thiopental, 8 $\mu\text{g}/\text{kg}$ is sufficient to abolish the hypertensive response to laryngoscopy and intubation.⁵ Wynands *et al.*, on the other hand, studied fentanyl/oxygen anesthesia and were unable to determine a plasma fentanyl concentration that blocked the hypertensive responses in 50% of patients undergoing coronary artery surgery.⁶ However, several investigators have suggested that sufentanil and fentanyl produce dose-related suppression of hemodynamic and hormonal stress responses during surgery.⁷⁻¹⁰ Some have also suggested that in the high-dose range used for cardiac surgery sufentanil is more effective than fentanyl in blunting autonomic responses.^{9-12,§}

The present study was designed to accomplish two related goals. First, we wished to test the assumption implicit in the FDA guidelines, that the intensity of opioid anesthetic effect is related to the dose administered. Second, if this assumption proved true, we wished to determine the relative potencies of fentanyl and sufentanil in sup-

§ Benthuyssen JL, Foltz BD, Smith NT, Sanford TJ, Dec-Silver H, Westover CJ: Prebypass hemodynamic stability of sufentanil-O₂ and morphine-O₂ anesthesia during cardiac surgery. A comparison of cardiovascular profiles. *J Cardiothoracic Anesth* 12:749-757, 1988.

pressing hemodynamic and hormonal stress responses during cardiac surgery.

The data from our first 40 patients (protocol I) did not reveal any relationship between opioid dose and intensity of effect. Given as a single bolus, neither fentanyl nor sufentanil completely blocked hemodynamic or hormonal responses to surgical stimulation. We therefore studied one drug, sufentanil (protocol II), with a large bolus followed by a continuous infusion to determine whether sustained high plasma concentrations would be more effective.

Methods

Eighty patients scheduled for elective coronary artery surgery were studied in two consecutive protocols. Written informed consent was obtained from each patient and both protocols were approved by the Institutional Review Board. All patients were classified as ASA physical status 3 or 4 and had an ejection fraction of greater than 0.4.

All patients received morphine, 0.1 mg/kg im, and scopolamine, 0.3–0.4 mg, im 90 min prior to induction. In addition, patients in protocol II received 1–2 mg of lorazepam orally. Preoperative cardiac medications were continued until the morning of surgery. Upon arrival in the induction room, peripheral venous, pulmonary arterial (PA), and radial arterial catheters were inserted under local anesthesia and the respective pressures monitored on a direct writing recorder with an oscilloscope. Standard leads II and V-5 of the electrocardiogram were continuously monitored. Baseline hemodynamic measurements consisting of radial arterial blood pressure (systolic, mean, diastolic), PA pressure, pulmonary capillary wedge (PCW) pressure, central venous pressure (CVP), heart rate, and cardiac output (triplicate, thermodilution) were obtained.

PROTOCOL I

This was a randomized, double-blind comparison of fentanyl (50 or 100 $\mu\text{g}/\text{kg}$) and sufentanil (10, 20, or 30 $\mu\text{g}/\text{kg}$). Forty patients were allocated to the five treatment groups as shown in figure 1. The opioids were prepared by the hospital pharmacy in individual coded bottles. Each bottle contained 200 ml of saline and either fentanyl (25 or 50 $\mu\text{g}/\text{ml}$) or sufentanil (5, 10, or 15 $\mu\text{g}/\text{ml}$). Each patient was to receive 2 ml/kg of coded solution at a rate of 8 ml/min.

Baseline hemodynamic measurements were recorded and an arterial blood sample was withdrawn for later assay of the following hormones: epinephrine and norepinephrine, renin activity, cortisol, and aldosterone.

Anesthesia was induced with the study medication, metocurine (0.3 mg/kg) and oxygen. Incremental doses of metocurine (0.1–0.2 mg/kg) were given as needed to maintain muscle relaxation. Hemodynamic measurements

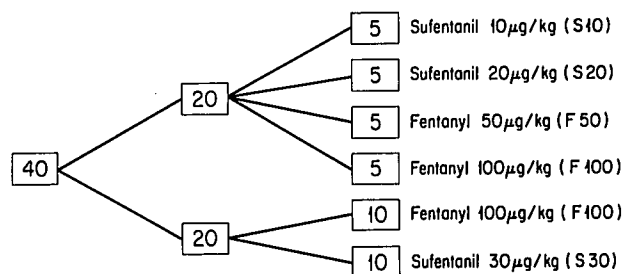


FIG. 1. A schematic illustration of patient group distribution for protocol I. Numbers in boxes represent the number of patients in each group.

were repeated following opioid administration, after intubation, and after sternotomy. Blood samples were obtained at these same points for hormonal analysis.

PROTOCOL II

This was a randomized open comparison of sufentanil with four different dosage regimens. Hemodynamic monitoring and assessment of hemodynamic responses were performed as in protocol I. Patients were randomly assigned to one of the following treatment groups: group 1 ($n = 10$)—a loading dose of sufentanil 30 $\mu\text{g}/\text{kg}$ with no maintenance infusion; group 2 ($n = 10$)—a loading dose of sufentanil 10 $\mu\text{g}/\text{kg}$ followed immediately by an infusion of 0.05 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; group 3 ($n = 10$)—a loading dose of sufentanil 20 $\mu\text{g}/\text{kg}$ followed immediately by an infusion of 0.1 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; group 4 ($n = 10$)—a loading dose of sufentanil 40 $\mu\text{g}/\text{kg}$ followed immediately by an infusion of 0.2 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$.

All sufentanil loading doses were administered at the rate of 500 $\mu\text{g}/\text{min}$. Maintenance infusions were continued until just prior to the institution of cardiopulmonary bypass. Muscle relaxation was achieved with a combination of pancuronium (0.03–0.06 mg/kg) and metocurine (0.1–0.3 mg/kg). Prior to induction, each patient received 10 ml/kg of lactated Ringer's solution. Hemodynamic measurements were made before and after induction, and after tracheal intubation, sternotomy, and aortic cannulation. Arterial blood samples were obtained for determination of plasma sufentanil concentrations at baseline, following the loading dose, and after tracheal intubation, sternotomy, and aortic cannulation. Plasma epinephrine and norepinephrine concentrations were also measured at these time points.

All blood samples for protocols I and II were drawn into heparinized glass tubes and placed immediately on ice. The plasma was separated in a refrigerated centrifuge and stored in polypropylene tubes at -70°C for later assay. The various hormonal assays have been described previously.^{13–16} Sufentanil concentrations were determined (in duplicate) by radioimmunoassay.¹⁷ This assay

TABLE 1. Number of Hemodynamic Responders: Protocol I

Group	Responders	% Increase SBP* (Range)	Time of Response	
			Intubation	Sternotomy
F50 (n = 5)	3	20 ± 3% (15-26%)	1	2
F 100 (n = 15)	5	22 ± 3% (15-30%)	2	3
S 10 (n = 5)	2	22 ± 7% (15-29%)	1	1
S 20 (n = 5)	3	23% ± 1% (21-24%)	2	1
S 30 (n = 10)	5	26% ± 5% (16-38%)		5

* Mean ± SEM.

has a sensitivity of 0.1 ng/ml and a coefficient of variation of less than 5% over the concentrations used in this study.

Hemodynamic and hormonal responses were assessed quantally for each patient. A hemodynamic response was defined as an increase of 15% or greater in the patient's systolic blood pressure relative to the average preoperative value on the ward. The time of the first response was noted after which treatment was instituted with an inhalational anesthetic, and if necessary, a vasodilator. Only the initial hemodynamic response was used for data analysis. A hormonal response was defined as an increase of 50% or more in the plasma concentration relative to the control value for that patient. Hemodynamic and hormonal responses were analyzed only for the period from induction to the completion of sternotomy in protocol I and from induction to aortic cannulation in protocol II.

Quantal data were analysed by chi-square or Fisher's exact test. Continuous variables were compared with Students *t* test and analysis of variance for repeated measures. Differences were deemed significant if *P* < 0.05.

Results

PROTOCOL I

The five groups were comparable for age, weight, height, and sex. All were receiving similar amounts of β-

and calcium channel-blocking drugs except for the F50 group which had a higher average dose of preoperative β-blocking drug (*P* < 0.01). The degree of pre-existing hypertension and coronary artery disease was not significantly different between groups.

The cardiovascular effects of the opioids themselves were relatively small and none of the treatment groups were judged to have significant cardiovascular instability during induction. Fentanyl and sufentanil produced an insignificant decrease in mean arterial pressure as well as statistically insignificant changes in HR, CVP, PCWP, and cardiac output. Two patients (one in group F50 and one in S10) required phenylephrine for blood pressure support for a brief period during induction.

Eighteen of 40 patients were hemodynamic responders (range of increase: 15-38%). All were treated with a volatile anesthetic and if necessary an intravenous vasodilator. The number of responses in each dose group and the time when the initial response occurred are listed in table 1. The frequency of hemodynamic response ranged from 33-60% per group with no significant difference between opioids and no relationship to opioid dose.

Hormonal responders were also found in each group (table 2). Many patients had an increase in more than one hormone, thus there were a total of 59 responses for the 40 patients. The time to maximal increase varied between hormones, but all responses occurred in the period before cardiopulmonary bypass. Increases in plasma renin activity occurred most frequently, increases in cortisol least frequently. Five patients had no response. The number of renin responses was significantly greater for patients receiving fentanyl than those receiving sufentanil (*P* < 0.05). Other than this, we found no relationship between the drug or dose given and the frequency of response.

PROTOCOL II

These 40 patients were comparable to those studied in protocol I in age, sex, type of operation, and degree of disease. There were no significant intragroup differences in either demographics or in control hemodynamic and hormonal measurements. The decrease in systolic arterial

TABLE 2. Hormonal Responses: Protocol I

Group	No Response	Renin	Aldosterone	Cortisol	Epinephrine	Norepinephrine
F 50 (n = 5)	0	4	1	0	3	1
F 100 (n = 15)	2	10	4	2	4	4
S 10 (n = 5)	1	2	0	1	2	2
S 20 (n = 5)	0	1	1	2	2	2
S 30 (n = 10)	2	3	3	0	3	2

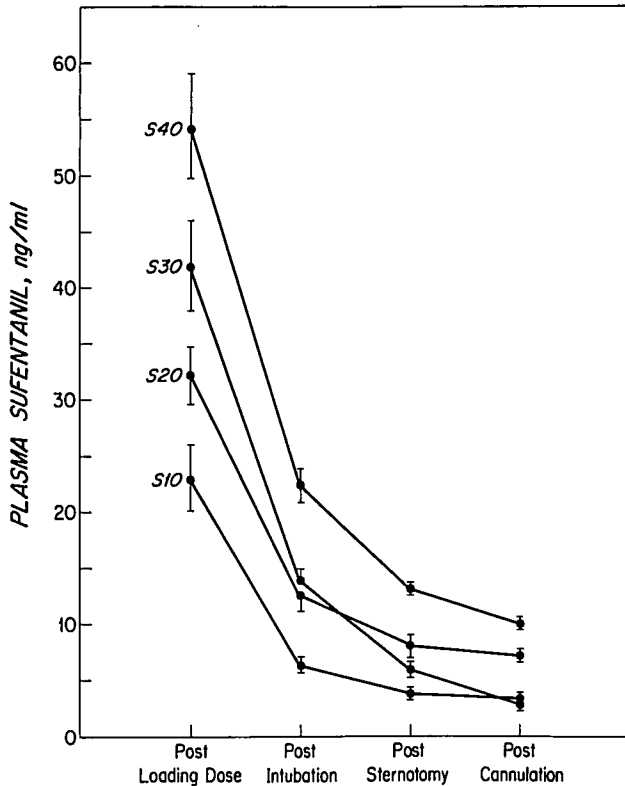


FIG. 2. Plasma sufentanil concentrations for all four groups (protocol II). Each point represents the mean + SEM for ten patients.

pressure with induction achieved significance in the S30 group (137 ± 8 to 120 ± 7 mm Hg; $P < 0.05$). Changes in other cardiovascular parameters were not statistically significant.

Plasma sufentanil concentrations followed a consistent pattern and were dose related (fig. 2). The higher doses of sufentanil produced extraordinarily high plasma concentrations that remained elevated throughout the pre-bypass period.

Twenty-four of the 40 patients were hemodynamic responders. These are listed in table 3 according to the time

HEMODYNAMIC RESPONDERS

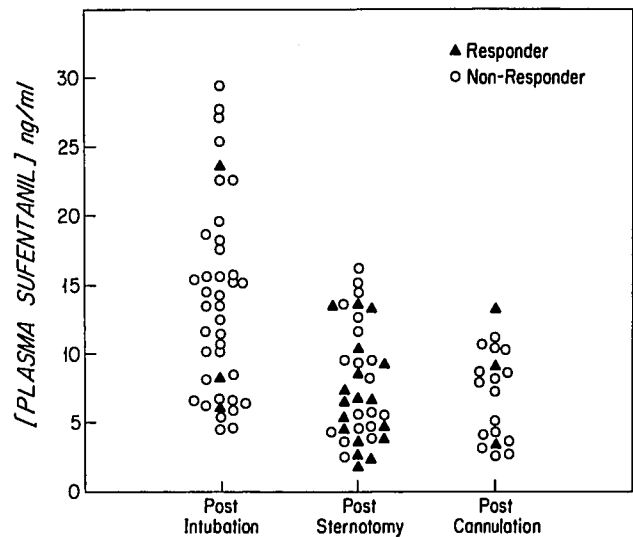


FIG. 3. Patients with a hemodynamic response and the plasma sufentanil concentration at that time as well as the sufentanil concentrations for the nonresponders. Therapy was initiated at the time of the initial response and no further data points included for those patients.

of the initial response. As was the case during protocol I, many of these responses were substantially larger than our criterion of a 15% increase in systolic pressure. The majority of responses (18/24) occurred following sternotomy. The frequency of response was not related to plasma sufentanil concentration (fig. 3).

Figure 4 illustrates individual catecholamine responses and simultaneously measured plasma sufentanil. An epinephrine response was measured in eight of 40 patients. In four of these cases simultaneously measured plasma sufentanil was greater than 15 ng/ml. A norepinephrine response occurred in seven of 40 patients, most frequently following intubation. The norepinephrine responses to sternotomy and cannulation appeared to be somewhat suppressed by sufentanil, but some of these patients were already receiving treatment for hypertensive responses

TABLE 3. Number of Hemodynamic Responders: Protocol II

Group (n = 10 for each)	Responders	% Increase in SBP* (Range)	(Time of Response)		
			Intubation	Sternotomy	Cannulation
S30	8	32% ± 1% (25-36%)		8	
S10	6	33% ± 1% (25-45%)	1	4	1
S20	4	27.5 ± 1% (25-32%)	1	3	
S40	6	33 ± 2% (23-48%)	1	3	2

* Mean ± SEM.

since the catecholamine concentrations were not available during surgery. Hemodynamic and catecholamine responses, when they occurred, were not consistently related (fig. 5). Fourteen patients had a hemodynamic response without a catecholamine response. Norepinephrine decreased in eight of these ($22 \pm 12\%$; range: 2–40%), and increased in six ($21 \pm 15\%$; range: 5–44%). Epinephrine increased in three of these ($6 \pm 2\%$; range: 4–8%) and decreased in the remaining eleven ($32 \pm 23\%$; range: 2–59%). Only 14 of the 40 patients had neither a catecholamine nor hemodynamic response.

Discussion

Protocol I of this study investigated the presumed relationship between opioid dose and suppression of hemodynamic and hormonal responses. We found no evidence for a dose-response relationship when fentanyl or sufentanil are administered in these dose ranges. The randomized double-blind nature of the protocol strengthens our confidence in the negative findings.

Early in the first part of the study it became clear that a high proportion of patients were hemodynamic responders. We interpreted this to mean that our opioid doses were inadequate. Without breaking the code, we assigned the last 20 patients to one of the two high doses (fentanyl 100 $\mu\text{g}/\text{kg}$ or sufentanil 30 $\mu\text{g}/\text{kg}$). The frequency of response remained virtually unchanged. Because the intensity of opioid effect was not related to dose, it was not possible to determine relative “anesthetic” potencies of fentanyl and sufentanil.

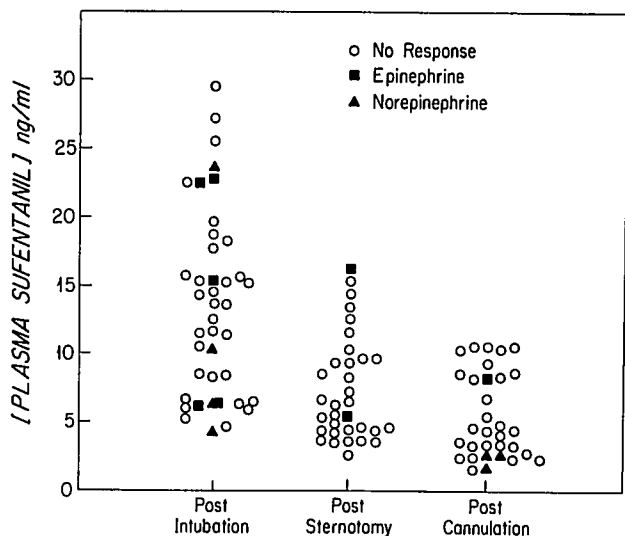


FIG. 4. Patients with a catecholamine response and plasma sufentanil concentration at that time as well as the sufentanil concentrations for the nonresponders. Because the assays were performed after surgery several patients at each time point were also being treated for a hemodynamic response.

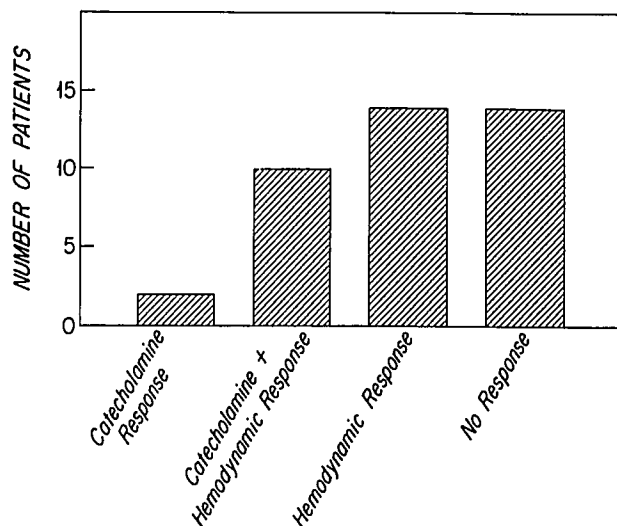


FIG. 5. A graphic illustration of patient responders and nonresponders. Note that 14 patients had a hemodynamic response without a catecholamine response and two a catecholamine response but no hemodynamic response.

We then raised the possibility that mode of administration might have influenced our results. Perhaps administering the entire dose of opioid at the beginning resulted in inadequate blood concentrations at a point later in the procedure. After re-examining the data, the responses in the S30 group did seem to occur later than in the F100 group. Protocol II, using a loading bolus followed by a continuous infusion of sufentanil, addressed this issue. A fourfold increase in the dose from 10 $\mu\text{g}/\text{kg}$ plus infusion of 0.05 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ to 40 $\mu\text{g}/\text{kg}$ plus infusion of 0.2 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ did not significantly reduce the incidence of responders. To our knowledge, these represent some of the highest doses of sufentanil administered in a clinical setting. It therefore seems improbable, and we believe clinically irrelevant, that even higher doses would be any more effective. Wynands *et al.*¹⁸ previously reported that the use of fentanyl infusions did not significantly reduce the incidence of hemodynamic responses during cardiac surgery. He also suggested that newer opioids might exhibit the same inability to reliably block sympathetic responses to noxious stimuli.¹⁸ Hug *et al.* found similar results with alfentanil infusions.¹⁹ It thus appears that even with increasingly more potent opioids and the use of infusions to maintain high plasma concentrations, no predictable dose or plasma concentration can reliably control hemodynamic responses to noxious stimuli. Many studies that claim to demonstrate such suppression have actually shown, in retrospect, that the average blood pressure and hormonal concentration was not significantly different at a specific point.^{3,4,10} Because each patient may respond at a different time, this type of anal-

ysis will minimize significant individual responses. In this study we defined hemodynamic response prospectively and looked for it continuously throughout the study period. We chose a quantal (all or none) analysis because we believe that any response necessitating an intervention is clinically important and relevant.

Nonetheless, potent opioids do blunt most responses to painful stimuli. These desirable analgesic effects are presumably due to selective and highly specific actions at μ -opioid receptors. But fentanyl and sufentanil produce useful intraoperative analgesia in doses an order of magnitude less than those studied here.^{5,8} Why then were these very high doses not completely effective in blocking autonomic and endocrine responses during surgery? There are several possible explanations. Despite their high intrinsic activity, fentanyl and sufentanil may behave as partial agonists. This seems to be the case if one measures somatic responses to painful stimuli: neither opioid can produce 100% depression of MAC for halothane or enflurane.²⁰⁻²² It may also be that some of these autonomic and endocrine responses are not susceptible to treatment with opioids. Direct stimulation of sympathetic efferents or infusions of norepinephrine produce arteriolar constriction that is not blocked by morphine.²³ Venous baroreflex responses appear to be preserved during fentanyl-diazepam anesthesia.²⁴ Finally, very high doses of fentanyl and sufentanil may produce acute tolerance to the analgesic and hypnotic effects. Bovill *et al.* have shown that with increasing doses of alfentanil patients return to consciousness at higher plasma concentrations.²⁵ Askitopoulou *et al.* demonstrated the rapid onset of tolerance to the analgesic effects of fentanyl.²⁶ They found that the ability of fentanyl to block the increase in heart rate and blood pressure caused by stimulation of the radial nerve in dogs was completely lost during a three hour infusion.

Whatever the reason for the limited effect, our data allow us to make several statements regarding the clinical use of these opioids. Enormous doses of fentanyl and sufentanil are well tolerated but may not actually produce a more "stable" anesthetic. Administration by infusion will reduce the total dose required to produce a given plasma concentration, and thus may offer a cost advantage, but it does not seem to offer any pharmacodynamic benefit because plasma concentrations are not related to preventing a response. Because increasing the dose of opioid does not produce better hemodynamic control, it seems reasonable to use a smaller dose and administer other anesthetic or vasoactive drugs when needed.

In conclusion, large doses of the opioids fentanyl and sufentanil can be administered with minimal hemodynamic effects in patients with good ventricular function. However, the suppression of hemodynamic or hormonal responses to surgical stimulation does not appear to be dose related. Administration of very high doses of opioid

or use of continuous infusions to maintain a high plasma concentration of opioid does not significantly reduce the incidence of responses and is therefore of no benefit. It is unlikely that any clinically useful dose of either fentanyl or sufentanil will successfully abolish such a response in all patients. On theoretical grounds it also seems unlikely that the introduction of even more potent synthetic opioids into clinical practice will result in less hemodynamic responsiveness when used as the sole anesthetic agent. Opioids, by the nature of their action, should not be expected to produce and maintain complete surgical anesthesia.

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