Anesthesiology
66:130–135, 1987

Comparison of Sufentanil–N_2O and Fentanyl–N_2O in Patients Without Cardiac Disease Undergoing General Surgery

Norman J. Clark, M.D., Thomas Meuleman, M.D.,† Wen-Shin Liu, M.D.,‡ Prisca Zwanikken,§ Nathan L. Pace, M.D.,‡ Theodore H. Stanley, M.D.¶*

Sufentanil (mean total dose 2 μg/kg) was compared with fentanyl (mean total dose 15 μg/kg) as a supplement to 60% N_2O anesthesia in 30 adult patients undergoing general surgical procedures. Comparisons were made with respect to stability of hemodynamic variables (heart rate and systolic and diastolic blood pressure), changes in stress hormones (cortisol, antidiuretic hormone, epinephrine, norepinephrine, and dopamine), recovery of alertness and orientation, time to extubation, postoperative analgesia, and measures of respiratory depression (resting end-tidal carbon dioxide tension [$P_{ET_{CO_2}}$], CO_2 response curve for minute ventilation [$\Delta V_E/\Delta P_{ET_{CO_2}}$]). Hemodynamic variables remained stable and similar in both groups throughout the study. Plasma hormone levels remained similar to baseline in both groups until 1 h postoperatively when epinephrine levels were significantly elevated in both groups ($P < 0.05$). Recovery times, including time to extubation, were similar in both groups. Patients given sufentanil had less pain 30 min postoperatively than those given fentanyl, although at 60 min postoperatively pain levels were similar in both groups. Small but significant elevations in resting $P_{ET_{CO_2}}$ were seen in both groups postoperatively ($P < 0.05$), but postoperative $\Delta V_E/\Delta P_{ET_{CO_2}}$ responses were significantly depressed only in patients receiving fentanyl ($P < 0.05$). The results of this study demonstrate that sufentanil–N_2O anesthesia is as effective as fentanyl–N_2O in attenuating the hemodynamic and hormonal responses to the stress of general surgery. Because continuous intraoperative $P_{ET_{CO_2}}$ monitoring was not employed in this study, intraoperative hypocapnea cannot be strictly excluded as a possible influence on the postoperative measures of ventilatory drive. However, the results of this study suggest that sufentanil–N_2O results in less profound respiratory depression and greater analgesia in the immediate postoperative period after general surgery. (Key words: Anesthetics, gases: nitrous oxide. Anesthetics, intravenous: fentanyl, sufentanil. Hormones: antidiuretic hormone; cortisol. Recovery: analgesia; ventilation. Sympathetic nervous system, catecholamines: dopamine; epinephrine; norepinephrine.

FENTANYL IS A POTENT synthetic opioid that has achieved widespread use in high doses (50–150 $\mu g \cdot kg^{-1}$) as a primary anesthetic in patients with cardiac disease.[1,2] Fentanyl is also used in lower doses as a component of nitrous oxide–narcotic anesthesia in patients with and without cardiovascular disease.[3] Sufentanil, the N-4 thienyl derivative of fentanyl, has recently become available for clinical use.[1,2,4,5] Clinical experience in patients with cardiac disease has confirmed that sufentanil is 5–10 times more potent than fentanyl[1,2,4–7] and that it shares with fentanyl the attractive qualities of rapid onset of action,[1,2,4,5,7] preservation of cardiovascular stability,[1,2,4,5] and absence of histamine release.[4,8,9] Moreover, a number of studies have suggested that sufentanil provides a more rapid induction[1,7] and greater blockade of the hemodynamic[1] and hormonal[10,11] responses to surgical stimulation, and produces less postoperative respiratory depression, allowing quicker recovery and earlier extubation[7] than equipotent doses of fentanyl.

Several reports comparing fentanyl and sufentanil in lower doses as a supplement to nitrous oxide anesthesia in patients undergoing general surgical operations have again suggested there is more effective blockade of the hemodynamic[12] and catecholamine[12,13] responses to surgical stimulation with sufentanil, although other studies have failed to demonstrate this.[14–16] Lower doses of sufentanil have also been reported to produce both longer[16] and shorter[17] duration of respiratory depression compared with equivalent doses of fentanyl, although rigorous, quantitative measurements of respiratory drive were not employed in these studies.

The purpose of this study was to compare and contrast equipotent doses of sufentanil and fentanyl as supplements to nitrous oxide anesthesia during general surgical procedures in patients without a history of cardiovascular disease. Comparisons were made with respect to: 1) stability of vital signs during induction and maintenance of anesthesia; 2) plasma hormonal changes during operation and the early postoperative period; 3) time for recovery and orientation after anesthesia; 4) incidence and magnitude of postoperative pain; 5) recovery of respiratory function in the early postoperative period; 6) and time to extubation.

Methods

The study was approved by the Institutional Review Board of the University of Utah Medical Center. Thirty patients, ASA physical status I–III, without a history of cardiac disease and scheduled for general surgical, orthopedic, or gynecologic operations, served as the experimental subjects. The patients were randomly divided into two groups of 15 each. Informed consent was obtained

* Assistant Professor of Anesthesiology.
† Clinical Instructor in Anesthesiology.
‡ Associate Professor of Anesthesiology.
§ Research Medical Student in Anesthesiology.
¶ Professor of Anesthesiology; Research Professor of Surgery.

Received from the Department of Anesthesiology, The University of Utah School of Medicine, 50 North Medical Drive, Salt Lake City, Utah 84132. Accepted for publication August 22, 1986. Funded in part by the Stanley Research Foundation.

Address reprint requests to Dr. Clark.

from each patient at the time of the preoperative visit. Patients in Group 1 were scheduled to receive sufentanil and those in Group 2 fentanyl as an analgesia supplement to 60% N_2O anesthesia. All patients were premedicated with diazepam 0.15 $mg \cdot kg^{-1}$ po and atropine 0.4 im 60 min prior to induction of anesthesia.

After the patient's arrival in the operating room a peripheral intravenous infusion was established, a standard blood pressure cuff was applied to the upper arm, and a lead II electrocardiogram continuously displayed. Following control measurements of heart rate and arterial blood pressure, each patient was given 100% O_2 by mask and pancuronium, 1 mg iv. Three minutes later anesthesia was induced with sodium thiopental, 3–5 $mg \cdot kg^{-1}$ iv, followed by succinylcholine, 1.5 $mg \cdot kg^{-1}$ iv. Following this an endotracheal tube was placed in the trachea and controlled ventilation was established with nitrous oxide and oxygen (60%/40%). Tidal volume was set at 10 $ml \cdot kg^{-1}$ and respiratory rate at 8–10 breaths/min. Patients in Group 1 then received sufentanil, 1 $\mu g \cdot kg^{-1}$ iv, and those in Group 2 were given fentanyl, 7 $\mu g \cdot kg^{-1}$ iv, over 1 min. Thereafter, sufentanil and fentanyl were given in 25 μg and 100 μg increments, respectively, whenever heart rate and/or systolic arterial blood pressure increased 15% or more above control values. A 5-min response time was allowed after each supplemental dose before determining whether another dose was needed. The identity of the study drug was concealed from the primary anesthesiologist administering it as well as the investigator responsible for evaluating and recording the patient's response. When the surgical procedure required muscle relaxation, pancuronium was administered in 1–2 mg increments intravenously. The degree of relaxation was monitored with ulnar nerve stimulation *via* surface electrode pads. Total ablation of the twitch response was not required or produced in any patient.

Heart rate and systolic and diastolic arterial blood pressures were recorded upon entry to the operating room (baseline), just prior to induction of anesthesia, immediately after endotracheal intubation, 2 min after initial administration of fentanyl or sufentanil, and at 5-min intervals throughout the remainder of operation and in the recovery room.

A 10-ml sample of venous blood was obtained from each patient upon arrival in the operating room (baseline) and again at 15, 30, 60, 120, 180, and 240 min following endotracheal intubation and 1 h postoperatively. Each blood sample was drawn into a fresh, heparinized syringe, and 6 ml of that sample (for catecholamine assay) was immediately transferred to a separate tube containing glutathione and EGTA (ethylene-glycol-bis [B-aminoethyl ether]-NN′ tetraacetic acid). This sample and the remaining 4 ml were placed on ice and then centrifuged at 7,000 rpm in a refrigerated centrifuge within 15 min of sample collection. The plasma was then separated into screw-topped vials and frozen at −20° C until analyzed. The plasma samples were analyzed for epinephrine, norepinephrine, and dopamine using the appropriate radioenzymatic assay[18,19] (coefficients of variation = 10, 9, and 12%, respectively; sensitivities = 25, 25, and 30 $pg \cdot ml^{-1}$, respectively). Plasma cortisol levels were determined by radioimmunoassay[20] (coefficient of variation = 8%; sensitivity = 0.1 $\mu g \cdot dl^{-1}$). Plasma antidiuretic hormone (ADH) was measured using the radioimmunoassay of Robertson *et al.*[21] as modified by Philbin *et al.*[22]

Respiratory drive was evaluated by measuring the ventilatory response to progressive hypercapnea using the Read rebreathing method[23] with modifications as described below. Measurements were taken on the morning of surgery prior to administration of preoperative medication (baseline), and then were repeated 30 and 60 min after anesthesia. After being placed supine, each patient was asked to rebreath a mixture of 5% CO_2 and 95% O_2 from a 7-l Neoprene® bag incorporated in a closed rebreathing circuit. The rebreathing circuit was interfaced with a Motorola Exorciser® Microcomputer Development System (Motorola Microsystems, Phoenix, AZ) *via* a 12-bit analog-to-digital convertor (Burr-Brown MP 7208 Data Acquisition System) having a resolution of 4.8 millivolts per analog-to-digital unit and a range of ±10 volts. The patient breathed through a mouthpiece attached to the circuit by a Collins® J valve separating the inspiratory and expiratory limbs. Nasal breathing was prevented with a padded nose-clip. (The circuit resistance of 1.9 cm $H_2O \cdot l^{-1} \cdot s^{-1}$ in the inspiratory limb and 1.7 cm $H_2O \cdot l^{-1} \cdot s^{-1}$ in the expiratory limb was constant between flow rates of 15–135 $l \cdot min^{-1}$.) End-tidal CO_2 ($P_{ET}CO_2$) was measured at the mouthpiece with a Beckman® LB-2 infrared CO_2 analyzer (Beckman Instruments, Inc., Schiller Park, IL). Tidal volume (V_T) was derived by electronic integration of the pressure signal from a #00 Fleisch Pneumotachograph® (Fleisch Instruments, Baltimore, MD) coupled with a Validyne Differential Pressure Transducer® (Model NP4S-1, Validyne Engineering Corp., Northridge, CA) in the inspiratory side of the circuit. This unit was calibrated with a 1.5-l syringe prior to each rebreathing trial. As the patient rebreathed through this circuit, V_T and $P_{ET}CO_2$ were measured, recorded, and stored on a breath-by-breath basis. For each breath, an "instantaneous" minute volume (V_E) was calculated as $V_T \times (60\ s \cdot min^{-1}/T_{tot})$, where T_{tot} equals total duration of that respiratory cycle in s. Each V_E, so calculated, was then plotted against $P_{ET}CO_2$ for that breath. The rebreathing trial was terminated when $P_{ET}CO_2$ had reached 55–60 mmHg, at which time a computer subroutine would plot and display the CO_2 response curve for minute ventilation ($\Delta V_E/\Delta P_{ET}CO_2$). Regression of V_E against $P_{ET}CO_2$ was performed by least-squares linear regression.

Immediately prior to evaluation of respiratory drive each patient was asked to report his or her degree of pain (pain level), which was rated by the patient on a scale from 0 (no pain) to 10 (severe, intolerable pain). The same investigator, an anesthesia research fellow, familiarized each patient with the pain evaluation scale preoperatively. All pain scores were then solicited and recorded in uniform manner by this same investigator. Following the pain evaluation, *resting* $P_{ET_{CO_2}}$, V_T, and respiratory rate were recorded as the patient breathed through the circuit while it was closed to the bag and open to room air.

Postoperatively, atropine, 15 $\mu g \cdot kg^{-1}$ iv, and neostigmine, 40 $\mu g \cdot kg^{-1}$ iv, were administered to all patients who had received pancuronium in excess of the 1 mg used for defasciculation. Recovery of twitch amplitude to baseline value was confirmed. Nitrous oxide was discontinued when the surgical dressing was in place. Time to extubation was measured in minutes from the time nitrous oxide was turned off. Each patient was extubated when the spontaneous respiratory rate exceeded 8 $\cdot$ min^{-1} and spontaneous V_T was estimated, from the excursions of the anesthesia breathing bag, to exceed 8 ml $\cdot$ kg^{-1} body weight. In the recovery room patients were evaluated every 5 min for response to verbal command and orientation to person, place, and time by the same investigator who obtained the pain ratings (see previous paragraph).

Statistical Methods

Mean values for heart rate, systolic and diastolic blood pressure, plasma hormone levels, and measures of ventilation and respiratory drive were compared between the two groups preoperatively (baseline) and at each subsequent measurement interval using Bonferroni adjusted *t* tests. The significance level for the study was held at 0.05, and Bonferroni adjustment was performed by multiplying any given individual *P* value by the maximum number of comparisons possible with respect to the null hypothesis governing that particular aspect of the study. All reported *P* values are those obtained *after* this correction and are considered significant if <0.05. Mean values at each intraoperative or postoperative measurement interval were compared with baseline values for that group using paired *t* tests with similar Bonferroni adjustment. The Kruskal-Wallis chi-square test was used to compare recovery and extubation times between groups and pain ratings were compared at baseline, 30, and 60 min postoperatively using the Mantel-Haenszel test.

It was determined that baseline values for plasma cortisol, ADH, and catecholamines were not normally distributed and a log transformation was necessary to validate the *t* tests used to compare the two treatment groups and to compare each group to its own baseline values. For the basic data, the transformation was applied to each individual data point, and for analysis of per cent change from baseline the transformation was applied to the quotient of the postbaseline measurement to its baseline. Mean responses were estimated by assuming the data were log normally distributed and then taking the antilog of the transformed data.

Results

Patients in Group 1 (sufentanil) and Group 2 (fentanyl) were similar with respect to sex, weight, average ASA physical status, baseline values of heart rate, arterial blood pressure, $P_{ET_{CO_2}}$, $\Delta V_E/\Delta P_{ET_{CO_2}}$, and duration of anesthesia (tables 1 and 4). Female patients in Group 1 (n = 10) were significantly older (mean age 41.5 yr; range 27–59 yr) than female patients (n = 7) in Group 2 (mean age 27.1 yr; range 19–48 yr) ($P < 0.05$). The mean total sufentanil dose (including supplements) was 2 $\mu g \cdot kg^{-1}$ with a range of 1–4 $\mu g \cdot kg^{-1}$, and the mean total fentanyl dose was 15 $\mu g \cdot kg^{-1}$ with a range of 8–32 $\mu g \cdot kg^{-1}$.

Heart rate and arterial blood pressure values in both groups were similar and were consistently within 15% of control values at all but two time periods during the study. Immediately after endotracheal intubation, patients in both groups experienced significant but transient increases in heart rate and arterial blood pressure. Patients in Group 1 also experienced a transient decrease in diastolic blood pressure 2 min after sufentanil administration ($P < 0.05$). There were no other differences during the remainder of the study.

Plasma concentrations of cortisol, ADH, dopamine, norepinephrine, and epinephrine were similar in the two groups prior to anesthesia and remained similar throughout the study (table 2). Plasma concentrations of epinephrine and norepinephrine tended to decrease from baseline values in both groups during operation, though not significantly. However, plasma epinephrine levels were significantly increased in both groups 1 h postoperatively ($P < 0.05$ for both groups). Plasma dopamine, ADH, and cortisol levels remained unchanged from control values during surgery, and at 1 h postoperatively.

There was no difference in times to extubation between the two groups (table 3). Likewise, recovery times as measured by response to verbal command and orientation to person, place, and time were similar in both groups. No patient in either group received naloxone at any time during the study.

Both treatment groups demonstrated a small but significant rise in resting $P_{ET_{CO_2}}$ postoperatively, although mean values in both groups remained in the normal range (table 4). Additional evidence of respiratory depression was seen in the patients receiving fentanyl. This group demonstrated significantly depressed responses to CO_2 rebreathing consisting of an 84% decrease in $\Delta V_E/\Delta P_{ET_{CO_2}}$ at 30 min postoperatively and a 67% decrease at 60 min postoperatively. In contrast, postoper-

ative $\Delta V_E/\Delta PET_{CO_2}$ responses were not significantly different from control in patients receiving sufentanil (table 4).

One patient in Group 2 gave a preoperative pain rating of 6 on the 0–10 scale. All other patients in the study were free of pain prior to operation. Thirty minutes postoperatively, seven patients (five who had received sufentanil and two who received fentanyl) remained drowsy and could not provide intelligible responses to the pain evaluation. All seven of these patients appeared comfortable, but in the absence of explicit verbal responses, their 30-min pain scores were ruled ungradable and eliminated from statistical analysis. Of the remaining 23 patients, those who had received sufentanil reported significantly less pain than the patients receiving fentanyl (table 5). Between 30 and 60 min postoperatively, four patients (one who had received sufentanil and three fentanyl) became nauseated and/or vomited and were given antiemetic medication. Another two patients (both in the fentanyl group) experienced severe enough pain to require analgesic therapy. All six of these patients were excluded from respiratory and pain evaluations 60 min postoperatively. Pain scores in the remaining 24 patients were similar between the two groups (table 5).

TABLE 1. Patient Characteristics and Duration of Anesthesia

	Group 1 Sufentanil (n = 15)	Group 2 Fentanyl (n = 15)
Sex		
M	5	8
F	10	7
Age (yr)		
Mean	42.8	38.7
Range	(26–62)	(19–61)
Weight (kg)		
Mean	68.8	68.9
Range	(48.6–109.1)	(50.0–90.9)
Duration of Anesthesia (h)		
Mean	2.4	2.2
Range	(0.8–5.9)	(1.4–3.7)

Discussion

The neurophysiologic, endocrine, and metabolic changes elicited by surgical trauma and collectively known as the *stress response* have been well defined by others.[24,**] The presence of opiate receptors in brain centers mediating the stress response[6,25] underlies the successful use of opioids in high doses to prevent or reduce the stress response to major surgery, including the prebypass phase of cardiac surgery.[1,2,5,6] However, the comparative stress-modifying potential of opioids used in lower doses during nitrous oxide anesthesia for noncardiac surgery has been investigated much less frequently.[12,13] The results of this study demonstrate that in moderate doses, as supplements to nitrous oxide anesthesia, sufentanil and fentanyl are comparable in their ability to attenuate the neuroendocrine and hemodynamic responses to the "moderate" stress produced by general surgical, orthopedic, and gynecologic operations. Although individual responses varied, mean values for cortisol, epinephrine, norepinephrine, dopamine, and ADH remained similar to control in both groups at each of the intraoperative test intervals. In this respect our results differ from those of Flacke *et al.*[12] and Ghoneim *et al.*,[13] who found sufentanil superior to other opioids, including fentanyl, at reducing intraoperative catecholamine levels[12,13] and maintaining hemodynamic stability.[12] These differences in results may reflect different dose ratios employed, because both the above investigators[12,13] studied a fentanyl–sufentanil dose ratio of 5:1 (*i.e.*, 5 $\mu g \cdot kg^{-1}$ fentanyl for every 1 $\mu g \cdot kg^{-1}$

** Kehlet H: The stress response to anaesthesia and surgery: Release mechanism and modifying factors. Clinics in Anaesthesia 2:315–339, 1984.

TABLE 2. Plasma Hormone Levels in $pg \cdot ml^{-1}$ (mean ± 1 SD)

	Baseline	Min Postintubation 15	30	60	1-h Postoperative
Cortisol					
S	13.4 ± 6.5	16.1 ± 7.6	14.0 ± 6.8	17.2 ± 10.2	22.5 ± 10.0
F	26.6 ± 48.4	18.6 ± 11.7	22.9 ± 31.1	20.6 ± 29.2	25.1 ± 18.1
Antidiuretic hormone					
S	11.8 ± 16.8	9.3 ± 10.5	10.5 ± 11.7	15.2 ± 23.8	54.4 ± 96.2
F	14.8 ± 14.2	20.9 ± 18.0	14.6 ± 11.5	22.8 ± 18.3	67.8 ± 99.9
Norepinephrine					
S	289.4 ± 94.1	198.0 ± 90.2	195.1 ± 101.3	300.9 ± 244.6	882.6 ± 1795.9
F	272.0 ± 93.7	168.6 ± 84.8	164.9 ± 59.4	188.7 ± 59.3	477.4 ± 119.2
Epinephrine					
S	31.7 ± 15.1	26.9 ± 33.4	24.9 ± 18.1	34.1 ± 35.5	155.1 ± 9.4*
F	36.0 ± 28.4	65.5 ± 158.9	15.9 ± 11.0	21.7 ± 12.9	175.9 ± 175.9*
Dopamine					
S	37.2 ± 33.5	27.9 ± 17.9	30.7 ± 30.3	47.8 ± 43.9	109.1 ± 284.2
F	33.3 ± 16.7	32.3 ± 14.9	25.2 ± 15.2	24.8 ± 14.6	47.6 ± 40.9

S = sufentanil; F = fentanyl.

* Significantly different from baseline. $P \leq 0.05$.

TABLE 3. Recovery Times in Minutes (mean ± 1 SD)

	Sufentanil	Fentanyl
Response to verbal command	6.9 ± 5.1	5.9 ± 4.4
Extubation	7.5 ± 4.1	8.5 ± 7.4
Orientation	31.1 ± 25.9	29.6 ± 19.2

sufentanil), whereas a dose ratio of 7:1 was employed in the present study.

Another major objective of this study was to compare the two treatment groups with respect to recovery of effective respiratory drive postoperatively. Fentanyl-induced respiratory depression has been well described and shown to be dose related.[26,27] In addition, recurrent or unexpectedly prolonged respiratory depression, occasionally requiring resuscitative measures, has been observed postoperatively in patients given doses of fentanyl similar to those used in this study.[28,29] Of interest is our finding that postoperative respiratory drive, as measured by the $\Delta V_E/\Delta PET_{CO_2}$ slope, was significantly depressed in patients given fentanyl but not in those given sufentanil.

As noted by other investigators,[26,27,30] evaluation of drug effects on respiratory drive by measurement of changes in resting ventilation is limited by the rather narrow range of observed responses and the relative insensitivity of resting ventilation to drug effects that profoundly alter stimulated respiration.[27,30] Measuring ventilatory responses to progressive hypercapnea introduces greater sensitivity,[27] markedly amplifies the range of responses,[26,30] and indicates how the "gain" of the closed-loop respiratory control system is affected by the study drug.[27,31] Taken as a measure of gain in the respiratory control system, the slope of $\Delta V_E/\Delta PET_{CO_2}$ reflects the system's ability to compensate for an imposed load.[31] This is illustrated by the finding of Kryger *et al.*[32] that the combination of an opioid (meperidine) plus an inspiratory flow resistive load produces a significantly greater decrement in the $\Delta V_E/\Delta PET_{CO_2}$ response than either the opioid or the resistive load alone. Thus our finding that postoperative $\Delta V_E/\Delta PET_{CO_2}$ slopes remained significantly depressed in patients given fentanyl but not in those given sufentanil implies a more profound impact by fentanyl on the respiratory control center, resulting in loss of gain

TABLE 4. Measurements of Respiratory Drive (as mean ± 1 SD)

	Baseline	Postoperative	
		30 min	60 min
Resting $P_{ET}CO_2$ (mmHg)			
S	32.8 ±4.4	37.6 ±4.7*	38.8 ±6.0*
F	32.3 ±3.1	35.9 ±5.3*	37.0 ±3.6*
$\Delta V_E/\Delta PETCO_2$ ($l \cdot min^{-1} \cdot mmHg^{-1}$)			
S	1.10 ± 0.67	0.77 ± 0.40	0.97 ± 0.63
F	1.60 ± 1.14	0.28 ± 0.70*	0.58 ± 0.57*

S = sufentanil; F = fentanyl.
* Significantly different from baseline. $P < 0.05$.

TABLE 5. Postoperative Pain Evaluation

	n	Pain Scores*					
		0	1–2	3–4	5–6	7–8	9–10
Baseline							
S	15	15					
F	15	14			1		
30 min postoperative†							
S	10	6	4				
F	13	5	2	2	1	3	
60 min postoperative							
S	14	5	5	2	2		
F	11	1	5	1	2	2	

S = sufentanil; F = fentanyl.
* Pain was rated by the patient on a scale of 0 (= no pain) to 10 (= severe pain).
† $P < 0.05$ for lower pain scores in sufentanil group at 30 min postoperative (by Mantel-Haenszel χ^2).

in the ventilatory response to hypercapnea. Not only were postoperative $\Delta V_E/\Delta PET_{CO_2}$ slopes significantly lower than control in the fentanyl group, they were clearly below the wide range of normal values reported by Irsigler[33] and Hirshman *et al.*[34] In contrast, postoperative $\Delta V_E/\Delta PET_{CO_2}$ slopes in the sufentanil group, although slightly depressed, were not significantly different from baseline and remained well within the established range of normal responses.

The slightly shorter time to extubation in our sufentanil group did not achieve significance. Thus, with the smaller doses used in this study, we were unable to reproduce the findings of Smith *et al.*,[7] who observed a more rapid recovery of adequate ventilation and shorter time to extubation in patients given sufentanil 18.9 ± 6.5 $\mu g \cdot kg^{-1}$ compared with those given fentanyl 95.4 ± 30.0 $\mu g \cdot kg^{-1}$ during open heart surgery (dose ratio of 1:5). However, because postoperative respiratory drive is largely determined by the opposing influences of pain and other external stimuli on one hand and residual opioid effect on the other, it is noteworthy that our fentanyl group reported significantly more pain than the sufentanil group at 30 min postoperatively, while nonetheless exhibiting greater depression of respiratory drive.

Whether these potentially important differences between sufentanil and fentanyl represent pharmacologically determined differences in drug action or rather artifacts of our study methods is uncertain. It is not known to what extent intraoperative hyperventilation contributed to depression of $\Delta V_E/\Delta PET_{CO_2}$ slopes in the present study. Sustained intraoperative hypocapnea depletes endogenous CO_2 reservoirs,[35] and Cartwright *et al.*[27] have clearly shown that this augments and prolongs postoperative depression of the $\Delta V_E/\Delta PET_{CO_2}$ response while CO_2 accumulates to replenish these internal stores. That intraoperative $P_{ET}CO_2$ values were not continuously monitored and known to have been similar in both groups constitutes a weakness of this study. The unverified assumption was that neither group was unduly hyperventilated. The

anesthesiologists responsible for ventilating the patients were blinded to the study drug, thereby rendering bias in ventilator settings unlikely. But theoretically, a greater degree of unintentional intraoperative hyperventilation in the fentanyl group could have contributed to depressed $\Delta V_E/\Delta P_{ET_{CO_2}}$ responses in this group postoperatively.

In summary, our findings suggest that, when used as an analgesic supplement with nitrous oxide anesthesia during general surgery, sufentanil possesses little, if any, advantage over fentanyl with respect to intraoperative suppression of hemodynamic and hormonal responses to surgical stress. However, rapid recovery from ventilatory depression and greater analgesia in the immediate postoperative period may confer an important postoperative advantage on sufentanil when used in this setting. We anticipate that further investigations will elucidate whether the relative lack of postoperative respiratory depression seen with sufentanil in this study represents a reproducible, drug-determined advantage with this opioid.

References

1. de Lange S, Boscoe MJ, Stanley TH, Pace N: Comparison of sufentanil–O_2 and fentanyl–O_2 for coronary artery surgery. ANESTHESIOLOGY 56:112–118, 1982
2. Rosow CE, Philbin DM, Moss J, Keegan CR, Schneider RC: Sufentanil *versus* fentanyl. I. Suppression of hemodynamic responses (abstract). ANESTHESIOLOGY 59:A323, 1983
3. Grell FL, Koons RA, Denson JS: Fentanyl in anesthesia: A report of 500 cases. Anesth Analg 49:523–532, 1970
4. Rosow CE: Sufentanil citrate: A new opioid analgesic for use in anesthesia. Pharmacotherapy 4:11–19, 1984
5. Sebel PS, Bovill JG: Cardiovascular effects of sufentanil anesthesia. Anesth Analg 61:115–119, 1982
6. Bovill JG, Sebel PS, Fiolet JWT, Touber JL, Kok K, Philbin DM: The influence of sufentanil on endocrine and metabolic responses to cardiac surgery. Anesth Analg 62:391–397, 1983
7. Smith NT, Dec-Silver H, Harrison WK, Sanford TJ, Gillig J: A comparison among morphine, fentanyl, and sufentanil anesthesia for open-heart surgery: Induction, emergence, and extubation. ANESTHESIOLOGY 57:A291, 1982
8. Flacke WE, Van Etten AP, Flacke JW, Bloor BC, Olewine SK: Plasma histamine levels during sufentanil anesthesia for coronary bypass graft surgery. Anesth Analg 62:260–261, 1983
9. Rosow CE, Philbin DM, Keegan CR, Moss J: Hemodynamics and histamine release during induction with sufentanil or fentanyl. ANESTHESIOLOGY 60:489–491, 1984
10. Philbin DM, Rosow CE, Moss J, Keegan CR, Alban J, Schneider RC: Hormonal responses to fentanyl or sufentanil: A double blind study. Anesth Analg 63:261, 1984
11. de Lange S, Boscoe MJ, Stanley TH, de Bruijin N, Philbin DM, Coggins CH: Antidiuretic and growth hormone responses during coronary artery surgery with sufentanil–oxygen and alfentanil–oxygen anesthesia in man. Anesth Analg 61:434–438, 1982
12. Flacke JW, Bloor BC, Kripke BK, Flacke WE, Warneck CM, VanEtten AP, Wong DH, Katz RL: Comparison of morphine, meperidine, fentanyl and sufentanil in anesthesia: A double blind study. Anesth Analg 64:897–910, 1985
13. Ghoneim MM, Dhanaraj J, Choi WW: Comparison of four opioid analgesics as supplements to nitrous oxide anesthesia. Anesth Analg 63:405–412, 1984
14. Rolly G, Kay B, Cockx F: A double blind comparison of high doses of fentanyl and sufentanil in man: Influence on cardiovascular, respiratory and metabolic parameters. Acta Anaesthesiol Belg 30:247–254, 1979
15. Kay B, Rolly G: Duration of action of analgesic supplements to anesthesia. A double blind comparison between morphine, fentanyl and sufentanil. Acta Anaesthesiol Belg 28:25–32, 1977
16. Van de Walle J, Lauwers P, Adriaensen H: Double blind comparison of fentanyl and sufentanil in anesthesia. Acta Anaesthesiol Belg 27:129–138, 1976
17. Kalenda Z, Scheijgrond HW: Anaesthesia with sufentanil-analgesia in carotid and vertebral arteriography: A comparison with fentanyl. Anaesthesist 25:380–383, 1976
18. DaPrada M, Zurcher G: Simultaneous radioenzymatic determination of plasma and tissue adrenaline, noradrenaline and dopamine within the femtomole range. Life Sci 19:1161–1174, 1976
19. Johnson GA, Kupiecki RM, Baker CA: Single isotope derivative (radioenzymatic) methods in the measurement of catecholamines. Metabolism 29:1106–1113, 1980
20. Ruder HJ, Guy RW, Lipsett MB: A radioimmunoassay for cortisol in plasma and urine. J Clin Endocrinol Metab 35:219–224, 1972
21. Robertson GL, Mahr EA, Athar S, Sinha T: Development and clinical application of a new method for the radioimmunoassay of arginine vasopressin in human plasma. J Clin Invest 52:2340–2352, 1973
22. Philbin DM, Wilson NE, Sokoloski J, Coggins C: Radioimmunoassay of antidiuretic hormone during morphine anesthesia. Can Anaesth Soc J 23:290–295, 1976
23. Read DJC: A clinical method for assessing the ventilatory response to carbon dioxide. Aust Ann Med 16:20–32, 1967
24. Wilmore DW, Long JM, Mason AD, Pruitt BA: Stress in surgical patients as a neurophysiologic reflex response. Surg Gynecol Obstet 142:257–269, 1976
25. Yaksh TL: Multiple opioid receptor systems in brain and spinal cord. Parts 1, 2. Eur J Anaesth 1:171–199, 201–243, 1984
26. Stoeckel H, Schuttler J, Magnussen H, Hengstmann JH: Plasma fentanyl concentrations and the occurrence of respiratory depression in volunteers. Br J Anaesth 54:1087–1095, 1982
27. Cartwright P, Prys-Roberts C, Gill K, Dye A, Safford M, Gray A: Ventilatory depression related to plasma fentanyl concentrations during and after anesthesia in humans. Anesth Analg 62: 966–974, 1983
28. Becker LD, Paulson BA, Miller RD, Severinghous JW, Eger EI: Biphasic respiratory depression after fentanyl-droperidol or fentanyl alone used to supplement nitrous oxide anesthesia. ANESTHESIOLOGY 44:291–296, 1976
29. Adams AP, Pybus DA: Delayed respiratory depression after use of fentanyl during anesthesia. Br Med J 1:278–279, 1978
30. Keats AS: The effects of drugs on respiration in man. Ann Rev Pharmacol Toxicol 25:41–65, 1985
31. Hickey RF, Severinghaus JW: Regulation of breathing, Drug effects, Regulation of Breathing. Edited by Hornbein TF. New York, Marcel Dekker, 1981, pp 1251–1312
32. Kryger MH, Yacoub O, Dosman J, Macklem PT, Anthonisen NR: Effect of meperidine on occlusion pressure responses to hypercapnia and hypoxia with and without external inspiratory resistance. Am Rev Respir Dis 114:333–340, 1976
33. Irsigler GB: Carbon dioxide response lines in young adults: The limits of the normal response. Am Rev Respir Dis 114:529 536, 1976
34. Hirshman CA, McCullough RE, Weil JV: Normal values for hypoxic and hypercapnic ventilatory drives in man. J Appl Physiol 38:1095–1098, 1975
35. Sullivan SF, Patterson RW: Posthyperventilation hypoxia: Theoretical considerations in man. ANESTHESIOLOGY 29:981–986, 1968