

## Nalbuphine Antagonism of Fentanyl-induced Ventilatory Depression: A Randomized Trial

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The authors anesthetized 18 patients with good pulmonary and ventricular function for coronary artery bypass grafting with high doses of fentanyl. When the patients were arousable and their vital signs stable in the intensive care unit, the authors administered nalbuphine or placebo (randomly and double-blinded) until extubation criteria were met, and subsequently gave nalbuphine for analgesia. In one of ten placebo patients, tracheal extubation was accomplished without nalbuphine. This patient then retained CO<sub>2</sub> and required nalbuphine; the other nine placebo patients could not be extubated after placebo trials and were given nalbuphine. In all other patients in both groups, tracheal extubation was successful following nalbuphine (median dose 60 µg/kg, range 30-180 µg/kg). One patient became renarcotized 4 h after tracheal extubation without an increase in plasma fentanyl concentration; he received an additional dose of nalbuphine and recovered without further incident. Nine patients required treatment with vasoactive agents or β-blockers for hypertension or tachycardia associated with the administration of nalbuphine. Eight of 18 patients were not satisfied with nalbuphine analgesia, and required morphine for relief of their pain. Recurrent elevations of fentanyl concentrations in plasma were observed and appeared to be related to increasing motor activity. Nalbuphine is an effective opioid antagonist after fentanyl anesthesia, but its use is associated with side effects, and analgesia for the post-sternotomy patient may be unsatisfactory unless the dose is carefully titrated to the minimum required to antagonize respiratory depression. (Key words: Analgesia: nalbuphine. Anesthesia: cardiovascular. Anesthetics, intravenous: fentanyl. Antagonists, narcotic: nalbuphine. Heart: coronary disease. Pharmacokinetics: fentanyl.)

ANESTHESIOLOGISTS FREQUENTLY select high-dose opioid anesthesia for major cardiovascular operations because the technique simplifies anesthetic management and minimizes anesthetic-induced hemodynamic changes. It also reduces the release of so-called stress

hormones which may produce undesirable hemodynamic responses and result in myocardial ischemia.<sup>1,2</sup> But high-dose opioid administration may prolong the patient's dependence on mechanical ventilation in the postoperative period. Prolonged ventilatory support has the liabilities of accidental disconnection of the endotracheal tube from the ventilator, pulmonary infection, discomfort with the requirement for sedatives that may further prolong recovery, and increased cost.<sup>3</sup> It has been shown that patients with good cardiopulmonary function after cardiac surgery are not harmed by early tracheal extubation.<sup>3-5</sup> Antagonism of ventilatory depression due to residual opioids would allow earlier tracheal extubation.

Naloxone is the antagonist usually used to treat over-narcotized patients. Its effects are not selective for ventilatory depression, and its use is often accompanied by antagonism of analgesia and undesirable hemodynamic changes.<sup>6</sup> Renarcotization can occur because the effects of small doses of naloxone are brief,<sup>7,8</sup> while the elimination of fentanyl after cardiopulmonary bypass is prolonged ( $t_{1/2\beta} = 5-11$  h).<sup>9,10</sup>†† Mixed agonist-antagonist opioids apparently can antagonize excessive narcosis while preserving analgesia in some patients.<sup>11,12</sup> Of the three commonly used agonist-antagonists (pentazocine, butorphanol, and nalbuphine), nalbuphine appears best suited to this purpose. Butorphanol has little antagonist activity in humans, and pentazocine has only one-tenth the antagonist activity of nalbuphine.<sup>13</sup> Nalbuphine produces fewer unpleasant psychic reactions than either pentazocine or butorphanol.<sup>14</sup> Nalbuphine produces minimal hemodynamic changes while pulmonary artery pressures increase after butorphanol or pentazocine.<sup>15-18</sup> The elimination half-time of nalbuphine is 3-5 h, similar to that for morphine, fentanyl, and sufentanil.<sup>19</sup>

This study was designed to test the efficacy and safety of nalbuphine antagonism of residual narcotic effect to speed tracheal extubation after high-dose fentanyl anesthesia for coronary artery bypass grafting surgery. A group given placebo was used to control for the possibility that tracheal extubation could have occurred just as early without the use of nalbuphine.

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### Materials and Methods

Twenty patients scheduled for elective coronary artery bypass grafting gave informed consent to the protocol which was approved by the Emory University Human Investigations Committee. We excluded patients who had a myocardial infarction within the previous 6 weeks, impaired myocardial function (left ventricular end-diastolic pressure  $> 18$  mmHg, ejection fraction  $< 0.4$ , or major ventricular wall motion abnormality), impaired pulmonary function ( $FEV_1/FVC < 50\%$ ,  $FVC < 20$  ml/kg,  $Pa_{CO_2} > 45$  mmHg or  $Pa_{O_2} < 60$  mmHg while breathing room air), a CNS disorder, or morbid obesity.

All patients received their usual cardiac medications (excluding diuretics) through the morning of surgery. They also received lorazepam 0.04 mg/kg orally approximately 90 min before induction of anesthesia. Fentanyl was administered incrementally (total doses ranged from 86–123  $\mu$ g/kg) along with diazepam (maximum 20 mg), thiopental (maximum 500 mg), enflurane, or isoflurane, and muscle relaxants at the discretion of each patient's anesthesiologist.

At the conclusion of the operation, patients were transferred to the post-cardiac surgical intensive care unit where they received standard care. They were randomly assigned to either the nalbuphine or placebo group when they were arousable with intact gag and cough reflexes and met the following criteria: stable cardiovascular function (systolic blood pressure  $> 90$  mmHg, pulmonary artery occlusion pressure  $< 18$  mmHg, cardiac index  $\geq 2.2$  l  $\cdot$  min $^{-1}$   $\cdot$  m $^{-2}$ , no new or uncontrolled dysrhythmias, limited requirement for inotropic drugs [epinephrine or norepinephrine  $< 5$   $\mu$ g/min], and no intra-aortic balloon counterpulsation), urine output  $> 0.5$  ml  $\cdot$  kg $^{-1}$   $\cdot$  hr $^{-1}$ , chest tube drainage  $< 2$  ml  $\cdot$  kg $^{-1}$   $\cdot$  hr $^{-1}$ , bladder temperature  $> 35.5^\circ$  C, satisfactory arterial blood gases ( $pH > 7.30$ , base deficit  $< 6$ ), and the  $FI_{O_2} < 0.7$  with  $PEEP \leq 5$  cm H $_2$ O.

Mechanical ventilation was then reduced until the  $Pa_{CO_2}$  was  $\geq 49$  mmHg, or the patient's trachea was extubated. Tracheal extubation occurred when the patient was hemodynamically stable and met the following criteria: spontaneous ventilatory frequency  $\geq 8$ /min, peak negative inspiratory pressure  $> -20$  cm H $_2$ O, vital capacity  $\geq 8$  ml/kg,  $Pa_{O_2} > 70$  mmHg with an  $FI_{O_2} \leq 0.7$ ,  $Pa_{CO_2} \leq 52$  mmHg, and  $pH \geq 7.32$ . These weaning criteria correspond to those normally used in our intensive care unit for patients in good condition after coronary artery bypass grafting surgery, and the moderate respiratory acidosis that we allow is, in our experience, well tolerated.

Incremental volumes of drug solution (representing either nalbuphine 30, 60, 90, or 120  $\mu$ g/kg, or normal

saline placebo) were given as long as the patient required mechanical ventilatory support. These incremental doses resulted in cumulative nalbuphine dosages of 30, 90, 180, and 300  $\mu$ g/kg, respectively. The patients received the incremental doses of nalbuphine or placebo at 30 min intervals to allow time for continued weaning from mechanical ventilatory support. If the patient received all four doses of either drug or placebo, the drug code was broken. Patients who had received placebo then received nalbuphine in the same incremental doses until weaned from ventilatory support. Patients who had received nalbuphine were then to be given naloxone in 20- $\mu$ g increments until tracheal extubation or to a maximum dose of 400  $\mu$ g; naloxone was never required.

Hemodynamic and respiratory measurements were recorded prior to the initial dose of the experimental drug, 5 and 15 min after each dose, and 5 and 15 min after tracheal extubation. We recorded systemic, central venous, pulmonary arterial, and pulmonary artery occlusion pressures, heart rate and rhythm, cardiac output, cardiovascular drug infusion rates,  $FI_{O_2}$ , level of PEEP, IMV rate, spontaneous ventilatory rate, tidal volume, vital capacity, peak inspiratory pressure,  $Pa_{CO_2}$ , and base excess/deficit. Blood samples for fentanyl analysis were obtained immediately prior to and 15 min after each dose of the experimental drug, at the time of tracheal extubation, and at least hourly until several hours after extubation of the trachea.

Five min following tracheal extubation, another set of measurements were made. Then, the patients who had required nalbuphine prior to extubation received an additional 10 mg dose of nalbuphine to avert renarcotization which we had observed in some patients in a previous study.<sup>11</sup> Subsequently, the patients received nalbuphine as required for analgesia up to a maximum of 40 mg/h. If this was ineffective, patients received morphine as needed. Renarcotization ( $Pa_{CO_2} > 50$  mmHg) was treated with nalbuphine 30  $\mu$ g/kg. A research nurse trained in pain assessment techniques asked the patients to rate their pain intensity (none, mild, moderate, severe) at the time of extubation (before the postextubation nalbuphine dose) and before each dose of nalbuphine given for analgesia. Patients also rated pain relief 5 min after nalbuphine administration (complete relief, a lot of relief, a little relief, no relief, worse pain). At the conclusion of the study, one of the investigators, the research nurse, and the patient each independently rated nalbuphine analgesia (unsatisfactory, satisfactory, good), and the investigator and the nurse each independently rated nalbuphine antagonism (unsatisfactory, satisfactory, good).

Blood samples to be analyzed for fentanyl were collected into plastic syringes wetted with heparin and

TABLE 1. Patient Characteristics\*

	Placebo	Nalbuphine†	P
Age (years)	54 (43-64)	61 (48-68)	0.06
Weight (kg)	82 (57-107)	83 (70-90)	NS
Preoperative beta adrenergic blocking drug therapy	6/10	5/8	NS
Preoperative calcium channel blocking drug therapy	6/10	5/8	NS
Intraoperative anesthetic drugs			
Fentanyl (μg/kg)	106 (86-123)	102 (91-112)	NS
Diazepam (mg)	16 (5-20)	12.5 (0-20)	NS
Thiopental (mg)	225 (0-500)	375 (0-500)	NS
Enflurane or isoflurane	8/10	4/8	NS
Number of coronary grafts	4 (3-6)	4 (2-6)	NS
Time from the induction of anesthesia to study entry (minutes)‡	525 (460-650)	560 (455-685)	NS

\* Values represent the median and range.

† The values in this column are for eight patients; data for two of the ten patients have been excluded because these two patients received

nalbuphine before CO<sub>2</sub> retention was demonstrated.

‡ When patient arousable and stable.

stored in ice until centrifuged. The plasma was transferred to polypropylene tubes and frozen until they were analyzed by radioimmunoassay (RIA). RIA kits were supplied by Janssen Pharmaceutica and the RIA procedure followed the modifications suggested by Schüttler and White.<sup>20</sup> Within assay variation was 2.6%, and between assay variation was 0.7% ( $n = 30$ ) for concentrations  $< 1$  ng/ml and 11.3% ( $n = 21$ ) for concentrations  $> 1$  ng/ml.

The Mann-Whitney U-test was utilized for comparisons. Statistical significance was defined as  $P \leq 0.05$ .

### Results

Table 1 summarizes patient data prior to nalbuphine or placebo administration. We excluded two patients in the nalbuphine group from the results because they were given nalbuphine before CO<sub>2</sub> retention was dem-

onstrated. Table 2 summarizes the effects of nalbuphine or placebo upon respiration and circulation. The median IMV rate before drug administration was four per minute. The placebo group had no significant change in IMV rate after placebo. All patients in the nalbuphine group had spontaneous respiratory rates of three/min or less prior to injection of the agonist-antagonist, and rates of ten/min or greater after nalbuphine (fig. 1A). The tracheas of all patients in the nalbuphine group were extubated after nalbuphine (median cumulative dose 90 μg/kg, range 30-180); no patient required naloxone.

Three patients in the placebo group were breathing at the start of the study (fig. 1B). Only one met requirements for tracheal extubation with a ventilatory frequency of 11 breaths/min and a PaCO<sub>2</sub> of 47 mmHg. Following tracheal extubation, he almost immediately required nalbuphine because of a PaCO<sub>2</sub> of 57 mmHg.

TABLE 2. Comparison of Nalbuphine and Placebo Administration\*

	P†	Nalbuphine Group		Placebo Group		
		Before	After	Before	After	After Nalbuphine‡
Respiratory rate (min <sup>-1</sup> )	<.0005	0 (0-3)	15 (10-23)	0 (0-25)	0 (0-15)	20 (8-33)
IMV rate (min <sup>-1</sup> )	<.0005	4 (4-5)	0 (0-0)	5 (3-12)	5 (0-7)	0 (0-0)
Tidal volume (ml)	.0005	0 (0-350)	450 (300-750)	0 (0-300)	0 (0-700)	500 (400-600)
Vital capacity (ml)	NS	550 (200-1500)	950 (500-1700)	250 (50-600)	625 (50-1400)	1100 (800-1400)
Peak inspiratory pressure (cm H <sub>2</sub> O)	NS	20 (2-35)	30 (25-60)	7 (3-50)	20 (5-50)	35 (25->60)
Pco <sub>2</sub> (mmHg)	<.01	53 (50-71)	48 (46-60)	55 (49-58)	52 (46-59)	46 (40-51)
pH	NS	7.29 (7.21-7.36)	7.33 (7.26-7.40)	7.28 (7.20-7.32)	7.31 (7.26-7.35)	7.35 (7.31-7.40)
PCWP (mmHg)	NS	11 (9-20)	11 (7-13)	11 (5-16)	12 (8-14)	11 (5-18)
Mean arterial pressure (mmHg)	<.05	80 (73-104)	93 (72-100)	77 (63-90)	69 (60-80)	90 (75-100)
Heart rate (min <sup>-1</sup> )	NS	103 (80-107)	105 (80-130)	104 (80-109)	104 (87-130)	105 (87-115)
Cardiac index (l · min <sup>-1</sup> · m <sup>-2</sup> )	NS	2.8 (2.1-4.0)	3.2 (2.1-4.1)	2.9 (2.3-3.5)	3.1 (2.2-4.1)	3.0 (2.4-4.9)
Systemic vascular resistance (dyne · cm · sec <sup>-5</sup> )	<.05	873 (724-1880)	1040 (742-1600)	913 (664-1310)	792 (470-1055)	966 (715-1290)

\* Values represent the median and range.

† Comparing change in nalbuphine group when given nalbuphine to change in placebo group when given placebo.

‡ One patient in the placebo group did not require nalbuphine prior to extubation. This column represents the data for the nine placebo patients who did require nalbuphine.

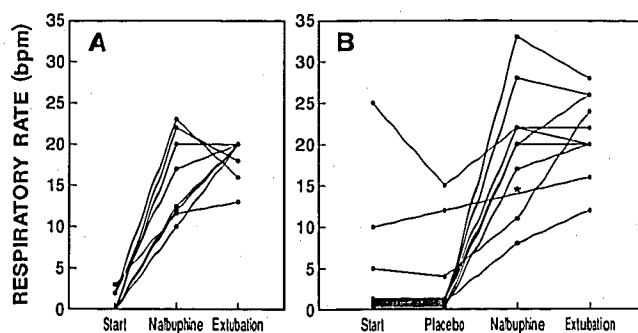


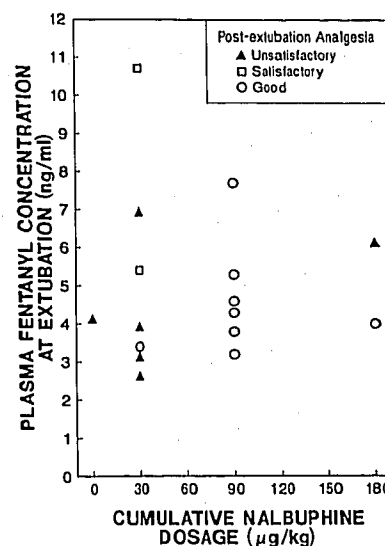
FIG. 1. Spontaneous respiratory rate immediately before start of drug administration (START), after placebo administration (PLACEBO), after antagonism of ventilatory depression with nalbuphine (NALBUPHINE), and after extubation and an additional 10 mg of nalbuphine (EXTUBATION). A is for the nalbuphine group; B represents the placebo group. One patient in the placebo group (asterisk) did not receive nalbuphine prior to extubation, but subsequently required nalbuphine because of recurrent hypercarbia.

Having failed to meet tracheal extubation criteria after four doses of placebo, the remaining nine of ten patients in the placebo group had their respiratory depression antagonized by nalbuphine (median cumulative dose 30  $\mu\text{g/kg}$ ; range 30–90) and their tracheas extubated. No one required naloxone. The median time from the start of nalbuphine administration to tracheal extubation was 60 min for both the placebo and nalbuphine groups.

Except for the one patient described below, the median  $\text{PaCO}_2$  at the start of the study for both groups combined was 54 mmHg (range 49–63). Placebo administration did not significantly alter  $\text{PaCO}_2$  (table 2). Both groups had a significant decrease in  $\text{PaCO}_2$  after nalbuphine to 47 mmHg median (range 40–52). One patient in the nalbuphine group was awake and fighting mechanical ventilation before drug administration. His  $\text{PaCO}_2$  was 71 mmHg. After nalbuphine administration his  $\text{PaCO}_2$  was 59 mmHg. He was still uncooperative, but his trachea was extubated because his peak negative inspiratory pressure exceeded 60 mmHg and his respiratory rate was 18/min. It was thought that tracheal extubation would lessen his agitation, which it did. Subsequent doses of nalbuphine calmed him, and his  $\text{PaCO}_2$  continued to decline as he calmed.

Four of the 18 patients required reduction of vasopressor therapy during nalbuphine administration. Another two patients required an increase in vasodilator dosage rate, and two patients had vasodilator therapy initiated to keep the mean arterial pressure less than 100 mmHg. In another patient, propranolol 3 mg was given to control a prolonged increase in heart rate. Eight of the 18 patients exhibited other adverse reactions attributable to nalbuphine administration. Six of

FIG. 2. Plasma fentanyl concentrations at extubation compared to total nalbuphine required to meet extubation criteria. Five of six patients with unsatisfactory subsequent analgesia required nalbuphine  $\leq 30 \mu\text{g/kg}$  for extubation. Seven of eight patients with good analgesia required  $\geq 90 \mu\text{g/kg}$ . Nalbuphine requirements did not correlate with plasma fentanyl concentrations.



these eight became restless, five diaphoretic, and three confused.

Analgesia was rated unsatisfactory by eight of 18 patients. These patients had required less nalbuphine to antagonize respiratory depression (fig. 2). They were comfortable until they received an additional 10-mg dose of nalbuphine given according to the protocol as a means of averting renarcotization. Additional doses of nalbuphine up to 40 mg/h did not provide relief. They subsequently required cumulative morphine doses larger than normally used in our ICU (median 31 mg; range 6–63). Of the remaining ten patients with satisfactory analgesia, one became renarcotized 4 h after tracheal extubation ( $\text{PaCO}_2$  57 mmHg) in spite of the prophylactic dose of nalbuphine and despite a progressive decline in plasma concentrations of fentanyl. This patient was treated with an additional nalbuphine 10 mg, and recovered satisfactorily thereafter.

Plasma fentanyl concentrations were comparable in the two groups at all points in the protocol (table 3). In the placebo group, approximately 2 h was required to administer the four placebo doses. Even with that delay,

TABLE 3. Plasma Fentanyl Concentration (ng/ml) Comparing Placebo to Nalbuphine Group\*

Time	Placebo Group	Nalbuphine Group	P
ICU admission	8.2 (4.8–20.3)	8.6 (5.8–13.8)	NS
Study entry†	5.7 (4.3–10.5)	5.2 (4.1–8.4)	NS
After placebo	5.2 (3.3–9.4)		NS‡
After nalbuphine	5.1 (2.6–8.1)	4.4 (4.0–6.6)	NS
Tracheal extubation	4.2 (2.6–10.7)	4.3 (3.1–6.1)	NS

\* Values represent the median and range.

† When patient arousable and stable.

‡ Comparing placebo group after placebo and nalbuphine group at study entry.

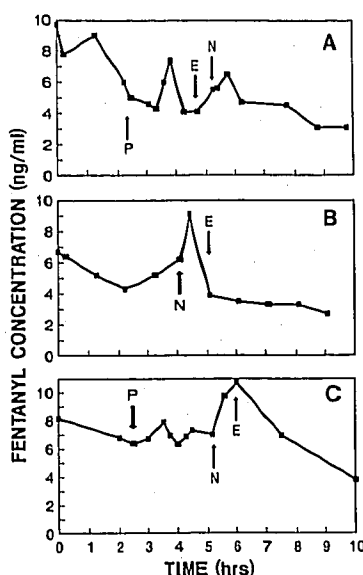


FIG. 3. Recurrent elevations of plasma concentrations of fentanyl in selected patients. P = start of placebo administration; N = start of nalbuphine administration; E = tracheal extubation. Patient in A was extubated after placebo, and subsequently required nalbuphine for renarcotization.

the plasma fentanyl concentration after placebo (and before nalbuphine) was not significantly different from the plasma fentanyl concentration in the nalbuphine group before nalbuphine administration. Plasma concentrations of fentanyl after antagonism of respiratory depression did not correlate with the cumulative nalbuphine dosage required to antagonize respiratory depression (fig. 2). Ten of the 16 patients<sup>††</sup> whose plasma fentanyl concentrations were assayed had recurrent peaks in plasma fentanyl concentrations (rise of at least 1 ng/ml, with at least two different samples at this higher level). These peaks frequently occurred in association with increased motor activity (fig. 3).

### Discussion

Nalbuphine effectively antagonized postoperative respiratory depression due to residual fentanyl. In another study of postcardiac surgical patients who had received "pure" high-dose fentanyl anesthesia, tracheal extubation was accomplished without the use of opioid antagonists when plasma concentrations of fentanyl averaged 2.9 ng/ml.<sup>§§</sup> In the present study, patients who had also received diazepam and thiopental showed significant respiratory depression at an average fentanyl concentration of 5.5 ng/ml of plasma. Yet they satisfied criteria for tracheal extubation after nalbuphine, but not after placebo. It is worth noting that fentanyl concentrations were declining very slowly during the study period, as might be expected from the prolongation of the elimination half-time ( $t_{1/2\beta}$ ) after cardiopulmonary

bypass.<sup>9,10</sup> In fact, the fentanyl concentrations did not differ significantly between the nalbuphine and placebo groups at the time of extubation, despite the delay associated with the placebo trials.

### SIDE EFFECTS

We found both small and large doses of nalbuphine had antagonist activity; the larger doses tended to antagonize analgesia and had side effects similar to those reported for naloxone. Along with complaints of pain we encountered other side effects of excessive narcotic antagonism: increasing systemic vascular resistance, altered vasopressor/vasodilator treatment in eight of 18 patients, tachycardia requiring treatment in one case, and signs of pain (restlessness and diaphoresis) or confusion in eight of 18 patients. Another study of cardiac surgical patients showed similar problems with excessive antagonism.<sup>21</sup> The incidence and intensity of side effects seemed to be greater in that study because the patients received progressive doses of nalbuphine until either a total of 10 mg was administered or pain was produced, whereas we titrated the nalbuphine dosage to produce a satisfactory level of spontaneous ventilation. Most patients complaining of pain in our study did so after receiving an additional 10-mg dose as prophylaxis against renarcotization, a step that we would omit in future protocols and in routine clinical practice. Rather, we would monitor patients for renarcotization and treat it if it occurred with additional small doses of nalbuphine (30  $\mu$ g/kg).

Contrary to our experience, general surgical patients (type of operation unspecified) did experience good pain relief after receiving a fixed, large dose of nalbuphine (20 mg) as an antagonist for fentanyl anesthesia ( $23 \pm 6$   $\mu$ g/kg total dose).<sup>12</sup>

The interactions of agonists-antagonists with pure agonists are complex, and depend on the dose of the agonist as well as that of the agonist-antagonist. In the presence of low agonist concentrations, the addition of an agonist-antagonist may increase opioid effects. For example, subjects without a painful incision showed continued narcotic effect when morphine 0.21 mg/kg was followed by nalbuphine 0.21 mg/kg.<sup>22</sup> When high levels of the agonist are present, administration of an agonist-antagonist such as nalbuphine can be expected to reduce signs of intoxication.<sup>23</sup> The interpatient and interstudy differences in relation to analgesic agonism and antagonism may also be due to differences in pain intensity among the subjects. Those patients in our

<sup>††</sup> Samples for two patients were stored incorrectly and were discarded without analysis.

<sup>§§</sup> Hug CC Jr, Moldenhauer CC: Pharmacokinetics and dynamics of fentanyl infusions in cardiac surgical patients (abstract). ANESTHESIOLOGY 57:A45, 1982.

study who required less nalbuphine for antagonism of respiratory depression were the same ones who had poor analgesia after the additional dose of nalbuphine dictated by the protocol (fig. 2).

#### SECONDARY PEAKS

Other investigators also have observed recurrent elevations of fentanyl concentrations in plasma. Two hypotheses have been proposed to account for these secondary peaks: gastroenterohepatic circulation and release from muscle storage sites.

Stoeckel *et al.* reported that, in dogs, fentanyl was rapidly sequestered as the ionized drug in the acidic medium of the stomach.<sup>24</sup> They postulated that gastric emptying into the usually alkaline fluid of the small intestine allowed the lipid-soluble fentanyl base to be absorbed into the portal circulation. The effect of this reabsorption on fentanyl concentrations in the systemic circulation would be reduced to the extent that fentanyl underwent first-pass extraction by the liver. Orally administered fentanyl produces very low plasma levels because of its large first-pass hepatic extraction.<sup>24,25</sup>

The distribution of fentanyl to skeletal muscle is extensive, representing more than 50% of an intravenous dose in rats.<sup>26</sup> Recurrent peaks in plasma levels of fentanyl were noted in human volunteers, and were thought to be related to increased muscle blood flow as the volunteers began to ambulate after several hours of bedrest.<sup>27</sup> Lehman produced secondary peaks by isolating a limb with a tourniquet after fentanyl administration, then releasing the tourniquet.<sup>25</sup> Recurrent ventilatory depression typically occurs when surgical patients are waking up, either in the recovery room or the ICU.<sup>5,28-32</sup>

In our study, the recurrent elevations of fentanyl concentrations in plasma were sometimes marked, and usually occurred during nalbuphine administration or after extubation. The fact that the peaks were high may be related to two factors unique to this study: 1) we gave more fentanyl than in the other studies exhibiting secondary peaks, and high muscle concentrations would be expected; and 2) as a result of hypothermic cardiopulmonary bypass (CPB), muscle blood flow is greatly reduced, and may not return to normal until after rewarming is nearly complete and the patient begins to move.<sup>33</sup> Most of the fentanyl was given prior to CPB, and that which was distributed to muscle may not have returned to the circulation until the muscle blood flow normalized. The prolonged elimination half-time of fentanyl after CPB may also be explained by low muscle blood flow, since the rate of fentanyl release from tissue stores, not clearance from blood, determines the  $t_{1/2}$   $\beta$  for fentanyl.<sup>26,27</sup> It is noteworthy that the one patient who became renarcotized after nalbuphine in our study

did not exhibit a recurrent elevation of fentanyl concentration in plasma during the episode.

In summary, the agonist-antagonist analgesic nalbuphine is an effective and long-acting antagonist of narcotic-induced ventilatory depression. Required nalbuphine dosage did not correlate with plasma fentanyl concentration. Following high-dose fentanyl anesthesia, nalbuphine should be administered carefully in small incremental doses until the desired degree of spontaneous ventilation is achieved. Doses larger than necessary may precipitate pain, which can be treated with morphine-type analgesics. Antagonism of analgesia in our patient population was frequently associated with undesired blood pressure increases or tachycardia. Rather than administer large doses to avert renarcotization, we recommend careful observation and treatment of recurrent ventilatory depression, if it occurs, with an additional small dose of nalbuphine. Recurrent ventilatory depression is not necessarily associated with a secondary peak in plasma fentanyl concentration.

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