J Anesth (2004) 18:1–8
DOI 10.1007/s00540-003-0214-4

Journal of
Anesthesia

Original articles

Naloxone reversal of opioid anesthesia revisited: clinical evaluation and plasma concentration analysis of continuous naloxone infusion after anesthesia with high-dose fentanyl

Masahiko Takahashi[1], Kimitoshi Sugiyama[2], Masaki Hori[1], Satoko Chiba[1], and Kiyoshi Kusaka[2]

[1]Division of Pain Control, Department of Anesthesiology and Emergency Medicine, Tohoku University Postgraduate Medical School, 1-1 Seiryo, Aoba-ku, Sendai 980-8574, Japan
[2]Department of Anesthesiology, Miyagi Prefectural Cancer Center, Natori, Japan

Abstract
Purpose. In spite of several advantages, the need for postoperative ventilatory support limits the use of high-dose opioid anesthesia. We prospectively evaluated the effectiveness of naloxone infusion for the reversal of high-dose fentanyl anesthesia.
Methods. Anesthesia was maintained with fentanyl in patients undergoing major abdominal surgery. After anesthesia, the trachea was extubated when intravenous naloxone, which was titrated in separate 50-μg doses, established an acceptable level of consciousness and arterial blood gas (ABG) status under spontaneous respiration; this was followed by continuous infusion started at the rate of the sum of the bolus doses per hour. The naloxone infusion was terminated based on evaluation of the level of consciousness, ABG, and acute abstinence symptoms. Postoperative pain was evaluated using self-reported four-step categorical terms (none, mild, moderate, and severe). Plasma concentrations of fentanyl and naloxone were analyzed in 12 patients, using high-performance liquid chromatography.
Results. Fifty-seven out of 59 eligible patients were successfully extubated at 34 ± 14 min after termination of fentanyl (total dose, 127 ± 64 μg·kg^{-1}; mean ± SD) with naloxone (total bolus, 3.4 ± 2.6 μg·kg^{-1}). All these patients recovered fully without ventilatory support under the naloxone infusion, which was terminated at 11 ± 7 h. The reduction of the naloxone infusion rate effectively relieved the increased pain, and no supplemental analgesic was used in any patients during the naloxone infusion. Pharmacokinetic analysis did not indicate any correlations between plasma fentanyl and naloxone concentrations.
Conclusion. The results suggest that naloxone infusion with individual dose titration facilitates the use of high-dose opioid anesthesia, maintaining the advantager of this anesthesia.

Key words Respiratory depression · Pharmacokinetics · Postoperative pain · Extubation

Address correspondence to: M. Takahashi
Received: August 11, 2003 / Accepted: November 13, 2003

Introduction

Anesthesia with pure μ-receptor agonists such as morphine or fentanyl has been used for major surgery in poor-risk patients [1–3]. Because noxious surgical stimuli vary both in their intensity and mechanisms [4] and the minimally effective dose of opioids has not been determined [5,6], the titration of opioids according to the surgical stimuli is a reasonable approach for obtaining better anesthetic control. However, such titration often results in very large amounts of total opioid use, justifying concerns about prolonged respiratory depression after surgery.

A pharmacological treatment strategy for avoiding opioid-induced respiratory depression is reversal with naloxone. Naloxone, at a clinically relevant single dose, effectively normalizes the depressed respiration even when it is caused by very high doses of opioids [7]. However, postoperative naloxone use can involve several adverse effects, including renarcotization due to the short duration of action of this agent, and symptoms that are, presumably, related to "acute abstinence" from the opioid effects, such as pain, psychological stimulation, or sympathomimetic responses, of which the most severe is pulmonary edema [7–9]. To avoid such disadvantages, several studies have previously evaluated the effectiveness of continuous naloxone infusion after high-dose opioid anesthesia [10–12]. However, because of the relatively small number of subjects and limited extent of the surgical procedures, as well as the fixed-dose protocols of both the opioid and the naloxone administration in these studies, a clinically relevant regimen for postoperative naloxone infusion remains to be clarified. In this clinical study, we sought to determine whether naloxone infusion with titrated doses could establish and maintain adequate spontaneous respiration and consciousness level after high-dose fentanyl anesthesia, and whether there was a possible pharmacokinetic relationship between fentanyl and

naloxone in the respiratory reversal in patients undergoing major abdominal surgery.

Subjects and methods

With the approval of our Institutional Ethics Committee, patients with an American Society of Anesthesiologists (ASA) physical status of II or less, scheduled for elective major abdominal surgery for visceral cancer from June 2001 to May 2002, were enrolled in this study after providing written informed consent. Exclusion criteria were the presence of significant cardiovascular, pulmonary, hepatic, or renal dysfunction, significant obesity, previous opioid medication, a history of psychiatric diseases or drug or alcohol abuse, and disturbances in hearing or speech. The patients were asked to express their pain intensity, using four-step categorical terms (none, mild, moderate, and severe) at any time postoperatively.

Anesthetic protocol

Patients were brought to the operating room nonpremedicated. An intravenous catheter for fluid replacement and drug administration, and a radial artery catheter for measuring arterial pressure and blood sampling were inserted prior to the induction of anesthesia. A standard three-lead electrocardiagram, end-tidal partial pressure of CO_2 ($P_{ET_{CO_2}}$), the train-of-four response of the adductor pollicis muscle induced by electrical stimulation on the ulnar nerve (AS/3 Anesthetic Monitor; Datex, Helsinki, Finland), and the bispectral index (BIS), derived from bispectral analysis of the electroencephalogram (BIS A-1050; Aspect Medical System, Natick, MA, USA) were monitored throughout the period of anesthesia. All drugs used during anesthesia were administered intravenously. Anesthesia was induced with fentanyl (8–10 $\mu g \cdot kg^{-1}$) and a minimal sleeping dose of propofol (40–60 mg) according to the verbal responsiveness of each patient. Tracheal intubation was facilitated with vecuronium (0.1 $mg \cdot kg^{-1}$) and adequate mechanical ventilation was immediately established. Fentanyl at 40 $\mu g \cdot kg^{-1}$ was loaded for more than 30 min before skin incision to ensure an adequate depth of anesthesia, unless the patient's hemodynamic response was profoundly depressed. Basal infusion of fentanyl at a rate of 4 $\mu g \cdot kg^{-1} \cdot h^{-1}$ was continued until the end of surgery. This protocol has been validated previously in a fixed-dose study of fentanyl-oxygen anesthesia for cardiac surgery [13]. Propofol was also infused, at a rate of 0.5 $mg \cdot kg^{-1} \cdot h^{-1}$, throughout the surgical procedure. This dose was chosen based on the previously reported minimal sedative doses of propofol for patients receiving mechanical ventilation [14]. During surgery, the participating anesthesiologists were asked to maintain the patients' hemodynamics in as stable a manner as possible, defined by ±20% changes of baseline values for both mean arterial pressure and heart rate. The baseline hemodynamic values were determined at least 1 day preoperatively. Although the reliability of BIS monitoring for opioid anesthesia has been controversial [15], in practice, our targeted intraoperative BIS value was less than 50. Increases in the hemodynamic parameters in response to surgical stimulation were treated by repeated bolus doses of fentanyl (200–400 μg) to keep the BIS value at less than 50 and, when needed, nicardipine or propranolol was used. Hypotension that remained after appropriate fluid replacement was treated with phenylephrine. Atropine was used to treat bradycardia (heart rate <40 beats·min^{-1}). The train-of-four response was maintained at less than 20% with supplemental vecuronium. Increased BIS without significant hemodynamic changes was also treated by supplemental fentanyl accompanied, when needed, by bolus propofol (20–30 mg).

Naloxone reversal protocol

Supervision of the recovery from anesthesia, and the postanesthetic care in each patient were performed by anesthesiologists who were not aware of the total doses of fentanyl used. After the completion of surgery, the sustained neuromuscular blockade was completely reversed with neostigmine and atropine. The extubation criteria included: (1) uneventful surgical course, (2) adequate response to verbal commands, with a BIS value of more than 95, (3) spontaneous respiratory frequency with 8 or more breaths·min^{-1}, (4) $Pa_{O_2}/F_{I_{O_2}}$ of 300 mmHg or more, with Pa_{CO_2} of 55 mmHg or less under spontaneous respiration through an endotracheal tube, (5) arterial-blood pH of 7.30 or more after significant metabolic acidosis was corrected, if it had existed. When these criteria were not fulfilled after the reversal of the neuromuscular blockade, naloxone was repeatedly administered in separate 50-μg doses at 2-min intervals until the patients fulfilled the extubation criteria. Naloxone was prepared at a concentration of 50 $\mu g \cdot ml^{-1}$ in saline and administered in 1 ml using an infusion pump (Terumo, Tokyo, Japan). Once adequate consciousness level and respiration were established, continuous infusion of naloxone was started at a rate consistent with the sum of the bolus doses (50 μg × the number of separate administrations) per hour. The endotracheal tube was removed after 10-min observation to ensure that no unacceptable change had occurred in the patient's condition. When the maximal 600 μg (12 separate administrations) of naloxone failed to reverse the respiratory depression, mechanical ventilation was continued and the patients were dropped out of the protocol. When

patients indicated significant pain (moderate or severe) before extubation, naloxone infusion was terminated and mechanical ventilation was continued with supplemental fentanyl when needed. These patients were also dropped out. Subsequently, all patients were brought to the Post Anesthetic Care Unit (PACU).

Up-and-down titration protocol of naloxone infusion in the PACU

In the PACU, humidified oxygen at an appropriate flow rate was administered via a nasal cannula or a face mask to maintain $S_{p_{O_2}}$ at 95% or more. Side-stream $P_{ET_{CO_2}}$ was continuously monitored. Arterial blood gases were analyzed at 3-h intervals, as well as when the physicians considered it necessary. A $P_{ET_{CO_2}}$ value of 60 mmHg or more was always followed by blood gas analysis. The infusion rate of naloxone was increased by 25% (minimally, 50 $\mu g \cdot h^{-1}$) following administration of the hourly-equivalent bolus dose when any of the following conditions were observed: respiratory rate 7 or fewer breaths·min^{-1} or respiratory interval 15 s or more, Pa_{O_2} less than 60 mmHg with Pa_{CO_2} of more than 46 mmHg, Pa_{CO_2} more than 55 mmHg or arterial blood pH more than 7.30 without metabolic acidosis, and an inadequate response to verbal commands. The rate of the naloxone infusion was also decreased by 25% stepwisely (minimally, 50 $\mu g \cdot h^{-1}$) according to criteria that included an increase in the self-reported pain intensity by at least one categorical term, acute sympathomimetic or psychomimetic symptoms under adequate hemodynamic and metabolic treatment, or a stable condition lasting for 4 h without any of the symptoms described. The patients were reevaluated after 30 min when the infusion rate was changed. Failure to maintain adequate spontaneous respiration was immediately followed by exclusion of the patients from the protocol, and alternative treatment, including mechanical ventilation, given at the discretion of the anesthesiologists. Increased pain intensity after decrease or termination of the naloxone infusion was treated with nonsteroidal anti-inflammatory drugs (NSAIDs), such as intravenous flurbiprofen, or diclofenac in suppository form. When the NSAIDs failed to relieve pain, supplemental opioid was used. Unless there was some untoward event, the patients were discharged from the PACU within 12 h after naloxone termination. The patients were followed up until they were able to walk.

Plasma concentrations of fentanyl and naloxone

To evaluate possible pharmacokinetic correlations between fentanyl and naloxone at effective reversal levels, the plasma concentrations of these two compounds were analyzed, using high-performance liquid chromatography (HPLC), in 12 consecutive patients who were included in the study. Heparinized blood was sampled at the preinduction of anesthesia, immediately before tracheal intubation, immediately after the initial fentanyl loading, 1 h after skin incision, at the termination of fentanyl infusion (end of surgery), immediately after tracheal extubation, and 3 h, 6 h, and 15 h after fentanyl termination. Each sample was immediately centrifuged and the plasma was stored at −80°C for later analysis. Electrochemical detection was performed in each sample, using a commercial HPLC system (Coul Array; ESA, Chelmsfold, MA, USA). Detection limits in these measurements were 0.2 ng·ml^{-1} for fentanyl and 0.6 ng·ml^{-1} for naloxone. The interassay coefficient of variation was less than 10% for both compounds.

Statistical analysis

Values for results were expressed as means ± SD. Postoperative changes in the arterial blood gas determinants were analyzed using repeated measures analysis of variance (ANOVA). The elimination rate constant (*k*el) for fentanyl was determined by linear regression analysis of the relationship between the logarithmic plasma concentration and the time after the cessation of the infusion in each patient. The terminal elimination half-life ($t1/2$) for fentanyl was calculated from $t1/2 = \ln 2/k\text{el}$. The plasma fentanyl concentration at the termination of naloxone infusion was determined by interpolation of the logarithmic concentration-time profile for each patient. The correlation between the logarithmic plasma concentrations of fentanyl and naloxone was analyzed by linear regression. The paired Student's *t*-test was used to compare the plasma naloxone concentrations at tracheal extubation and 3-h postoperation.

Results

Patient profiles and anesthetic course

Fifty-nine patients who fulfilled the inclusion criteria participated in the study. Two patients were dropped out of the protocol, due to a complicated surgical course in one, and, in the other, due to failure to establish adequate spontaneous respiration with the maximal dose of naloxone for extubation. In these patients, early extubation was not attempted and mechanical ventilation was continued in the PACU. Profiles of the remaining 57 patients are summarized in Table 1.

In all of the 57 patients, extubation was successfully completed in the operating room, at 34 ± 14 min after fentanyl termination. All the patients needed naloxone for the extubation (3.4 ± 2.6 $\mu g \cdot kg^{-1}$, total bolus dose). Single bolus doses of propranolol (40–80 $\mu g \cdot kg^{-1}$) were administered for hypertension accompanied by tachy-

cardia during the naloxone titration for extubation in 9 patients (16%). No patient complained of more than mild pain in the operating room after extubation. Nausea, vomiting, or other adverse symptoms were not observed in this period.

Table 1. Patient and surgical profiles ($n = 57$)

Sex (male/female)	34/23
Age (years)	63 ± 12
Body weight (kg)	61 ± 10
Surgical procedure	
Gastric resection	29
Liver resection	6
Pancreatic resection	4
Colorectal resection	10
Extended gynecological and urogenital surgery	8
Surgical time (min)	215 ± 133
Anesthesia time (min)	292 ± 156
Total fentanyl dose ($\mu g \cdot kg^{-1}$)	127 ± 64
Additional treatment	
Propofol	15 (26)[a]
Nicardipine	18 (32)[b]
Propranolrol	0
Phenylephrine	12 (21)
Atropine	3 (5)

Data values are expressed as numbers of patients (%) or means ± SD
[a] One to three separate bolus administrations
[b] All of these patients had a history of hypertension and previous medication with antihypertensive drugs, and five patients were treated with continuous infusion

Postanesthetic course

The duration of naloxone infusion in the PACU was 10.8 ± 6.7 h (range, 3–19.5 h). The total administered dose of naloxone was 26.9 ± 23.2 $\mu g \cdot kg^{-1}$. Table 2 shows the postanesthetic changes in Pa_{O_2}, Pa_{CO_2}, and base excess. Pa_{CO_2} decreased significantly during the postoperative 12 h. The other two determinants were stable in the PACU. Unacceptable changes in the arterial blood gas determinants, resulting in dropping out of the study, were not observed in any patients throughout the observation period. Table 3 summarizes the events that necessitated the up-and-down titration of postoperative naloxone infusion. Changing the naloxone infusion rates resolved every symptom. All patients were discharged from the PACU on the second postoperative day (POD). No surgery-related complication occurred during the observation period. The mean duration until patients were able to walk in the ward was 3.1 ± 1.9 POD (range, 2–5 PODs). Twenty-six patients (46%) required NSAIDs (1.8 ± 0.8 times per patient for 3 PODs), but none received supplemental opioids for postoperative pain after naloxone termination throughout the observation period. Figure 1 demonstrates the self-reported pain intensities after surgery. No patient reported severe pain during the observation period. Nausea and vomiting were observed in 14 patients (25%; 2.4 ± 1.1 times per patient for 3 PODs), but no specific treatment was required in any of these patients. No patient developed intraoperative memories.

Table 2. Postanesthetic changes in Pa_{O_2}, Pa_{CO_2}, and base excess ($n = 57$)

	Time after tracheal extubation (h)				
	0	1	3	6	12
Pa_{O_2} (mmHg)	98.4 ± 28.7	104.4 ± 31.2	99.1 ± 18.8	94.6 ± 13.6	89.5 ± 11.1
Pa_{CO_2} (mmHg)*	51.2 ± 8.3	49.6 ± 7.5	45.6 ± 7.0	45.9 ± 6.4	43.3 ± 5.2
Base excess ($mEq \cdot l^{-1}$)	0.3 ± 4.0	0.4 ± 3.2	−0.2 ± 2.9	−0.1 ± 2.5	0.6 ± 3.0

Data values are expressed as means ± SD. The decrease in Pa_{CO_2} was statistically significant (repeated measures analysis of variance [ANOVA], $*P < 0.01$)

Table 3. Events that necessitated postoperative titration of the naloxone infusion rate

Event	Number of patients (% in total of 57 patients)[a]	Number of events (% of total events)
Rate increase		
Suppressed respiration	7 (12)	9 (69)
Suppressed consciousness level	3 (5)	4 (31)
Total	10 (17)	13 (100)
Rate decrease		
Increased pain intensity	47 (82)	87 (55)
Sympathomimetic response	5 (9)	7 (4)
Psychomimetic response	3 (5)	3 (2)
None (every 4 h)	38 (67)	61 (39)
Total	93 (163)	158 (100)

[a] Some patients had more than one event

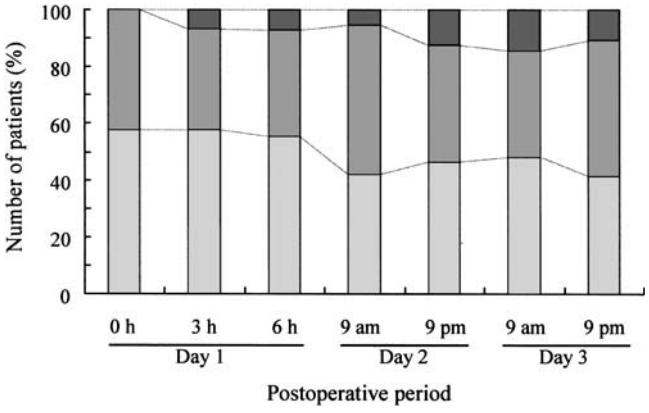

Fig. 1. Self-reported categorical pain intensities during postoperative 3 days. Rate (% in total of 57 patients) of the maximum intensities in each evaluated period are presented. No patient reported severe pain during the observation period. *Bars* show maximum pain intensity. *Dark gray*, moderate; *pale gray*, mild; *very light gray*, none

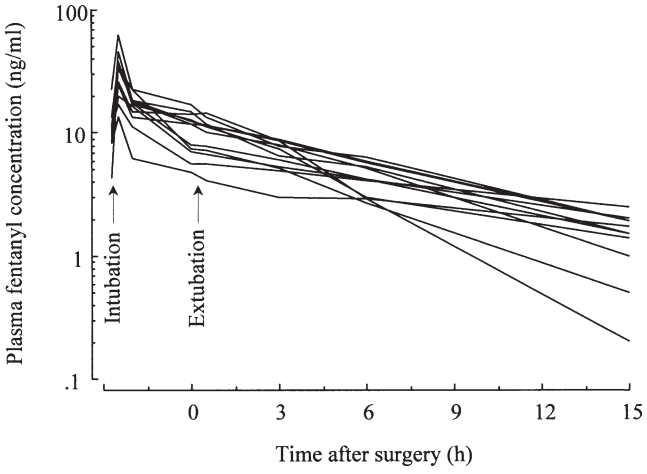

Fig. 2. Individual plasma concentration versus time profiles of fentanyl in 12 patients. *Time 0* represents the end of surgery

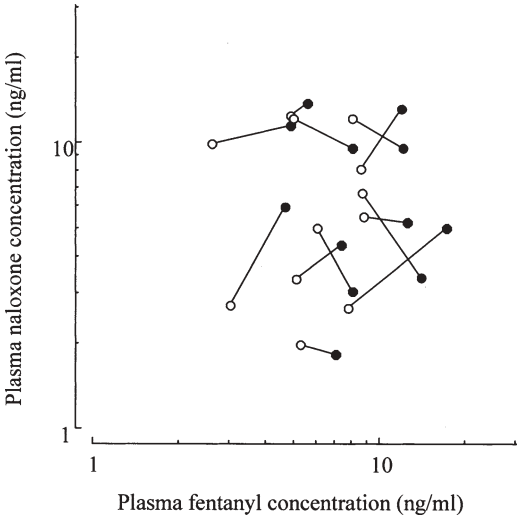

Fig. 3. Scatter plots of plasma naloxone and fentanyl concentrations in 12 patients immediately after extubation and 3 h after surgery. The *closed circles* represent the concentration at 2 min post-extubation and the *open circles* represent that at 3 h postoperation. No correlation was found between the two agents at either sampling period

Plasma concentrations of fentanyl and naloxone

Blood was sampled in 12 consecutive patients (8 male and 4 female; 62 ± 14 years; 62 ± 10 kg) among the 57 enrolled patients for measuring fentanyl and naloxone concentrations in the plasma; 120 ± 40 μg·kg^{-1} of fentanyl was administered during surgery and 4.3 ± 1.8 μg·kg^{-1} of naloxone was used for tracheal extubation in these patients. The patients were extubated at 32 ± 17 min after fentanyl termination. The total postoperative dose of naloxone was 23.9 ± 12.1 μg·kg^{-1} over a period of 10.7 ± 3.2 h (range, 7–16 h). These profiles did not differ significantly from those in the other 45 patients (data not shown). Figure 2 shows the changes in plasma fentanyl concentration in each of the 12 patients during and after surgery. The average *t*1/2 for fentanyl, calculated from the individual plasma concentration-time profiles after the cessation of infusion, was 6.5 ± 3.2 h. The estimated plasma fentanyl concentration at the termination of naloxone infusion was 2.6 ± 1.5 ng·ml^{-1}. The calculated time for the fentanyl levels to decrease by 2 ng·ml^{-1} was 13.1 ± 4.8 h. The plasma naloxone concentrations were 6.9 ± 4.1 ng·ml^{-1} at extubation and 5.7 ± 3.7 ng·ml^{-1} at 3 h postoperation (not significant vs the value at extubation), with the infusion being maintained at a mean rate of 4.2 ± 2.0 μg·kg^{-1}·h^{-1}. No correlation was found between the plasma concentrations of fentanyl and naloxone at either sampling period (Fig. 3).

Discussion

In the present study, naloxone, at a total dose of 3.4 ± 2.6 μg·kg^{-1}, titrated in repeated small doses (0.8 μg·kg^{-1}, approximately) successfully established sufficient spontaneous respiration and levels of consciousness that enabled tracheal extubation immediately after surgery in 57 of the 59 enrolled patients. Subsequent naloxone infusion, started at the rate of the sum of the bolus doses (in μg) per hour, maintained the arterial blood gas determinants stably within acceptable ranges in all extubated patients throughout the observation period, with minimal adverse effects. Although this was an uncontrolled study, the findings that, during their postoperative course the patients had a low overall level of postoperative pain, needed no supplemental analgesics during the naloxone infusion, and used small doses of

NSAIDs without opioids until they were walking on the third POD seemed to be clinically acceptable. Postoperative naloxone infusion may facilitate early tracheal extubation, making high-dose opioid anesthesia a potentially useful alternative not only for very poor-risk patients but also for other patients undergoing major surgery.

The effectiveness of continuous naloxone infusion for the reversal of high-dose opioid anesthesia has been evaluated previously in three studies. Johnstone et al. [10] reported that, in 7 healthy volunteers, naloxone infused at a dose of 3.66 $\mu g \cdot kg^{-1} \cdot h^{-1}$ effectively reversed the decreased CO_2 response induced by 2 $mg \cdot kg^{-1}$ of morphine. Shupak and Harp [11] successfully maintained each of 10 neurosurgical patients without mechanical ventilation after 20-$\mu g \cdot kg^{-1}$ sufentanil or 100-$\mu g \cdot kg^{-1}$ fentanyl, using bolus naloxone followed by infusion at doses of 4–5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ for 16 h postoperatively. Takatori [12] extubated the tracheae of 20 cardiac patients within 5 h after 150-$\mu g \cdot kg^{-1}$ fentanyl anesthesia, using naloxone infusion at a rate of 4–8 $\mu g \cdot kg^{-1} \cdot h^{-1}$. It is interesting that the initial dose of naloxone used in the present study (3.4-$\mu g \cdot kg^{-1}$ bolus followed by 3.4-$\mu g \cdot kg^{-1} \cdot h^{-1}$ infusion on average), which resulted from individual titration, was similar to that used in these fixed-dose studies.

Although the effectiveness of BIS for monitoring the levels of consciousness during opioid anesthesia has been controversial [15], a BIS value of less than 60 is often regarded as the criterion for adequate anesthesia [16]. We used a BIS value of 50 as the practical target threshold for preserving a safety margin against wakefulness, based on our own clinical experience of single-agent anesthesia with fentanyl. In the present study, supplemental fentanyl easily yielded a BIS value of less than 50 in most patients, and no patients developed intraoperative memories.

The pharmacokinetic profiles obtained from the 12 patients examined (Fig. 2) demonstrated that the plasma fentanyl levels exceeded 10 $ng \cdot ml^{-1}$ on average throughout the surgical procedures and decreased with a $t1/2$ of 6.5 ± 3.2 h after terminating the administration. The present $t1/2$ values were within the range (5–8 h) reported in previous investigations of high-dose fentanyl anesthesia [17–19]. Although fixed-dose studies have failed to demonstrate the minimally effective dose for opioids [5,6], it has generally been accepted that a dose range of 50–150 $\mu g \cdot kg^{-1}$ and a plasma concentration range of 10–15 $ng \cdot ml^{-1}$ are required to accomplish satisfactory hemodynamic control using single-agent anesthesia with fentanyl in cardiac surgery [5,6,13]. The total doses and plasma concentrations of fentanyl obtained in the present study as a result of the discretional titration were surprisingly consistent with these findings. The results therefore suggest that the clinical practice of fentanyl anesthesia for cardiac surgery can be extended to major abdominal surgery and can yield similar benefits related to the opioid.

The plasma concentration analysis also revealed that, for extubation, fentanyl levels as high as 9.3 ± 4.3 $ng \cdot ml^{-1}$ (range, 5–11 $ng \cdot ml^{-1}$) could be effectively antagonized by naloxone at total sum doses of 4.3 ± 1.6 $\mu g \cdot kg^{-1}$. In clinical practice, separate, repeated injections of naloxone at a bolus dose not exceeding 1–1.5 $\mu g \cdot kg^{-1}$ have been recommended to avoid the adverse symptoms that are probably related to acute and excessive reversal of opioid effects [20]. Using such repeated dosing with naloxone, at 116 μg in total, Shupak and Harp [11] successfully extubated patients immediately after neurosurgery performed under 100-$\mu g \cdot kg^{-1}$ fentanyl anesthesia. Their average plasma fentanyl levels were approximately 5 $ng \cdot ml^{-1}$ at extubation. In contrast, we needed much higher doses (280 ± 120 μg) of naloxone for tracheal extubation. The difference may be accounted for by the higher plasma concentration of fentanyl in our patients when extubation was attempted. However, we found no correlation between fentanyl and naloxone, either in the doses used or in the plasma concentrations (Fig. 3). These results indicate the large interindividual variability in the balance between fentanyl and naloxone for respiratory reversal, supporting the practical recommendation that intravenous naloxone should be titrated in separate small doses until patients establish sufficient spontaneous respiration.

To our knowledge, a pharmacokinetic profile for continuous naloxone infusion after high-dose opioid anesthesia has not yet been determined. In the present study, analysis of the concentration-time relationships for naloxone could not be accomplished because our protocol of up-and-down titration resulted in wide interindividual variability both in the duration (3–19.5 h) and the total dose (8–56 $\mu g \cdot kg^{-1}$) of this agent. In previous single-dose studies, rapid elimination of naloxone from the plasma (with $t1/2$ ranging from 50 to 110 min) has been demonstrated [21–23]. The range of plasma naloxone concentrations 5 min after injection with clinically relevant doses (400 μg) was 4.3 ± 1.3 (SE) $ng \cdot ml^{-1}$ [21]. The present protocol of naloxone administration achieved a similar plasma concentration range at the time of tracheal extubation (7 $ng \cdot ml^{-1}$) and maintained the concentration in a stable manner for several hours (Fig. 3). Without an initial loading, Rawal et al. [24] reported a steady-state concentration of 4 $ng \cdot ml^{-1}$ obtained after 5-h naloxone infusion at a rate of 5 $\mu g \cdot kg^{-1} \cdot h^{-1}$. Therefore, naloxone infusion with an appropriate initial loading would appear to be important for reversing postoperative respiratory depression.

In the plasma concentration-time profiles, the average plasma fentanyl level at naloxone termination in our study was similar to those previously reported as the

threshold level for clinically relevant respiratory depression (2–3 ng·ml^{-1}) [25]. Thus, we believe that decremental titration according to the clinical symptoms can be used to effectively terminate the naloxone infusion. In fact, in the present study, the average duration of the postoperative naloxone infusion (11 h) and the total naloxone dose (27 μg·kg^{-1}) were much smaller than those reported in the previous fixed-dose studies (67–75 μg·kg^{-1} for 17–20 h) in which similar doses of fentanyl (100–150 μg·kg^{-1}) were administered [10–12].

In the present study, an increase in the self-reported pain intensity was the major determinant for decreasing the infusion rate of naloxone (reduced at least once in 82% of the patients, representing 55% of the total events; Table 3). Reduction of the naloxone infusion rate successfully relieved the pain in all of these patients without suppressing respiration. These results suggest that the reappearance of pain can be a sensitive indicator for reducing naloxone infusion. However, it might be more difficult to terminate naloxone infusion with the appropriate timing in patients who show no specific symptoms. The obtained pharmacokinetic profiles revealed that the plasma fentanyl levels remained at 5 (3–8) ng·ml^{-1} during the first 4 h. Therefore, the 25% reduction of the naloxone rate during this 4-h period might have been done too early, at least in some patients, although none of the patients in this study, developed respiratory depression after decreasing of the rate. Because the plasma fentanyl levels were calculated to have decreased to less than 2 ng·ml^{-1} after 13 ± 5 h, we assume that naloxone can be terminated without the risk of renarcotization in most patients by the morning of the second POD at the dose range of fentanyl used in the present study.

In conclusion, naloxone, at titrated loading followed by subsequent continuous infusion, maintained adequate spontaneous respiration and consciousness levels in patients who received major abdominal surgery under high-dose fentanyl anesthesia throughout the postoperative period. Decremental titration, performed mostly according to over-reversal-related symptoms, effectively terminated the naloxone infusion without any serious adverse effects. The results suggest that naloxone infusion can enable the use of opioids at a high-dose range in a large patient population. However, the plasma concentration analysis revealed large interindividual variability in the balance between fentanyl and naloxone for respiratory reversal, highlighting the importance of individual naloxone titration. Further studies are warranted for validating the benefits of high-dose opioid anesthesia in noncardiac surgery.

Acknowledgments. The authors wish to thank Mr. Isao Hashiguchi for his technical assistance with HPLC and Mr. Brent Bell for reading the manuscript.

References

1. Waller JL, Hug CC, Nagle DM, Craver JM (1981) Hemodynamic changes during fentanyl-oxygen anesthesia for aortocoronary bypass operation. Anesthesiology 55:212–217
2. Lunn JK, Stanley TH, Eisele J, Webster L, Woodward A (1979) High dose fentanyl anesthesia for coronary artery surgery: plasma fentanyl concentrations and influence of nitrous oxide on cardiovascular responses. Anesth Analg 58:390–395
3. Bovill JG, Sebel PS, Stanley TH (1984) Opioid analgesics in anesthesia: with special reference to their use in cardiovascular anesthesia. Anesthesiology 61:731–755
4. Kazama T, Ikeda K, Morita K (1998) The pharmacodynamic interaction between propofol and fentanyl with respect to the suppression to skin incision, peritoneum incision, and abdominal wall retraction. Anesthesiology 89:894–906
5. Philbin DM, Rosow CE, Schneider RC, Koski G, D'Ambra MN (1990) Fentanyl and sufentanil anesthesia revisited: how much is enough? Anesthesiology 73:5–11
6. Wynands JE, Wong P, Townsend GE, Sprigge JS, Whalley DG (1984) Narcotic requirement for intravenous anesthesia. Anesth Analg 63:101–105
7. Longnecker DE, Grazis PA, Eggers GWN Jr (1973) Naloxone for antagonism of morphine-induced respiratory depression. Anesth Analog 52:447–453
8. Taff RH (1983) Pulmonary edema following naloxone administration in a patient without heart disease. Anesthesiology 59:576–577
9. Partridge BL, Ward CF (1986) Pulmonary edema following low-dose naloxone administration. Anesthesiology 65:709–710
10. Johnstone RE, Jobes DR, Kennell EM, Behar MG, Smith TC (1974) Reversal of morphine anesthesia with naloxone. Anesthesiology 41:361–367
11. Shupak RC, Harp JR (1985) Comparison between high-dose sufentanil-oxygen and high-dose fentanyl-oxygen for neuroanalgesia. Br J Anaesth 57:375–381
12. Takatori M (1990) Reversal of high-dose fentanyl anesthesia by naloxone (in Japanese with English abstract). Masui (Jpn J Anesthesiol) 39:1007–1014
13. Sprigge JS, Wynands JE, Whalley DG, Bevan DR, Townsend GE, Nathan H, Patel YC, Srikant CB (1982) Fentanyl infusion anesthesia for aortocoronary bypass surgery: plasma levels and hemodynamic response. Anesth Analg 61:972–978
14. Ronan KP, Gallagher J, George B, Hamby B (1995) Comparison of propofol and midazolam for sedation in intensive care unit patients. Crit Care Med 23:286–293
15. Barr G, Anderson RE, Samuelsson S, Owall A, Jakobsson JG (2000) Fentanyl and midazolam anaesthesia for coronary bypass surgery: a clinical study of bispectral electroencephalogram analysis, drug concentrations and recall. Br J Anaesth 84:749–752
16. Katoh T, Suzuki A, Ikeda K (1998) Electroencephalographic derivatives as a tool for predicting the depth of sedation and anesthesia induced by sevoflurane. Anesthesiology 88:642–650
17. Ahonen J, Olkkola KT, Hynynen M, Seppälä T, Ikävalko H, Remmerie B, Salmenpera M (2000) Comparison of alfentanil, fentanyl and sufentanil for total intravenous anaesthesia with propofol in patients undergoing coronary arterial bypass surgery. Br J Anaesth 85:533–540
18. Hudson RJ, Thomson IR, Cannon JE, Friesen RM, Meatherall RC (1986) Pharmacokinetics of fentanyl in patients undergoing abdominal aortic surgery. Anesthesiology 64:334–338
19. Bovill JG, Sebel PS (1980) Pharmacokinetics of high-dose fentanyl. Br J Anaesth 52:795–801
20. Shupak RC, Harp JR, Steveson-Smith W, Rossi D, Buchheit WA (1983) High-dose fentanyl for neuroanesthesia. Anesthesiology 58:579–582
21. Ngai SH, Berkowitz BA, Yang JC, Hempstead J, Spector BS (1976) Pharmacokinetics of naloxone in rat and man: basis for its potency and short duration of action. Anesthesiology 44:398–401

22. Stile IL, Fort M, Wurburger RJ, Rodvold KA, Scector S, Hiatt IM, Hegyi T (1987) The pharmacokinetics of naloxone in the premature newborn. Dev Pharmacol Ther 10:454–459
23. Albeck H, Woodfield S, Kreek MJ (1989) Quantitative and pharmacokinetic analysis of naloxone in plasma using high-performance liquid chromatography with electrochemical detection and solid-phase extraction. J Chromatogr 488:435–445
24. Rawal N, Schoett U, Dahlstoerm B, Intunisi CE, Tandon B, Sjoestrand V, Wennhager M (1986) Influence of naloxone infusion on analgesia and respiratory depression following epidural morphine. Anesthesiology 64:194–201
25. Cartwright P, Prys-Roberts C, Gill K, Dye A, Stafford M, Gray A (1983) Ventilatory depression related to plasma fentanyl concentrations during and after anesthesia in humans. Anesth Analg 62:966–974