Early extubation after high-dose fentanyl anaesthesia for aortocoronary bypass surgery: reversal of respiratory depression with low-dose nalbuphine

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To investigate the possibility of selective reversal of narcotic-induced respiratory depression following fentanyl anaesthesia, we studied 20 patients after aortocoronary bypass surgery. All patients were anaesthetized with fentanyl, $40 \mu\text{g}\cdot\text{kg}^{-1}$ and oxygen, with isoflurane as indicated. In a random double blind fashion either incremental doses of nalbuphine, or normal saline were administered approximately four hours after cardiopulmonary bypass. Respiratory depression was evaluated using blood gas and end tidal CO_2 (PETCO_2) measurement, and in addition, a ventilatory response to CO_2 was obtained preoperatively and at selected intervals postoperatively. Despite randomization, patients with more respiratory depression were assigned to nalbuphine. There appeared to be a reversal of respiratory depression with nalbuphine, indicated by a fall in the resting PETCO_2 value. This

apparent reversal of respiratory depression was associated with a significant increase in pain, requiring treatment in three patients. We conclude that low-dose nalbuphine is not an acceptable method of antagonism of respiratory depression in this group of patients. Many patients who did not receive nalbuphine were able to breathe adequately at an earlier stage than was previously suspected. Close monitoring of the respiratory system may permit earlier extubation without the requirement of a narcotic antagonist after this dose of fentanyl.

Key words

ANAESTHETICS, INTRAVENOUS: fentanyl; ANTAGONISTS, NARCOTICS: nalbuphine; ENDOTRACHEAL TUBE: extubation.

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No reprints will be available.

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Supported by a grant from the Canadian Heart Foundation.

High-dose fentanyl anaesthesia has become a technique of choice for cardiac surgery due to haemodynamic stability and absence of adverse effects.^{1,2} Conventional management of patients after this type of surgery usually includes a period of elective ventilation in the intensive care unit for 6 to 24 hours, regardless of the type of anaesthesia. After high doses of fentanyl, this period allows the narcotic-induced respiratory depression to wear off. In the absence of large doses of narcotic, however, recent studies show that extubation within six hours of cardiac surgery is not associated with complications, and may in fact reduce morbidity.³⁻⁵ After abdominal aortic reconstructive surgery, early extubation may permit earlier normalization of the FRC.⁶ Other advantages include reduced intensive care unit and hospital stay,⁴ and reduced requirements for sedation.³

Nalbuphine is one of the newer "agonist-

antagonist" opiates, thought to have a greater affinity for those opiate receptors mediating analgesia than those causing respiratory depression.⁷ It has been used in high doses prior to cardiac surgery with good haemodynamic stability,⁸ and has been used to reverse postoperative respiratory depression due to oxymorphone and dihydromorphone.⁹ In the latter case, analgesia was preserved, and blood pressure and pulse rose only to pre-anaesthetic levels. Nalbuphine has recently been reported to reverse postoperative respiratory depression due to fentanyl, without reversal of analgesia.¹⁰

Preliminary observations suggested to us that small doses of nalbuphine (less than 10 mg) could reverse the postoperative respiratory depression resulting from a dose of 40 $\mu\text{g}\cdot\text{kg}^{-1}$ of fentanyl for aortocoronary bypass surgery, while allowing patients to remain analgesic and haemodynamically stable. Based on a plasma level of fentanyl of approximately 14 $\text{ng}\cdot\text{ml}^{-1}$ at the beginning of the elimination phase,¹¹ and an elimination half-life of approximately four hours,¹² pharmacodynamics of fentanyl are such that in a 70 kg man, plasma levels at which significant respiratory depression occurs (elevation of end-tidal CO_2 by 1.3 kPa (10 mmHg)) may be expected for approximately 12 hours after this dose.¹² If nalbuphine, with a half life of 3.5 hours after coronary artery surgery¹³ is given approximately eight hours after administration of fentanyl, then plasma levels of fentanyl below those causing significant respiratory depression should be reached by one half-life of nalbuphine. Thus, nalbuphine could be administered at this time with little fear of "renarcotization."

We wished to assess the efficacy of nalbuphine in selective reversal of postoperative respiratory depression, after a dose of 40 $\mu\text{g}\cdot\text{kg}^{-1}$ of fentanyl for aortocoronary bypass surgery. We wished also to compare the postoperative course of patients treated with nalbuphine and extubated early to a similar group of patients who did not receive nalbuphine. Our goal was to provide patients with the demonstrated advantages of both high-dose fentanyl anaesthesia and early extubation.

Methods

Twenty patients undergoing elective aortocoronary bypass surgery were studied. Informed consent was obtained from all patients the day prior to surgery, and the study was approved by the hospital ethics committee. The criteria for entry of a patient into

the study were: left ventricular ejection fraction greater than 0.5; no history of pulmonary disease; normal preoperative chest x-ray and blood gases; and no major extracardiac systemic disease.

The day prior to surgery patients were given a CO_2 challenge, using a modified Read technique.¹⁴ During this procedure (taking three to four minutes) a modified lead II EKG was monitored continuously while the patient rebreathed a mixture of five per cent CO_2 in 95 per cent O_2 through a pneumotachograph and CO_2 analyser (Hewlett Packard, Model 47210-A). This enabled determination of the slope of the ventilatory response to CO_2 where minute ventilation is plotted vs end tidal CO_2 concentration (PETCO_2).

Patients were maintained on their preoperative medications until the night before surgery, with the exception of beta-blockers, nitrate preparations and calcium channel antagonists, which were continued up to the time of the operation. The patients were premedicated with diazepam (0.15 $\text{mg}\cdot\text{kg}^{-1}$ given orally), morphine (0.15 $\text{mg}\cdot\text{kg}^{-1}$ IM) and scopolamine (0.005 $\text{mg}\cdot\text{kg}^{-1}$ IM) one hour before induction of anaesthesia. Oxygen was administered by nasal prongs while intravenous, intra-arterial, and pulmonary artery catheters were inserted under local anaesthesia in the operating theatre.

Anaesthesia was induced with fentanyl (40 $\mu\text{g}\cdot\text{kg}^{-1}$) given at a rate of 1 $\text{mg}\cdot\text{min}^{-1}$. Fentanyl was preceded by 1 mg of pancuronium to prevent chest wall rigidity, with additional pancuronium given to a total dose of 0.1 $\text{mg}\cdot\text{kg}^{-1}$, after loss of consciousness. Patients were ventilated with 100 per cent O_2 using a modified T-piece and fresh gas flows to maintain normocarbida. Anaesthesia was supplemented with isoflurane as required, but no additional opiates or sedatives were given. Fluid management, vasoactive drugs and inotropes were titrated to haemodynamic measurements.

Patients were transferred to the postoperative intensive care unit with the endotracheal tube *in situ*, and controlled intermittent positive pressure ventilation with a Bennett MA 1 ventilator was instituted. All patients fulfilled the following criteria before continuing in the study: (1) rectal temperature greater than 37.5°C; (2) minimal bleeding; (3) blood pressure and pulmonary capillary wedge pressure close to preoperative values; (4) heart rate less than 100 min; (5) responsive to commands; (6) normal neuromuscular function (sustained grasp); (7) pain free; (8) no gross pathology apparent on

TABLE I Study protocol

†IMV set at 4 breaths per minute.

*Only in patients with PETCO₂ less than 8 kPa.

chest x-ray; (9) acceptable arterial blood gases (pH 7.35–7.45, PaCO₂ 4.7–6.0 kPa (35–45 mmHg), PaO₂ greater than 13.3 kPa (100 mmHg) on FiO₂ of less than 0.5, HCO₃⁻ 23–27 mEq·L⁻¹).

PETCO₂ was measured continuously, and blood gas measurements were taken regularly to confirm the accuracy of the PETCO₂ measurements. During all spontaneous ventilation tests (*vide infra*), measurement of ventilatory responses to CO₂, and during administration of test drugs EKG, blood pressure and pulmonary artery pressure were continuously observed by one of the investigators or the patient's nurse.

When the above criteria were fulfilled, the patient was allowed to breathe spontaneously on an intermittent mandatory ventilation circuit (IMV) set at a rate of 4 breaths·min⁻¹ for five minutes. A CO₂

response curve was obtained only in patients who breathed to an PETCO₂ of less than 8.0 kPa. Controlled ventilation was then reinstituted until PETCO₂ returned to 4.7–6.0 kPa. The IMV circuit was once again connected, set at 4 breaths·min⁻¹, and patients were given either normal saline (ten patients) or nalbuphine (ten patients) in a randomized double-blind manner. Ten ml syringes contained either normal saline 10 ml, or nalbuphine 10 mg made up to 10 ml with sterile saline (concentration of 1 mg·ml⁻¹). The syringe contents were given at a maximum rate of 1 ml every three minutes, until the patient experienced either discomfort or pain, or until all 10 ml were given. The experimental protocol is illustrated in Table I.

The IMV breaths were discontinued as soon as a PETCO₂ of less than 6.7 kPa (50 mmHg) was

TABLE II Anthropomorphic data, drug history, and recovery times (mean $\pm$ SEM)

	Age (years)	Height (cms)	Weight (kg)	Drugs taken (no. patients)				Time in OR (hrs)	Time to 37.5°C Post fentanyl (hrs)
				BB	CaA	N	O		
Saline group (n = 10)	57 $\pm$ 1.6	172 $\pm$ 1.8	75 $\pm$ 1.7	10	8	5	3	4.2 $\pm$ 0.3	8.4 $\pm$ 0.3
Nalbuphine group (n = 10)	53 $\pm$ 2.7	172 $\pm$ 2.2	78 $\pm$ 3.3	8	7	5	4	3.8 $\pm$ 0.3	7.9 $\pm$ 0.2

Key: BB = Beta Blockers; CaA = calcium antagonist; N = nitrates; O = other drugs (diuretics, ASA, quinidine).

maintained spontaneously. Immediately following drug administration the resting PETCO₂, and a CO₂ response curve (in patients breathing to a PETCO₂ of less than 8.0 kPa) were obtained. Patients were extubated if they were awake and co-operative and had acceptable arterial blood gases (pH greater than 7.3, PaCO₂ less than 6.7 kPa, PaO₂ greater than 13.3 kPa on an FiO₂ of less than 0.5, HCO₃⁻ greater than 22 mEq·L⁻¹). Further measurements of resting PETCO₂ and PaCO₂, and CO₂ response curves were made at one and three hours post-extubation. Controlled ventilation was continued in those patients who did not meet the requirements for extubation after drug administration. They were extubated when they fulfilled these requirements, but further CO₂ response curves were not obtained in these patients.

Initially, a linear analogue scale for pain (15) was explained at the preoperative visit and used in the postoperative intensive care unit. It became clear, however, that patients experienced difficulty in using a visual scale at this time. For this reason, pain was assessed by direct questioning, beginning with "Are you comfortable?" If patients experienced incisional pain that was increasing during the administration of the test drug, then administration was terminated. If the pain continued to increase or was intolerable (as judged by restlessness, visible discomfort, or response to direct questioning) then morphine was administered. Patients were questioned prior to each injection (of 1 ml solution) or more frequently if indicated. The following scale was used to record pain:

- 0 – comfortable
- ± – slight discomfort
- + – tolerable pain, not increasing
- ++ – increasing pain (drug administration was terminated)
- +++ – pain requiring morphine.

Tachycardia (heart rate greater than 100 min) was treated with increments of propranolol, and hypertension (systolic pressure greater than 2.7 kPa (20 mmHg) above preoperative value) was treated with either nitroglycerine or nitroprusside infusion. Nausea was treated with droperidol 1.25 mg, in the absence of abdominal distension.

Morphine requirements in the 12 hours following drug administration were recorded. Chest x-ray and EKG were assessed immediately postoperatively, and at 24 and 48 hours. Blood loss and blood/fluid requirements were assessed over the 24-hour post-operative period.

Statistical analysis was made using two-way analysis of variance with Duncan's multiple range test for identification of differences within the analysis of variance. Friedman's test statistic and chi-square analysis were also used where appropriate. The null hypothesis was rejected when p was less than 0.05. Linear regression was used to calculate the slope of the CO₂ response curves. All values are quoted as mean $\pm$ 1 standard error of the mean.

Results

The anthropomorphic details of the subjects studied, a list of their medications, and the operative and recovery times are given in Table II. The two groups are comparable in all respects.

Antagonism of respiratory depression

RESTING PETCO₂ RESULTS

Table III gives the resting PETCO₂ results at the various times. In the saline group the only differences in resting PETCO₂ appear between the preoperative and the pre-saline, and the preoperative and post-saline values. There was no significant effect of administration of saline on resting PETCO₂, and

TABLE III Respiratory parameters

	Saline group				
	Preoperative	Pre-saline	Post-saline	Post-extubation	3 hours Post-extubation
Time post-fentanyl (hrs) n = 10		8.4 ± 0.3	9.4 ± 0.3	11.1 ± 0.3	13.1 ± 0.3
Resting PETCO ₂ (kPa) n = 10	5.24 ± 0.19	7.17 ± 0.35*	6.65 ± 0.25*	6.10 ± 0.23	6.09 ± 0.23
Slope of response to CO ₂ (L·min ⁻¹ ·kPa ⁻¹) n = 7	4.35 ± 0.97	5.78 ± 1.20	7.95 ± 2.01	4.20 ± 1.05	4.73 ± 0.53
	Nalbuphine group				
	Preoperative	Pre-nalbuphine	Post-nalbuphine	Post-extubation	3 hours Post-extubation
Time post-fentanyl (hrs) n = 10		7.9 ± 0.2	9.45 ± 0.37	10.9 ± 0.3	12.6 ± 0.4
Resting PETCO ₂ (kPa) n = 7	5.44 ± 0.12	8.20 ± 0.47*	6.48 ± 0.29*†	6.49 ± 0.23*†	6.49 ± 0.20*†
Slope of response to CO ₂ (L·min ⁻¹ ·kPa ⁻¹) n = 7	4.58 ± 0.53		4.65 ± 1.50	4.88 ± 0.83	3.83 ± 1.20

*indicates $p < 0.05$ vs preoperative; †indicates $p < 0.05$ vs pre-nalbuphine.

by the time the post-extubation values were recorded the mean value had fallen sufficiently that it was not different from the preoperative value.

In the nalbuphine group three of the patients required morphine during the administration of nalbuphine (*vide infra*), and these patients were dropped from the analysis. For the other seven patients, the preoperative PETCO₂ was significantly lower than all subsequent values, and the pre-nalbuphine value was significantly higher than all post-nalbuphine values. Administration of nalbuphine was associated with a significant lowering of the resting PETCO₂; however, it remained above the preoperative value.

Comparing the values between groups (unpaired *t* test), the resting PETCO₂ was higher in the saline group than the nalbuphine group before administration of the test drug ($p < 0.05$). Otherwise there was no difference between groups at any time.

SLOPE OF THE VENTILATORY RESPONSE TO CO₂

Postoperatively we did not subject patients with resting PETCO₂ of greater than 8 kPa to a formal CO₂ challenge (Read rebreathing). This meant that seven of the patients in the nalbuphine group and three in the saline group could not have an objective assessment of the slope of their CO₂ response before administration of the test drug.

The three patients in the saline group were

dropped from the analysis of variance, which when performed on the remaining seven patients indicated no significant difference between the slopes measured at the times indicated (Table III). Although the slope after administration of saline appeared to be increased compared to the preoperative value, there was a large range in results (indicated by the large standard error) and considerable within-patient variability.

Rather than drop all seven patients from the nalbuphine group results, we elected to analyse the slopes of the CO₂ response in this group at all times except before administration of the drug. The three patients in this group who required morphine were dropped from the analysis. For the remaining seven patients, analysis of variance revealed no difference between the slopes at the times shown (Table III).

As lack of spontaneous ventilation despite a PETCO₂ of greater than 8 kPa might be considered as an "absent" ventilatory response to CO₂ (up to this level), Friedman's rank test was performed on the slope of the CO₂ response results, assigning the lowest value to patients who did not have a formal CO₂ challenge because of their high resting PETCO₂. A comparison was then possible using all ten patients within each group, at the preoperative, pre-drug, and post-drug times. Again, due to the within-patient variability this test failed to reach statistical significance.

TABLE IV Non-respiratory effects of saline/nalbuphine administration

Subject no.	ml drug injected ^a	PAIN		Nausea	BP or HR increase	Treatment
		pre	post			
(saline group)						
1	10	—	—	—	—	—
2	10	—	—	—	+	Propranolol
3	10	—	—	—	—	—
4	10	—	—	—	—	—
5	10	—	+	—	+	—
6	10	±	—	—	—	—
7	10	—	+	—	—	—
8	10	—	—	—	—	—
9	10	—	—	+	—	Droperidol
10	10	—	—	—	—	—
(nalbuphine group)						
11	2	±	++	—	+	Propranolol, nitro-prusside
12	4	—	++	+	+	Droperidol
13	4	—	+++	—	—	Morphine
14	10	—	—	—	+	Propranolol
15	10	—	+	+	+	Droperidol, propranolol, nitroglycerin
16	10	—	—	—	—	—
17	2	±	++	—	—	—
18	2	—	+++	+	+	Morphine
19	6	—	++	—	—	—
20	5	—	+++	—	+	Morphine, althesin
P value (chi square)		NS	0.025	NS	NS	0.025

^a — normal saline, or nalbuphine 1 mg·kg⁻¹.

See text for definitions of pain, nausea, BP or HR increase and treatment.

There was no difference in slopes between groups at any time.

Non-respiratory effects

Two patients experienced tolerable pain during the saline administration, and one of these also showed a transient increase in heart rate and blood pressure which did not require treatment (Table IV). There were few other effects in this group, and all patients received the entire contents of the test syringe (10 ml).

In contrast, one patient in the nalbuphine group experienced tolerable pain during the drug administration, while four others experienced increasing pain necessitating that the drug administration be stopped. None of these patients required analgesia once the drug administration had been stopped, however. Three patients experienced more severe pain, requiring that intravenous morphine be given. It was necessary to sedate one of these patients with

an alfathesin infusion as he remained agitated after 15 mg of intravenous morphine. Thus only three patients in this group did not experience pain as a result of the drug administration, and only these three patients received the full contents of the syringe (10 ml).

Three patients who received nalbuphine required droperidol for nausea, six became hypertensive (two of which required treatment), and four developed tachycardia which was treated with propranolol. The incidence of pain, and the requirements for treatment of adverse effects during drug administration were significantly higher ($p < 0.025$, Chi square) in the nalbuphine group.

Extubation

The mean time to extubation after fentanyl administration was 11.3 ± 1.0 hrs in the saline group, and 9.9 ± 0.3 hrs in the nalbuphine group, excluding the three patients who received morphine during the

drug administration. There is no difference (unpaired *t* test) between these times. While the times to extubation are given for completeness, they were influenced by the study protocol and should not be interpreted as an independent measure of respiratory depression.

Postoperative course

There were no adverse effects during measurement of the CO₂ response curves. No patient required reintubation and no additional nalbuphine or other narcotic antagonist was required. Excluding the three patients who required morphine immediately after nalbuphine administration, the morphine requirements of both groups were not different in the following 12 hours.

There was no difference in the blood loss or blood/fluid requirements between the two groups in the 12 hours following drug treatment. There were no differences in the incidence and severity of EKG and chest x-ray changes between the two groups either at 24 or 48 hours post-operation. One patient (who was randomized to the nalbuphine group) had EKG evidence of a new intraoperative myocardial infarction on the first, and all other postoperative cardiograms. However, this patient did well clinically. There were no other major cardiopulmonary complications.

Discussion

The results show a significant lowering of resting PETCO₂ with nalbuphine, but at the price of a significant increase in pain. Administration of saline did not significantly reduce resting PETCO₂, nor was there an increase in undesirable side effects.

Our inability to perform a ventilatory response to CO₂ in half of the patients at the pre-test drug stage made analysis of this aspect of the results difficult. Even when Friedman's rank test was performed on the slope of the CO₂ response results utilizing all the patients as described, the within-patient variability in slopes obscured any drug effect which may have been present. We were surprised that there were no differences from the preoperative and postoperative measured slopes in the saline group. After the high dose of fentanyl, and in association with elevation of PETCO₂, depression in the slope was expected.¹⁶

Most studies utilizing the ventilatory response to CO₂ have not been on awake, intubated, postopera-

tive patients, and none have been conducted post-cardiac surgery. This method of assessing respiratory depression is more sensitive than resting CO₂ levels.¹⁷ Degree of arousal affects the slope of the response,¹⁷ and our patients certainly experienced varying levels of comfort, alertness, and stimulation throughout the postoperative period. We do not know whether such factors could outweigh the depressant effect of fentanyl on the ventilatory response to CO₂. As a result, and due to the small number of patients we were able to assess before nalbuphine, the results do not permit us to conclude that there was either a significantly different slope postoperatively compared to control, or that either saline or nalbuphine had a significant effect on the slope.

The resting PETCO₂ results do indicate antagonism of respiratory depression with nalbuphine. The degree of respiratory depression present before nalbuphine was given suggests that many of the patients in this group may not have met extubation criteria when they did, had it not been for the drug. The greater degree of respiratory depression present in this group compared to the saline group before drug administration, however, makes comparison of the groups (i.e., drug vs "placebo") difficult.

The pharmacodynamics of fentanyl related to the respiratory system appear to be highly variable. In our 20 patients respiratory depression ranged from minimal to severe, eight to ten hours after our induction dose. This is in keeping with other studies of both the respiratory and analgesic effects of smaller doses of fentanyl.¹⁸⁻²⁰ Thus, despite the prediction that unacceptable respiratory depression should persist until 12 hours after a dose of 40 µg·kg⁻¹ of fentanyl, we found that six of 20 patients had a resting PETCO₂ of less than or equal to 6.7 kPa (50 mmHg) only eight hours after this dose. The greater elevation in PETCO₂ in the nalbuphine group at the pre-treatment stage despite randomization may have been a result of this large variation, coupled with the small sample size. Certainly there was no difference between groups in the preoperative slope, resting PETCO₂, or any other factor (Table II), nor was any difference apparent after the drugs had been given.

The very disturbing aspect of our results appears in Table IV. At approximately 4 hours following surgery, only three of the 20 patients experienced slight discomfort. Following the injection of saline

or nalbuphine a clear difference with respect to pain emerges between the two groups. In the saline group, the one patient with slight discomfort became pain-free following the injection, while two other individuals developed either slight discomfort or tolerable pain. In contrast, the slight discomfort experienced by two individuals before administration of nalbuphine progressed to pain sufficiently severe that the injection had to be discontinued. Of the remaining eight patients initially pain free, only two remained so after nalbuphine administration. All the others developed pain that necessitated cessation of the injection, and three patients required intravenous morphine to control their pain.

This is in contrast to a recent report where adequate analgesia was maintained following the administration of nalbuphine to patients after fentanyl anaesthesia.¹⁰ In that study, 20 mg of nalbuphine was given immediately on arrival in the recovery room. In our study, much smaller doses of nalbuphine were given some eight hours after a much larger dose (1½ to 2 times) of fentanyl. There were in addition major differences between our patients and those of Latasch *et al.* Our patients had major and lengthy surgery while those in the Latasch study had "elective general surgery" lasting a mean of 80 minutes.

The mechanism of pain relief after agonist-antagonist opiates given in the presence of pure agonist agents is unclear. We suspect the different results of the two studies may arise as a result of the very different doses of both fentanyl and nalbuphine administered. In our study, a very small dose of nalbuphine (5.5 ± 1.1 mg) after $40 \mu\text{g}\cdot\text{kg}^{-1}$ of fentanyl seemed to act mainly as an antagonist, while in the study by Latasch 20 mg of nalbuphine after a mean dose of $22.5 \mu\text{g}\cdot\text{kg}^{-1}$ of fentanyl appeared to act as a true agonist-antagonist. It may be that a higher bolus dose of nalbuphine would have resulted in less reversal of analgesia in our patients.

Concomitant with the development of pain, a number of patients receiving nalbuphine developed tachycardia and/or hypertension. It is not surprising that a sympathetic response should accompany pain. What is surprising to us is the unpredictability of the response. Some patients after very little nalbuphine developed all the expected signs of narcotic antagonism, while others developed none

even after the full 10 mg had been given. Once the drug had been given, many of the patients who had experienced increasing discomfort became more comfortable, and they did not require more analgesia in the following 12 hours than those who did not receive the drug. Once again, large differences in individual patient pharmacodynamic effects appear to exist.

As a result of these severe adverse responses, we believe that nalbuphine, as given in this study, may be hazardous after a large dose of fentanyl for major surgery. Especially in this group of patients where myocardial oxygen balance is critical,²¹ pain and other sympathetic responses are undesirable. Severe consequences have resulted from antagonism of narcotic drugs after major surgery with naloxone.^{22,23} In addition, any technique which results in increased pain to patients is unacceptable. Thus, the results suggest that reversal of respiratory depression should not be attempted in these patients with small doses of nalbuphine.

Despite these disappointing and worrisome results with low-dose nalbuphine, our results do suggest that our patients, given $40 \text{ mg}\cdot\text{kg}^{-1}$ of fentanyl at the start of anaesthesia, did not experience morbidity as a result of their early extubation. Patients who received saline were able to be extubated at a similar time following fentanyl administration as those who received nalbuphine. Thus with close monitoring of respiratory status, such patients who are healthy apart from their coronary artery disease, and who have preserved ventricular function, can be considered for extubation within a few hours of aortocoronary bypass surgery. This conclusion should not be generalized to patients receiving much higher doses of fentanyl, as is common in some centres, however. Further study is required to (a) clarify the relationship of high dose fentanyl pharmacokinetics to the respiratory effects in patients, and (b) clarify the relationship between resting PETCO_2 and the slope of the ventilatory response to CO_2 after cardiac surgery and this dose of fentanyl. Further study is also needed to determine if a higher bolus dose of nalbuphine would selectively reverse respiratory depression after high dose fentanyl anaesthesia, without precipitating the complications seen in this study.

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Résumé

La possibilité d'antagoniser sélectivement la dépression respiratoire morphinique consécutive à l'anesthésie par le fentanyl a été étudiée chez 20 patients ayant subi une chirurgie de revascularisation coronaire. Quarante $\mu\text{g}\cdot\text{kg}^{-1}$ de fentanyl ont été administrés à tous les patients, ventilés en oxygène pur avec de l'isoflurane si nécessaire. Des doses croissantes de nalbuphine ou de serum salé isotonique ont été administrées au hasard et en double aveugle, quatre heures environ après le circulation extracorporelle. La dépression respiratoire a été évaluée par la mesure des gaz du sang artériel et de la pCO_2 téléexpiratoire (PETCO_2). La réponse ventilatoire au CO_2 a été étudiée avant et à intervalles réguliers, après l'intervention. Malgré la répartition au hasard des patients on retrouve dans le groupe soumis à la nalbuphine ceux présentant une dépression respiratoire plus marquée. La nalbuphine a provoqué une diminution de la dépression respiratoire morphinique post opératoire comme l'indiquent la chute de la PETCO_2 . L'évidente diminution de la dépression respiratoire fut cependant associée à une augmentation notable de la douleur. Nous concluons que l'utilisation de faibles doses de nalbuphine pour antagoniser les dépressions respiratoires profondes n'est pas une méthode à recommander chez ce type de patients. La plupart des patients n'ayant pas reçu de nalbuphine furent capables de respirer normalement plus tôt que prévu. Un monitoring attentif de la ventilation pourrait donc permettre une extubation précoce sans l'aide d'un antagoniste morphinique après l'administration de la posologie de $40 \mu\text{g}\cdot\text{kg}^{-1}$ de fentanyl.