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Influence of Naloxone Infusion on Analgesia and Respiratory Depression Following Epidural Morphine

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The influence of two different concentrations of iv naloxone infusion on the analgesia and adverse effects of epidural morphine were compared in a double-blind, placebo-controlled study. Forty-five patients undergoing gallbladder surgery were provided postoperative analgesia by 4 mg epidural morphine; they then received an iv infusion over a 12-h period consisting of either 5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ naloxone, 10 $\mu g \cdot kg^{-1} \cdot h^{-1}$ naloxone, or saline. Pain relief was assessed by hourly visual analog scoring (VAS) and by direct questioning of the patient. Requirement of additional analgesia was noted. Respiratory frequency was monitored every 15 min and arterial blood gases were analyzed every 2 h for 24 h. Peak expiratory flow (PEF) was recorded 6 and 24 h postoperatively. Steady-state kinetics of naloxone were determined by a modified radioimmunoassay (RIA) method. All patients had good to excellent postoperative pain relief. Naloxone, 5 $\mu g \cdot kg^{-1} \cdot h^{-1}$, did not appear to have any effect on epidural morphine analgesia. However, naloxone infusion at the rate of 10 $\mu g \cdot kg^{-1} \cdot h^{-1}$ reduced the duration of analgesia by about 25%, and more frequent injections of epidural morphine were required to give effective analgesia. Complete reversal of analgesia was not seen in any patient. A dose-related stimulatory effect on respiratory frequency was noted in the groups receiving naloxone. Pa_{CO_2} values also were better in these groups as compared to values in the placebo group. The steady-state plasma concentration of naloxone was 2.8–3.7 ng/ml during infusion at the rate of 5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ and 4.3–5.1 ng/ml during 10 $\mu g \cdot kg^{-1} \cdot h^{-1}$ naloxone infusion. The plasma clearance of naloxone was 30.5 and 35.4 $ml \cdot min^{-1} \cdot kg^{-1}$ for the low and high dose groups, respectively, and showed a four-fold interindividual variation. The authors conclude that naloxone reverses epidural morphine analgesia in a dose-dependent manner. Low-dose naloxone infusion (5 $\mu g \cdot kg^{-1} \cdot h^{-1}$)prevents respiratory depression due to epidural morphine without affecting its analgesia. (Key words: Analgesics: narcotic, morphine. Antagonist narcotic: naloxone. Anesthetic techniques: epidural. Pain: postoperative. Ventilation: depression.

THE TREATMENT OF acute and chronic pain by injecting opiates in the epidural or subarachnoid space has gained widespread acceptance. Postoperative pain relief by epidural opiates has become a standard procedure, and its superiority over alternative techniques has been reported in a number of studies.[1-3] However, due to the rare risk of delayed respiratory depression, most workers recommend strict surveillance of patients for at least 12 h after injection of epidural opiates.[4,5]

Respiratory depression and other adverse effects of epidural opiates can be reversed by naloxone.[4] However, it is unclear if analgesia also is reversed. Naloxone has a short duration of action, so multiple intravenous bolus injections are recommended as often as needed to counteract the adverse effects of the opiate. The optimal treatment would be to find the proper dosage scheme for constant intravenous infusion of naloxone,[6,7] but very little literature exists on this subject. This prospective, randomized, double-blind study was undertaken with the following aims:

1. To determine whether the adverse effects of epidural morphine can be selectively counteracted without affecting the analgesia.
2. To find the proper dosage to achieve this purpose.
3. To study the corresponding steady-state concentrations of naloxone and the plasma clearances.

Methods

Forty-five ASA class I or II patients scheduled for gallbladder surgery participated in the study, which was approved by the Ethics Committee of Örebro County Council. Informed consent was obtained from each patient.

The day before operation, the patient was informed about the anesthetic technique (epidural block combined with general anesthesia) and marking of the visual analog scale (VAS). Preoperative pulmonary function was assessed by chest x-ray, peak expiratory flow (PEF), and arterial blood gas analysis. PEF was recorded with the

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patient half-sitting and the best value of three measurements was registered. All patients were premedicated with 20–30 mg im dixyrazine (Esucos®), a neuroleptic and antiemetic agent belonging to the phenothiazine group.[8] Epidural block was performed with the patient in the sitting position. A Tuohy® needle was introduced at T10 and, with the bevel pointing cephalad, a Portex® catheter was introduced 3–4 cm after aspiration for spinal fluid or blood. To confirm successful placement and to provide analgesia during surgery, 8–10 ml of 2% mepivacaine was injected through the catheter. In all cases, the upper level of analgesia was T4–5. No further local anesthetic was injected in the epidural catheter. Anesthesia was induced by a sleep dose of thiopental and, following intubation using pancuronium, maintained by N_2O:O_2 and fractionated doses of 0.1–0.2 mg fentanyl. A radial artery was cannulated. All operations were performed *via* a subcostal incision. At the end of surgery, neuromuscular block was reversed by neostigmine and the patient extubated. Naloxone was avoided to treat any respiratory depression due to residual fentanyl effect; instead, the patient was ventilated until complete recovery of consciousness and breathing.

After surgery, the patients were nursed at the intensive care unit (ICU). When the patients started to complain of pain, postsurgical analgesia was provided by 4 mg preservative-free morphine in 10 ml saline injected in the epidural catheter. For 24 h after administration of epidural morphine, the ECG was monitored continuously and pulse, blood pressure, and respiratory frequency registered every 15 min. Samples were analyzed for arterial blood gases every 2 h for 24 h. All patients with a postoperative Pa_{O_2} below 75 mmHg (10 kPa) were given humidified nasal oxygen to maintain arterial oxygen tension near preoperative levels. PEF was recorded 6 and 24 h after surgery.

The patients were randomly divided into three groups of 15 each, and naloxone infusion was given in a double-blind fashion. Patients in group A received a bolus injection of 0.4 mg iv naloxone, followed by an iv infusion of naloxone at the rate of 10 $\mu g \cdot kg^{-1} \cdot h^{-1}$. Patients in group B were given half the dose (*i.e.*, 0.2 mg bolus injection followed by infusion of 5 $\mu g \cdot kg^{-1} \cdot h^{-1}$). Patients in group C received saline as a bolus injection and an infusion.

On the basis of randomization and the weight of the patient, the naloxone solution was freshly prepared by the hospital pharmacist and delivered to the ICU after surgery. The loading dose was delivered in a coded syringe and the infusion in a similarly coded 500-ml plastic infusion bag. The ICU staff, the patient, and the anesthetist all were unaware of the nature of the infusion drug.

The bolus injection was given 30 min after the relief of pain by epidural morphine. The iv injection was given slowly over a period of 5 min, after which the infusion was started through an automatic pump that infused 500 ml of the solution over 12 h at a constant rate.

Pain relief was assessed by VAS. Corresponding to the intensity of experienced pain, the patient placed a mark on a 10-cm vertical line, the bottom end of which represented "no pain," and the top end "worst possible pain." VAS was marked by the patient every hour on a new sheet of paper for 24 h. Reappearance of pain following naloxone bolus injection or infusion was treated by a second injection of epidural morphine and by im injection of 0.3–0.6 mg buprenorphine (a partial agonist–antagonist opiate) if the patient was still not pain-free. Sleep periods were considered pain-free, and a score of 0 was allotted. Analgesia also was assessed by direct questioning of the patient and was graded excellent, good, fair, or poor. (Analgesia was considered excellent when the patient was completely pain-free after a single injection of morphine epidurally, good when the patient required another injection, fair when additional analgesics were necessary (*e.g.*, buprenorphine), and poor when the patient had pain in spite of epidural morphine and im buprenorphine.) The ward nurse's assessment of pain relief also was noted.

The epidural catheter was removed 12 h after the last morphine injection. All analgesia after removal of the epidural catheter was provided by ketobemidone (Ketogin®), an opiate equipotent with morphine.* The duration of analgesia between injections of epidural morphine and the total number of analgesic injections before and during naloxone infusion and after removal of epidural catheter were noted. Requirement of additional analgesia before and after removal of epidural catheter also was noted. The total requirement of analgesia was noted for 48 h. PEF was repeated 6 and 24 h after the first epidural morphine injection. A 10-ml sample of blood was taken before surgery and 3, 4, and 5 h after start of naloxone infusion for the determination of plasma concentrations. The samples were centrifuged and the plasma was separated and stored frozen until assayed for naloxone.

The naloxone assays were performed blind with respect to patient naloxone dosage. Naloxone was determined using a modification of the RIA reported by Hahn *et al.*[9] An extraction step was included to remove the presence of any naloxone-3-glucuronide. The lower limit of sensitivity is 0.5 ng/ml when using a sample volume of 0.05

* Tamsen A: A patient-controlled analgesic therapy. The pharmacokinetics of three opiate analgesics in surgical patients and their relation between postoperative demand for analgesics and individual levels of endorphines and substance P in cerebrospinal fluid. Dissertation. Uppsala University, 1981.

TABLE 1. Patient Data

	Group A (n = 15) Naloxone infusion 10 $\mu g \cdot kg^{-1} \cdot h^{-1}$		Group B (n = 15) Naloxone infusion 5 $\mu g \cdot kg^{-1} \cdot h^{-1}$		Group C (n = 15) Saline infusion	
	Mean ± SEM	Range	Mean ± SEM	Range	Mean ± SEM	Range
Age (yr)	52 ± 3.8	29–75	53 ± 3.7	23–73	49 ± 3.4	26–69
Weight (kg)	71 ± 2.9	50–89	72 ± 5.4	46–133	75 ± 3.5	54–92
Sex (male/female)	3/12		5/10		2/13	
Duration of operation (min)	105 ± 15	50–285	96 ± 8.8	40–170	101 ± 8.7	40–180
Duration of anesthesia (min)	135 ± 15.2	60–310	125 ± 10.0	75–230	137 ± 10.4	70–240
Duration of hospitalization (days)	5.5 ± 0.6	(4–10)	5.7 ± 0.9	(3–16)	5.6 ± 0.6	(3–10)

ml of plasma. The coefficient of variation of 0.8 ng/ml is 5.4% and, at 20 ng/ml, 8.6%. The assay is highly specific and does not cross-react with any of the commonly used narcotic analgesics.

Untoward effects and complications were noted. Urinary retention was defined as the inability to micturate spontaneously within 6 h of surgery. The duration of hospitalization, which included the day of operation and the day of discharge, was recorded. The total plasma clearance of naloxone was calculated according to the equation:

$$Cl_{plasma} = K_0/C_{ss}$$

where C_{ss} was calculated as the average of the naloxone concentrations at 4 and 5 h. K_0 is the constant infusion rate. Analysis of variance was used for inter- and intragroup comparisons. The differences then were subjected to Mann-Whitney u-test. The results are expressed as mean ± SEM.

Results

There were no major differences among the three groups regarding age, weight, male:female ratio, duration of operation, or duration of anesthesia (table 1). After surgery, none of the patients required ventilatory assistance because no patient exhibited respiratory depression due to residual effects of fentanyl.

Pain Relief

All of the patients were kept pain-free by epidural morphine; the use of buprenorphine was not necessary in any patient. Statistical analysis of the 10-point VAS showed that all patients had somewhat high scores during the first 4–5 h postoperatively; the scores then improved, indicating effective analgesia (fig. 1). VAS scores among naloxone groups were not statistically different. However, the scores were significantly higher at 4, 6, 7, 12, and 23 h ($P < 0.05$) in the placebo group as compared to naloxone groups. All patients in the three groups rated their analgesia as good or excellent. Ward nurse assessment also indicated that none of the patients was dissatisfied with the pain relief. In addition, none of the patients complained of pain after bolus injection of naloxone. Three patients (20%) in the group receiving 10 $\mu g \cdot kg^{-1} \cdot h^{-1}$ naloxone infusion and four patients each in the other two groups were completely pain-free during the entire postoperative period following a single injection of 4 mg of morphine epidurally. In the remaining patients, the mean duration of epidural morphine analgesia was 13.7 ± 2.3 h in group A (10 $\mu g \cdot kg^{-1} \cdot h^{-1}$ naloxone), 17.8 ± 3.5 h in group B (5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ naloxone), and 18.5 ± 3.4 h in group C (saline).

The difference in duration of analgesia between group A (high-dose naloxone) and group C (placebo) was statistically significant ($P < 0.005$). This is reflected in the amount of morphine administered epidurally, *i.e.*, 9.6 ± 1.2 mg in group A, 6.4 ± 0.7 mg in group B, and 5.9 ± 0.5 mg in group C. During the 24-h postoperative period, additional analgesia by im ketobemidone after removal of epidural cathether was 1.3 ± 0.27 mg in group A, 1.3 ± 0.27 mg in group B, and 2.7 ± 0.53 mg in group C. In the next 24 h period, the requirement of ketobemidone was 1.7 ± 0.33 mg, 2.0 ± 0.4 mg, and 5 ± 1.0 mg in groups A, B, and C, respectively (table 2).

Respiration

The mean respiratory frequency during the 24-h postoperative period was lower in the placebo group. The reversal of respiratory depressant effect of epidural morphine was more marked in patients receiving the larger dose of naloxone. None of the patients in the two groups receiving naloxone had a respiratory rate below 10/min at any time during the 24-h postoperative period. While in the placebo group, three patients (20%) had respiratory

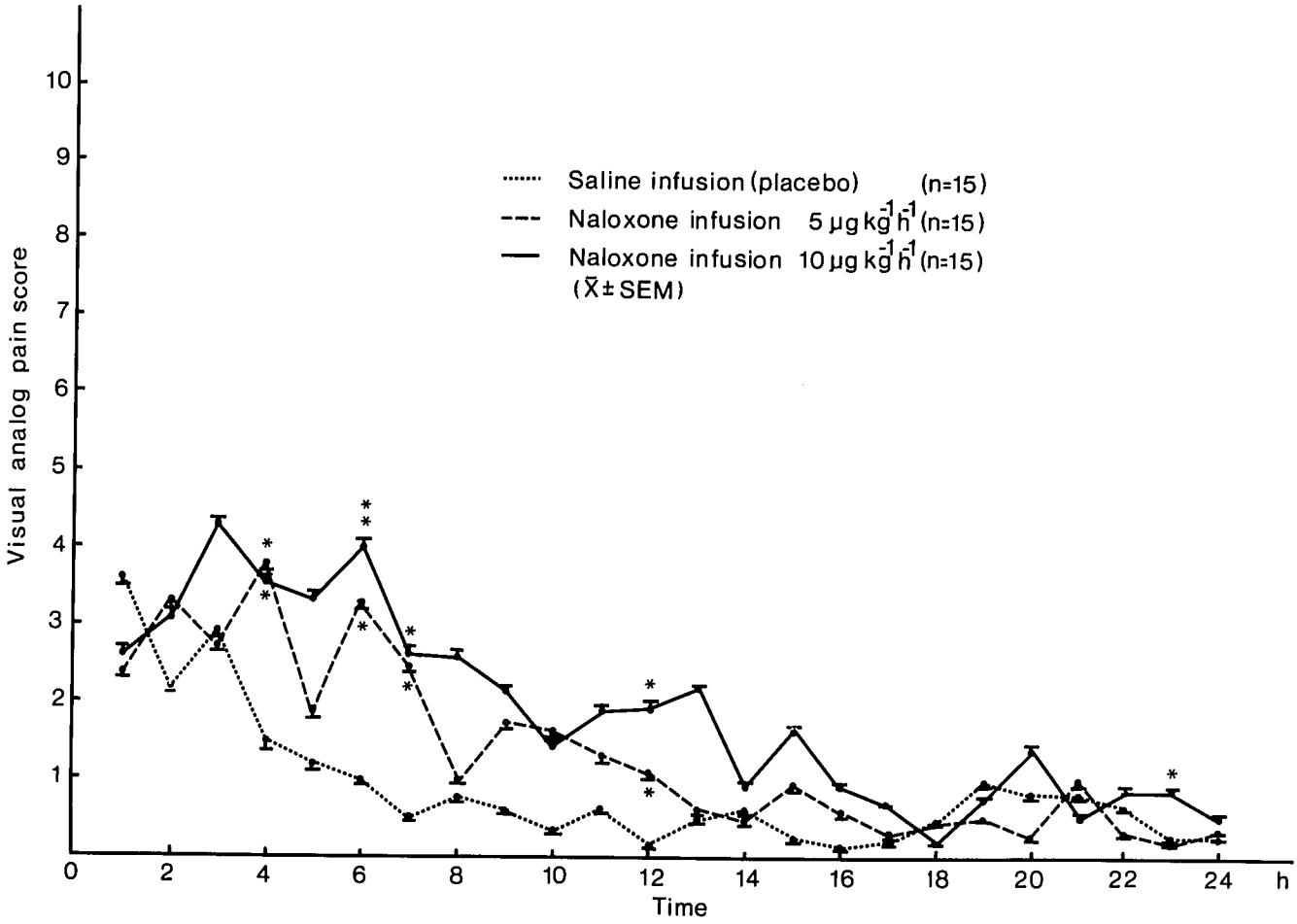

FIG. 1. Assessment of pain relief by visual analog scoring (VAS). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.
P values refer to differences between placebo and naloxone groups. For differences between naloxone groups, see text.

rates of 10 or below on different occasions during the 24-h period. The mean respiratory rate was highest in group A and lowest in group C (fig. 2). As compared to the placebo group, respiratory frequency was significantly higher from 5 to 17 h in group A ($P < 0.05$ to $P < 0.001$), and at 7, 8, 9, 10, 13, 14, and 16 h in group B ($P < 0.05$; fig. 2). Among the groups receiving naloxone, the differences were dose-dependently, significantly higher at 5, 10, 11, 12, 13, 15, and 17 h ($P < 0.05$).

As compared to preoperative values, all patients showed greater Pa_{CO_2} levels in the postoperative period. The Pa_{CO_2} was greatest in the placebo group and least in patients receiving 10 $\mu g \cdot kg^{-1} \cdot h^{-1}$ naloxone. Postoperative Pa_{CO_2} values in the placebo group were significantly

TABLE 2. Data on Analgesics and Pain Relief

	Group A (n = 15) Naloxone 10 $\mu g \cdot kg^{-1} \cdot h^{-1}$ Mean ± SEM	Group B (n = 15) Naloxone 5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ Mean ± SEM	Group C (n = 15) Saline Mean ± SEM
Number of patients completely pain-free after single injection	3 (20%)	4 (27%)	4 (27%)
Duration of analgesia (h)	13.7 ± 2.3*	17.8 ± 3.5	18.5 ± 3.4
Total dose of epidural morphine (mg)	9.6 ± 1.2	6.4 ± 0.7	5.9 ± 0.5
Additional analgesic† during first 24 h after surgery (mg)	1.3 ± 0.27	1.3 ± 0.27	2.7 ± 0.53
Additional analgesic† during next 24 h after surgery (mg)	1.7 ± 0.33	2.0 ± 0.4	5.0 ± 1.0

* $P < 0.01$ *versus* placebo values.

† Ketobemidone.

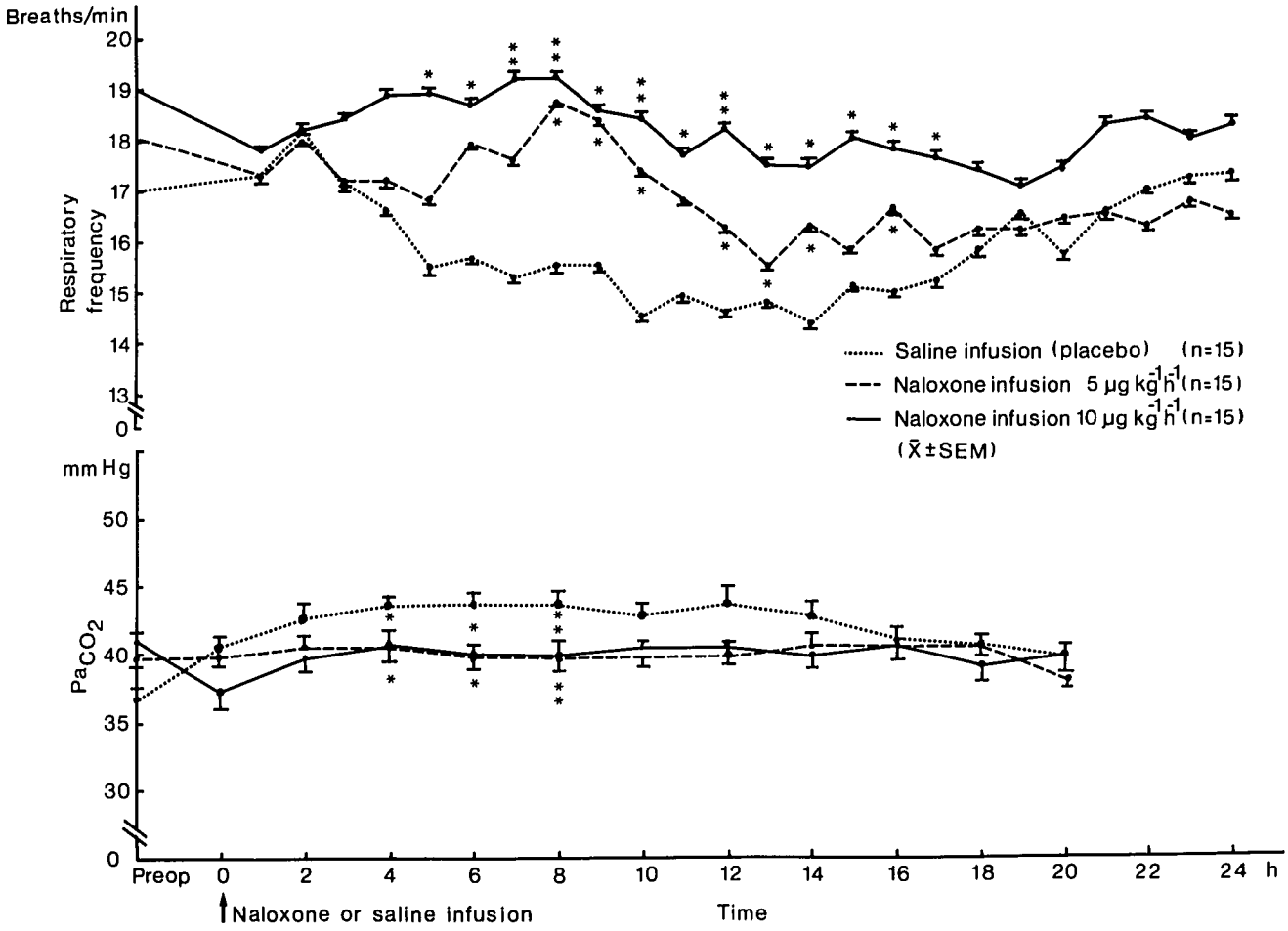

FIG. 2. Respiratory frequency and Pa_{CO_2} values (mean ± SEM) during 24 h following injection of epidural morphine. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$. P values refer to differences between placebo and naloxone groups. For differences between naloxone groups, see text. Hourly respiratory frequency values are mean values of respiratory frequencies at 15, 30, 45, and 60 min (1 kPa = 7.5 mmHg).

greater at 4, 6, and 8 h as compared to both naloxone groups ($P < 0.05$ and 0.01; fig. 2).

As compared to preoperative values, all patients showed a reduction of PEF 6 h after surgery. In group A, PEF decreased by 50%; in groups B and C, PEF decreased by 35%. Twenty-four h after surgery, some restoration of PEF values was noted. These changes were not statistically significant.

TABLE 3. Steady-state Kinetics of Naloxone

	Naloxone 5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ Mean ± SEM	Naloxone 10 $\mu g \cdot kg^{-1} \cdot h^{-1}$ Mean ± SEM
Plasma concentration (ng/ml)		
0 h	0.10 ± 0.027	0.07 ± 0.033
3 h	2.79 ± 0.42	4.29 ± 0.51
4 h	2.83 ± 0.28	5.30 ± 0.53
5 h	3.68 ± 0.71	5.07 ± 0.40
Plasma clearance ($ml \cdot min^{-1} \cdot kg^{-1}$)	30.5 ± 3.11	35.4 ± 3.33

STEADY-STATE KINETICS OF NALOXONE

The average steady-state concentrations of naloxone are shown in table 3. During the 3- to 5-h period, mean naloxone levels varied between 2.8–3.7 at the lower dose, and between 4.3–5.3 at the higher dose. The total plasma clearances averaged 30.5 ± 3.11 $ml \cdot min^{-1} \cdot kg^{-1}$ (low dose) and 35.4 ± 3.33 $ml \cdot min^{-1} \cdot kg^{-1}$ (high dose). The individual clearance values varied between 14.0 and 56.0 $ml \cdot min^{-1} \cdot kg^{-1}$.

UNTOWARD EFFECTS

Postoperative chest x-rays showed evidence of perenchymal infiltrations and/or basal atelectases in five of the 45 patients studied (11%). Three of these belonged to

TABLE 4. Influence of Naloxone Infusion on Adverse Effects of Epidural Morphine and on Postoperative Pulmonary Complications

	Group A (n = 15) Naloxone infusion 10 $\mu g \cdot kg^{-1} \cdot h^{-1}$		Group B (n = 15) Naloxone infusion 5 $\mu g \cdot kg^{-1} \cdot h^{-1}$		Group C (n = 15) Saline Infusion		
	No. of Patients	Percentage	No. of Patients	Percentage	No. of Patients	Percentage	Level of Significance
Urinary retention*	5	33	8	53	10	67	NS†
Pruritis	—	—	1	7	1	7	NS
Nausea/vomiting	1	7	2	13	3	20	NS
Pulmonary complications	1	7	1	7	3	20	NS

* Inability to micturate spontaneously within 6 h after surgery; †NS = not statistically significant.

the placebo group and one each to the groups receiving naloxone infusions (table 4). These differences were not statistically significant.

As compared to some recent reports, the incidence of postoperative nausea/vomiting and pruritis was generally low in this study (table 4). However, these untoward effects were seen least frequently in patients receiving naloxone. The number of patients who were unable to micturate spontaneously within 6 h of surgery were five (33%) in group A, eight (53%) in group B, and 10 (67%) in group C (table 4). Although naloxone appeared to dose-dependently reduce the risk of postoperative urinary retention, these differences were not statistically significant. No episodes of tachycardia, dysrythmias, hypertension, etc. were seen in any patient receiving naloxone bolus injection or infusion.

Discussion

A number of controlled studies have shown that analgesia by opiates injected epidurally is superior to that following the drugs given parenterally and to other alternatives for the management of postoperative pain.[1,4] In spite of the advantages of early ambulation, low risk of pulmonary complications, and shorter postoperative hospitalization,[3] the widespread use of this technique is restricted by the requirement of strict postoperative surveillance due to the rare but life-threatening risk of delayed respiratory depression.[4,5] The occurrence of adverse effects such as urinary retention, nausea/vomiting, and pruritis is another restriction. It has been reported that these untoward effects of epidural morphine are reversed by naloxone, while analgesia is unaffected.[4,7,10] However, controlled studied on this subject are lacking.

The present double-blind study shows that naloxone has a dose related antagonistic effect on epidural morphine induced analgesia. The duration of analgesia was unchanged in patients receiving 5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ naloxone, however, 10 $\mu g \cdot kg^{-1} \cdot h^{-1}$ doses of naloxone showed a partial but significant reversal of analgesia. In the latter group naloxone reduced the duration of analgesia by about 25% and consequently more frequent injections of epidural morphine were required to keep the patients pain-free. Larger doses of naloxone can be expected to reduce the duration further or even completely reverse the analgesia. Continuous infusions of naloxone over a 12 h period did not appear to influence the quality of analgesia. This is evidenced by the results of VAS and assessment of analgesia by the patients and wardnurses. Our results are in agreement with those of Brookshire *et al.* who reported non-reversal of intrathecal morphine labour analgesia by low dose (0.6 mg/h for 23 h) iv naloxone infusion.[11]

In this study, epidural morphine analgesia was associated with decreased respiratory frequencies and mild hypercapnia in the placebo group. Naloxone infusion prevented this tendency toward respiratory depression following epidural morphine. Thus, patients receiving naloxone infusion had consistently higher respiratory frequencies and lower Pa_{CO_2} values. The effects of naloxone on respiratory frequency were dose-dependent. A similar pattern was seen in our earlier CO_2 response studies in volunteers and in patients undergoing gallbladder surgery. In volunteers, 5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ iv naloxone infusion not only prevented the reduction in minute volume seen after epidural morphine, but increased it somewhat over control values. A 10 $\mu g \cdot kg^{-1} \cdot h^{-1}$ dose of naloxone caused a 35% increase in minute volume.[5] Similar effects of naloxone have been reported by Foldes *et al.*, who showed that 5 ug/kg doses reversed the respiratory depression following 20 μg/kg iv oxymorphone, and also caused a substantial increase in ventilation to above normal.[12]

Morphine and other opiates decrease the responsiveness of the respiratory centers to carbon dioxide. It is postulated that excessive occupancy of opiate receptors may assume pathological significance. Opiate antagonists are believed to resensitize the respiratory center to increase its sensitivity to carbon dioxide.[13]

Intermittent im injection of 0.4 mg naloxone has been reported to reverse respiratory depression following epidural morphine.[14] However, in view of the short half-life of naloxone in brain and serum, the agonist action of epidural morphine far outlasts the antagonist reversal of single or repeated doses of naloxone. Therefore, continuous iv infusion can be expected to more effectively maintain reversal of respiratory depression. In the present study, both 5 and 10 $\mu g \cdot kg^{-1} \cdot h^{-1}$ prevented postoperative respiratory depression after 4 mg epidural morphine. It is conceivable that weaker concentrations of naloxone are adequate for this purpose. Respiratory depression due to methadone and heroin overdose has been treated successfully by 2.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ naloxone.[15]

Postoperative urinary retention was seen in 67% patients receiving epidural morphine. This is considerably higher than the incidence previously reported in a similar group of patients,[1] probably due to this study's stricter definition of urinary retention (inability to micturate within 6 h of surgery). The reported incidence of urinary retention following epidural morphine varies from 15–100%.[16] The lack of information regarding definition of urinary retention, bladder catheterization routine, and the time interval between epidural morphine injection and catheterization makes comparisons difficult between different studies. This time interval is important because cystometric studies have shown that epidural morphine causes urinary retention due to detrusor relaxation, and that spontaneous recovery of urinary bladder function occurs after an average of 14–16 h.[16] The risk of postoperative urinary retention following epidural morphine may be reduced somewhat by infusing naloxone at the rate of 5 $\mu g \cdot kg^{-1} \cdot h^{-1}$; larger doses tended to have a more pronounced effect. However, in contrast to our earlier findings in volunteers,[16] complete prevention of urinary retention could not be achieved in the present study, possibly due to the residual effects of epidural block and/or anesthetic drugs and surgery.

After iv injection plasma naloxone levels decrease in a biexponential manner, with a half-life of the distribution phase of about 4 min.[17] In adult volunteers and patients, the terminal half-life of naloxone has been reported in the range of 1–2 h.[9,17–19] A somewhat longer half-life of 2.6–3.5 h is reported in newborns.[20] Therefore 90% of steady-state theoretically should be achieved within 3.3–6.6 h using a constant infusion rate. To shorten this period, an iv bolus was administered before starting the infusion in the present study. The steady-state levels of naloxone after the low (2.8–3.7 ng/ml) and high (4.3–5.3 ng/ml) dosage agree with data reported by Hahn *et al.*[9] The plasma clearance was 30.5 and 35.4 $ml \cdot min^{-1} \cdot kg^{-1}$ for the low and high doses, respectively. The interindividual variation in clearances was fourfold. The reported clearances are similar to clearance values of 16.1–34.6 $ml \cdot min^{-1} \cdot kg^{-1}$ in three patients reported by Hahn *et al.* and 1500–1667 ml/min reported in three subjects by Fishman 1973.[18]

Effective analgesia in spite of ongoing iv naloxone infusion is most likely due to a local high concentration of morphine near the site of action in the spinal cord. However, higher doses of iv naloxone appear to reverse analgesia in a dose-related manner. The partial reversal of epidural morphine analgesia by 10 $\mu g \cdot kg^{-1} \cdot h^{-1}$ presumably is due to displacement of morphine from the spinal opiate receptors. Still, larger doses given intravenously or smaller doses given in the epidural or subarachnoid space near receptor sites can be expected to completely reverse the analgesia. Our results are consistent with the observations in animal studies in rats and dogs suggesting that, at lower doses, naloxone binding takes place only at high affinity mu receptors, which mediate respiratory depression. Therefore, respiratory depression is antagonized but spinal analgesia, which is mediated by low affinity kappa receptors, is not affected. With larger doses, naloxone binding is believed to take place at mu as well as kappa receptors, leading to reversal of both respiratory depression and analgesia.[21]

In conclusion, our study shows that naloxone reverses epidural morphine analgesia in a dose-dependent fashion. Low-dose naloxone infusion (5 $\mu g \cdot kg^{-1} \cdot h^{-1}$) has no effect on analgesia, while larger doses (10 $\mu g \cdot kg^{-1} \cdot h^{-1}$) decrease the duration of analgesia by over 25%. Both doses of naloxone prevented respiratory depression following epidural morphine. The pharmacokinetic data show that naloxone is a high clearance drug with a four-fold, interindividual variation in clearance in postoperative patients.

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