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Prophylactic Oral Naltrexone with Epidural Morphine: Effect on Adverse Reactions and Ventilatory Responses to Carbon Dioxide

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The influence of two different doses of oral naltrexone on the adverse effects and the analgesia of epidural morphine were compared in a double-blind, placebo-controlled study. Forty-five patients undergoing cesarean section were provided postoperative analgesia with 4 mg epidural morphine. Five minutes later they received 6 mg naltrexone, 9 mg naltrexone, or placebo as an oral solution. Pain relief was assessed by the Visual Analog Scale (VAS) and by direct questioning of the patients. Requirement for additional analgesics and side effects were noted. Respiratory effects of epidural morphine and naltrexone were assessed using the ventilatory responses to CO_2 and by monitoring O_2 saturation (Spo_2) using pulse oximetry. All patients in the placebo group had adequate analgesia. One of the 15 patients who received naltrexone 6 mg had inadequate analgesia *versus* five of the 15 patients who received naltrexone 9 mg ($P < 0.05$), 9 mg *versus* placebo. Ten patients (67%) in the placebo group had pruritus while no patient in the 6 mg naltrexone group and one patient in the 9 mg group experienced mild pruritus ($P < 0.05$), placebo *versus* other two groups. The CO_2 response slopes were depressed compared to control values from 6–16 h in the placebo group, from 6–12 h in the 6 mg naltrexone group. No significant depression was noted in the 9 mg naltrexone group.

The authors conclude that oral naltrexone 6 mg significantly reduces the incidence of pruritus associated with epidural morphine without affecting analgesia and that 9 mg naltrexone is associated with shorter duration of analgesia than 6 mg naltrexone. (Key words: Anesthesia: obstetric. Anesthetic technique: epidural. Analgesics: morphine. Antagonists, opioid: naltrexone. Pain: postoperative.)

THE TREATMENT of acute and chronic pain by epidural or intrathecal injection of opioids has gained widespread use.[1] However, the technique is associated with a high incidence of side effects.[2–4] Respiratory depression and other adverse effects such as pruritus can be reversed or attenuated by naloxone.[5,6] Naloxone has a short duration of action such that multiple iv injections or continuous infusions are necessary.[6,7] Naltrexone is a long-acting orally administered opiate antagonist that produces plasma concentrations up to 24 h following a single oral administration.[8] This prospective randomized, double-blind study is undertaken with the following objectives.

1) To determine whether the adverse effects of epidural morphine can be selectively counteracted with naltrexone without affecting the analgesia; and 2) To find the proper dosage of naltrexone to achieve this purpose.

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Materials and Methods

We studied 45 healthy women at term who underwent cesarean delivery with epidural anesthesia. Indications for cesarean section are listed in table 1. Informed consent was obtained from each patient and the study was approved by the Committee on Human Research. Only healthy patients with no medical complications were included in the study.

For anesthesia during cesarean section, 2% lidocaine with 1:200,000 epinephrine was given through a lumbar epidural catheter inserted *via* the L2-3 or L3-4 interspace. These catheters were left in place after surgery. When patients first requested pain relief after surgery, they were given 4 mg of epidural morphine diluted in 8 ml of saline. Patients were randomly assigned using a randomized table to receive one of three oral regimens in a double-blind fashion: 6 mg of naltrexone (n = 15), 9 mg of naltrexone (n = 15), or placebo (n = 15). Naltrexone or placebo was given as oral solution in 20 ml volume 5 min after administration of epidural morphine. The solution was prepared by an anesthesiologist not involved in the study.

The intensity of pain and pain relief were assessed using a visual linear analog scale (VAS).[9] This scale consisted of a 10-cm line on which the patient represented the degree of pain she was experiencing by placing a point somewhere between "no pain" and "the worst pain I have ever experienced." Each patient made such an assessment immediately before administration of morphine and again at .5, .75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, and 24 h afterward. Onset of analgesia was defined as the time from administration of morphine until patient obtained at least 50% pain relief as determined by the VAS. Maternal respiratory rate, blood pressure and heart rate, appearance of adverse effects, including pruritus, nausea, vomiting, respiratory depression (*i.e.*, respiratory rate of less than 10 breaths per min), somnolence, and herpes simplex virus labialis (HSVL) were also noted and recorded at the same time by a trained anesthesia research fellow. At the end of the 24-h observation period or at the time of remedication, the patient and the same observer each gave a global assessment of the overall effectiveness of the analgesic treatment as follows:

TABLE 1. Indication for Cesarean Section

	Placebo n = 15	Naltrexone 6 mg n = 15	Naltrexone 9 mg n = 15
Elective cesarean section	1	0	1
Repeat cesarean section	3	2	2
Breech and transverse	—	—	—
Presentation	3	5	7
Failure to progress	8	4	3
Twin gestation	0	0	1
Macrosomia	0	2	1
Fetal distress	0	2	0

No significant difference between groups.

1 = poor relief;
2 = fair relief;
3 = good relief;
4 = excellent relief.

Possible respiratory effects of morphine and naltrexone were assessed according to the ventilatory responses to progressive hypercapnea using a modified Read's rebreathing technique[10] with a computer-controlled data acquisition system.[11] Baseline measurements were obtained before administration of morphine and repeated at 1.5, 3, 6, 12, 16, and 24 h if the patient stayed in the study. Hemoglobin oxygen saturation (Sp_{O_2}) was also recorded continuously using a pulse oximeter.

If patients requested additional analgesia, an opioid was administered intramuscularly and assessments of pain relief and ventilatory measurements were discontinued. Patients were observed for 24 h for the occurrence of adverse side effects.

Statistical analysis of data was performed using: 1) analyses of variance for comparison between groups; 2) paired *t*-test to compare data to control values within the same group (*P* value adjustments were made for multiple comparisons); and 3) chi-squared test to compare the incidence of side effects between groups using raw data. Differences were considered statistically significant when $P < 0.05$. Incremental dropping of patients data was taken into account during the statistical analyses.

TABLE 2. Demographic Data

	Placebo n = 15	Naltrexone 6 mg n = 15	Naltrexone 9 mg n = 15
Maternal age (yr)	29.9 ± 6.9*	25.3 ± 4.9	25.5 ± 4.4
Maternal weight (kg)	72.1 ± 10.5	71.4 ± 9.6	69.9 ± 9.2
Maternal height (cm)	155.7 ± 5.9	154.4 ± 8.2	156.6 ± 6.7
Gestational age (wk)	39.4 ± 2.4	40.6 ± 0.8	39.1 ± 1.9
Parity			
Nulliparous	3	8	3
Multiparous	12	7	12

Values are mean ± SD.
* $P < 0.05$ compared to the other two groups.

TABLE 3. Pain Relief Data

	Placebo n = 15	Naltrexone 6 mg n = 15	Naltrexone 9 mg n = 15
Onset of analgesia (h)	0.7 ± 0.4	0.8 ± 0.5	0.7 ± 0.4
Duration of analgesia (h)	28.0 ± 11.7	33.2 ± 17.2*	19.8 ± 14.7
Number of patients remedicated during first 24 h	3	2	8
Number of patients remedicated† during first 72 h	7	5	10
Time to first remedication	30.0 ± 13.6*	24.8 ± 12.8	19.1 ± 9.9
Satisfactory (3+ and 4+) analgesia scores (%)			
Observer	93*	93	67
Patient	93*	93	67

Values are mean ± SD.
* $P < 0.05$ compared to the 9 mg naltrexone group.
† Patient remedicated during first hours included.

Results

Indications for cesarean section are listed in table 1. Table 2 summarizes patients' characteristics. These characteristics differed between groups only with respect to maternal age.

Tables 3 and 4 and figure 1 presents pain relief data. All but one patient in the placebo group had good analgesia with a mean duration of 28 ± 12 h ($\bar{X}$ ± SD). Mean duration of analgesia was significantly shorter in the 9 mg naltrexone group compared to that in the 6 mg group, 20 ± 15 *versus* 33 ± 17 h ($\bar{X}$ ± SD), respectively; $P < 0.05$ but did not differ significantly from the placebo group. One patient in the placebo group had unsatisfactory analgesia due to severe pruritus. One patient in the 6 mg naltrexone group and five patients in the 9 mg naltrexone group had unsatisfactory analgesia ($P < 0.05$). Onset of analgesia did not differ significantly between the three groups. All patients who required supplemental analgesics had good pain relief after intramuscular administration of meperidine or morphine.

SIDE EFFECTS

Table 5 summarizes data on the incidence of side effects, including pruritus, herpes simplex virus labialis, nausea, vomiting, and somnolence. Urinary retention could not be assessed because catheters in the urinary bladder were left in place for approximately 24 h postoperative. Ten of 15 patients who received placebo had pruritus. None of the patients in the 6 mg naltrexone group experienced any pruritus and one patient in the 9 mg group developed mild pruritus around the face and the body 6 h after administration of epidural morphine

TABLE 4. Visual Analog Pain Scores after Epidural Morphine with and without Prophylactic Oral Naltrexone

	Placebo n = 15	Naltrexone 6 mg n = 15	Naltrexone 9 mg n = 15
Control	9.0 ± 0.3 n = 15	9.2 ± 0.3 n = 15	8.3 ± 0.4 n = 15
0.5 h	5.2 ± 0.7 n = 15	5.1 ± 0.7 n = 15	4.9 ± 0.8 n = 15
0.75 h	4.0 ± 0.6 n = 15	4.5 ± 0.8 n = 15	3.5 ± 0.8 n = 15
1.0 h	2.8 ± 0.6 n = 15	3.4 ± 0.8 n = 15	2.6 ± 0.6 n = 15
1.5 h	2.3 ± 0.6 n = 15	2.7 ± 0.7 n = 15	2.7 ± 0.7 n = 15
2.0 h	2.1 ± 0.6 n = 15	1.4 ± 0.4 n = 14	2.1 ± 0.6 n = 14
2.5 h	2.1 ± 0.5 n = 15	1.1 ± 0.4 n = 14	2.0 ± 0.7 n = 13
3.0 h	1.9 ± 0.6 n = 15	0.9 ± 0.4 n = 14	1.8 ± 0.8 n = 12
4.0 h	1.3 ± 0.4 n = 15	0.7 ± 0.3 n = 14	0.6 ± 0.3 n = 10
6.0 h	1.4 ± 0.6 n = 15	0.7 ± 0.3 n = 14	0.6 ± 0.4 n = 10
8.0 h	1.0 ± 0.6 n = 15	0.5 ± 0.2 n = 14	0.3 ± 0.2 n = 10
12.0 h	0.4 ± 0.2 n = 14	0.8 ± 0.3 n = 14	0.4 ± 0.3 n = 10
16.0 h	0.6 ± 0.3 n = 14	0.7 ± 0.3 n = 14	0.4 ± 0.3 n = 10
24.0 h	2.3 ± 0.7 n = 14	1.0 ± 0.3 n = 14	0.8 ± 0.4 n = 9

No significant differences between groups.
Values are mean ± SEM.

and she had excellent pain relief. One patient in the placebo group developed HSVL lesions on the mouth 2 days after administration of morphine.

TABLE 5. Number of Patients with Side Effects

	Placebo n = 15	Naltrexone 6 mg n = 15	Naltrexone 9 mg n = 15
Pruritus	10 (67%)*	0 (0%)	1 (7%)
Nausea	3 (20%)	0 (0%)	1 (7%)
Vomiting	1 (7%)	0 (0%)	1 (7%)
Somnolence	15 (100%)	13 (87%)	13 (87%)
Herpes simplex virus labialis	1 (7%)	0 (0%)	0 (0%)

* $P < 0.05$ compared to the other two groups.

OXYGEN SATURATION

Table 6 summarizes data for the Sp_{O_2}. Fourteen patients in the placebo group had periods of Sp_{O_2} between 90–95, and in four patients Sp_{O_2} decreased below 90 which increased after O_2 was given *via* mask. None of the patients in the two naltrexone groups had any Sp_{O_2} below 90.

CARBON DIOXIDE RESPONSE TEST

CO_2 response curves were obtained in patients up to 24 h or up to the time of remedication. Complete sets of CO_2 response curves were not obtained in one patient in each of the three groups due to lack of patient cooperation. Table 7 shows depression of the CO_2 response slope in the placebo group from 6–16 h, and from 6–12 h in the 6 mg naltrexone group compared with control values. No depression of the slopes was noted in the 9 mg naltrexone group. Significant reduction in VE50 was noted in all groups compared to baseline values with no significant differences between groups (table 7).

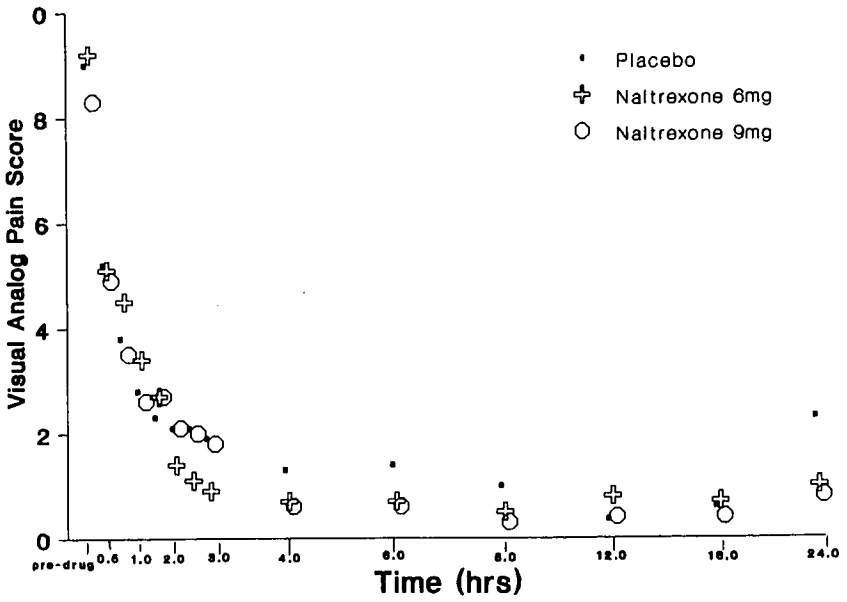

FIG. 1. Time course of analgesia expressed as mean pain scores with epidural morphine with and without oral naltrexone. One patient in 6 mg naltrexone group and five patients in the 9 mg naltrexone groups did not remain in the study due to unsatisfactory analgesia.

TABLE 6. Hemoglobin Saturation (Sp_{O_2})

	Placebo n = 15	Naltrexone 6 mg n = 15	Naltrexone 9 mg n = 15
Number (%) of patients with saturation episodes of 90–95%	14 (93%)	10 (67%)	11 (73%)
Number (%) of patients with saturation episodes of < 90%	4 (27%)	0 (0%)	0 (0%)

No significant differences between groups.

Discussion

Results from the present study indicate that oral naltrexone 6 and 9 mg decreased the incidence of pruritus, and that 9 mg attenuated the respiratory depressant effects of epidural morphine on the ventilatory response to carbon dioxide. The 6 mg naltrexone did not diminish the quality or the duration of analgesia, except in one patient who did not get adequate pain relief. However, analgesia was antagonized with the 9 mg dose in five of 15 patients. Results from our study indicate that good postoperative analgesia could be obtained using only 4 mg epidural morphine. However, the incidence of pruritus was similar to that reported with 5 mg of morphine.[12]

Naltrexone is a potent opioid antagonist that is 17 times more potent than nalorphine and approximately twice as potent as naloxone.[13] It is effective orally and has a long duration of action. After oral administration it is rapidly absorbed from the gastrointestinal tract and reaches peak plasma concentrations in one hour.[8] Naltrexone has been administered in doses of 50 mg per day without apparent side effects.[14,15] A large portion of the oral dose undergoes rapid first-pass metabolism; the remaining portion is distributed into tissues in equilibrium with plasma and is subsequently released slowly from the tissues back into the plasma.[16]

Respiratory depression and other adverse effects of epidural opioids can be reversed by naloxone.[1,5,6,17,18] However, naloxone has a short duration of action and multiple iv injections or continuous infusion are often recommended.[6,7] There have been conflicting reports of the value of naloxone infusions in preventing the side effects associated with epidural morphine. Rawal, *et al.*[5] reported that 5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ of naloxone infusion prevented the respiratory depressant effects of epidural morphine without affecting the analgesia. On the other hand, naloxone infusions at a rate of 100 μg/hr failed to prevent the side effects of epidural morphine in post-cesarean section patients.[7] Gowan *et al.* also reported that naloxone infusions at three different dosages of 0.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$, 2.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$, or 4.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$ did not prevent the side effects associated with epidural morphine in post-thoracotomy patients.[19] In addition, the low cost of oral naltrexone can ease the economic burden that continuous infusion of naloxone places on patients and hospitals.

Results from the present study are in agreement with those previously reported by Mok *et al.* who also found that 6 mg of oral naltrexone significantly attenuated the side effects of epidural morphine in female patients scheduled for elective abdominal surgery. Pretreatment with naltrexone significantly decreased the incidence of pruritus, vomiting, dizziness, and urinary retention associated with epidural morphine without affecting the analgesia.[20] Effective analgesia, in spite of oral naltrexone, is most likely due to high concentration of morphine near the site of action in the spinal cord. However, a higher dose of naltrexone (9 mg) appears to antagonize analgesia, presumably due to displacement of morphine from the spinal opiate receptors. Naltrexone, a pure antagonist, binds as a competitive antagonist at the opiate receptors.[21]

In conclusion, our study shows that 6 mg naltrexone has no significant effect on analgesia. Both doses of naltrexone decreased the incidence of pruritus. Further studies are needed to evaluate the efficacy of oral nal-

TABLE 7. CO_2 Response Slopes ($l \cdot min^{-1} \cdot mmHg^{-1}$) and VE50 Minute Volume (l/min) at a Pa_{CO_2} 50 mmHg after Epidural Morphine with and without Prophylactic Oral Naltrexone

	Placebo n = 15	Naltrexone 6 mg n = 15	Naltrexone 9 mg n = 15	*P* Values Between Groups
Control				
Slope	2.0 ± 0.2	1.5 ± 0.2	1.6 ± 0.1	NS
VE50	32.0 ± 3.6	23.4 ± 2.3	25.7 ± 1.9	NS
	n = 15	n = 15	n = 15	
1.5 h				
Slope	1.8 ± 0.2	1.3 ± 0.1	1.4 ± 0.1	
VE50	20.5 ± 2.6†	15.6 ± 1.4†	18.4 ± 2.3†	NS
	n = 15	n = 15	n = 15	
3 h				
Slope	1.8 ± 0.3	1.2 ± 0.2	1.5 ± 0.2	NS
VE50	16.0 ± 2.6†	15.3 ± 1.8†	19.2 ± 3.1*	NS
	n = 15	n = 13	n = 11	
6 h				
Slope	1.4 ± 0.2*	1.0 ± 0.1*	1.4 ± 0.2	NS
VE50	14.0 ± 1.6†	14.9 ± 1.5†	17.0 ± 2.8†	NS
	n = 15	n = 14	n = 10	
12 h				
Slope	1.3 ± 0.3*	1.0 ± 0.1*	1.5 ± 0.3	NS
VE50	13.8 ± 1.6†	15.1 ± 1.7†	19.6 ± 3.9*	NS
	n = 14	n = 13	n = 10	
16 h				
Slope	1.2 ± 0.2†	1.1 ± 0.1	1.7 ± 0.4	NS
VE50	16.2 ± 2.3†	13.9 ± 1.6†	21.1 ± 3.9	NS
	n = 14	n = 14	n = 10	
24 h				
Slope	1.6 ± 0.2	1.0 ± 0.1	1.6 ± 0.3	
VE50	20.6 ± 2.6†	13.2 ± 1.7†	18.9 ± 3.5†	NS
	n = 14	n = 13	n = 9	

Values are mean ± SEM.
* $P < 0.05$ compared to control values.
† $P < 0.01$ compared to control values.

trexone prophylaxis when using intrathecal morphine or with other intraspinal opioids.

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