

# *Analgesic and Respiratory Depressant Activity of Nalbuphine: A Comparison with Morphine*

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To compare the respiratory depressant and analgesic effects of nalbuphine and morphine, six healthy male subjects were given the drugs as single 0.15-mg/kg doses, and as four successive doses of 0.15 mg/kg. Respiratory depression was monitored by ventilatory and mouth occlusion pressure responses during CO<sub>2</sub> rebreathing, while analgesia to experimental pain was tested with the submaximal effort tourniquet ischemia test. When given as single 0.15-mg/kg doses, both drugs significantly increased the threshold and tolerance for experimental pain. The analgesic effect was similar for both drugs at this dosage, as was depression of the ventilatory and occlusion pressure responses to CO<sub>2</sub>. Morphine administered in multiple doses progressively increased pain tolerance from 30 ± 13% above control with the first dose of 0.15 mg/kg to 107 ± 13% above control after the fourth dose (cumulative total 0.60 mg/kg). Nalbuphine produced a 40 ± 12% increase in pain tolerance with an initial dose of 0.15 mg/kg, but additional increments of nalbuphine did not result in significantly greater analgesia. The increasing morphine dosage was associated with progressive rightward displacement and ultimately decreases in the slope of the CO<sub>2</sub> response curves. Nalbuphine produced an initial rightward displacement of the CO<sub>2</sub> response curves similar to morphine, but continued administration of the drug did not result in further displacement or changes in slope. These findings demonstrate that nalbuphine, in contrast to morphine, exhibits a ceiling effect for respiratory depression which is paralleled by its limited analgesic effect on experimental pain. (Key words: Analgesics: morphine; nalbuphine. Carbon dioxide: ventilatory response. Pain: experimental, measurement. Ventilation: airway occlusion pressure; carbon dioxide response.)

ANALGESIA produced by the classical opiod, morphine, is associated with depression of ventilation in direct proportion to drug dosage.<sup>1</sup> This essentially additive respiratory effect does not appear to be shared by analgesics possessing combined agonist-antagonist activity. These drugs have instead demonstrated a ceiling effect for respiratory depression with increasing doses.<sup>2</sup> Nalbuphine, a recently introduced agonist-antagonist analgesic, is considered to have analgesic potency similar to morphine in common clinical doses of 10 mg or less.<sup>3</sup> This comparison of analgesia was made in postoperative patients who experienced pain stimuli of varying intensity.

Recent work in healthy volunteers utilizing cumulative doses more than four times as great, suggests that nalbuphine, unlike morphine, produces a ceiling effect for respiratory depression.<sup>4</sup> The authors assumed that such nalbuphine doses were equi-analgesic with morphine, and thus possessed a therapeutic advantage. However, no such data concerning the relative analgesic potency of higher doses of nalbuphine are available. There have been no controlled studies which have compared the analgesic potencies of nalbuphine and morphine, particularly with concurrent measurements of respiratory depression.

This study was performed to compare directly the respiratory depressant and analgesic effects of these two drugs at both high and low dosage levels. We did this by measuring responses to CO<sub>2</sub>-stimulated breathing while also assessing responses to a form of experimental pain known to identify the analgesic effects of morphine.<sup>5</sup>

## Methods

Six healthy non-smoking male volunteers (ages 22–30 years) served as subjects for the study. All had normal baseline pulmonary function and gave informed consent for the study, which was approved by the Human Studies Committee of the University of Virginia. All subjects were tested while they were in the supine position. Experimental pain was produced by a modification of the submaximal effort tourniquet-induced ischemia test.<sup>5</sup> The subject's arm was exsanguinated by application of an Esmarch bandage prior to inflating a tourniquet on the upper arm to a pressure of 250 mmHg. Following one minute of ischemia, the subject squeezed a hand-held rubber ball once each second for an additional minute and then placed the arm at his side. A stopwatch recorded the times from the inflation of the tourniquet to the point at which subjects initially sensed pain (threshold) and the point at which pain became unbearable (tolerance). Three such trials prior to administration of the analgesic drugs served as controls for each day's experiment.

The ventilatory response to carbon dioxide was measured by Read's rebreathing method.<sup>6</sup> Subjects rebreathed 6–7 liters of a mixture of 7% CO<sub>2</sub> and 93% O<sub>2</sub> from an electronic spirometer (Model 840, Ohio Medical Products) which measured flow and volume. End-tidal carbon dioxide tension (PET<sub>CO<sub>2</sub></sub>) was measured

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by an infrared analyzer (Beckman LB-2®). Subjects breathed through a circuit divided into inspiratory and expiratory limbs by a unidirectional two-way J valve (Warren E. Collins). The circuit resistance was  $2 \text{ cmH}_2\text{O} \cdot \text{l}^{-1} \cdot \text{s}$  linear to a flow of 4 l/s. During rebreathing runs which lasted 5–6 min, the inspiratory limb was occluded at 30-s intervals by closing a stopcock as subjects breathed out through the expiratory limb. The pressure generated by the respiratory muscles during the first 0.1 s of occlusion ( $P_{0.1}$ ) was measured at the mouth with a differential pressure transducer (Validyne MP-45, range  $\pm 50 \text{ cmH}_2\text{O}$ ). This occlusion pressure represents a mechanical transform of respiratory center output which rises linearly with  $\text{CO}_2$ , but unlike minute ventilation, is not affected by the mechanical characteristics of the respiratory system.<sup>7</sup> Minute ventilation ( $\dot{V}_E$ ) was calculated from the average of tidal volume ( $V_T$ ) and frequency ( $f$ ) for the three breaths preceding such occlusion. Since  $f$  is inversely related to total respiratory cycle duration ( $T_{\text{tot}}$ ), it was calculated as the reciprocal of the total cycle duration times 60 (*i.e.*,  $f = 1/T_{\text{tot}} \times 60$ ). Other indices of respiratory timing calculated from the three breaths preceding each occlusion included the duration of inspiration ( $T_i$ ) and the mean inspiratory flow rate ( $\dot{V}_T/T_i$ ).

Ventilatory responses were analyzed by computing by least-squares linear regression the slope responses relating changes in  $\dot{V}_E$  to  $\text{PET}_{\text{CO}_2}$  ( $\Delta\dot{V}_E/P_{\text{CO}_2}$ ), and changes in occlusion pressure to  $\text{PET}_{\text{CO}_2}$  ( $\Delta P_{0.1}/P_{\text{CO}_2}$ ). To detect any changes in  $\text{CO}_2$  sensitivity not reflected as a change in slope, we also examined changes in  $\dot{V}_E$  and  $P_{0.1}$  during rebreathing at a fixed elevated level of  $\text{CO}_2$  ( $\text{PET}_{\text{CO}_2} = 60 \text{ mmHg}$ ). This point was chosen because it was encompassed by response curves in all subjects so that  $\dot{V}_{E60}$  and  $P_{0.160}$  could be derived by interpolation rather than extrapolation. Control measurements of  $\text{CO}_2$  response were made in duplicate. The reproducibility of slope measurements in individual subjects was estimated from the difference between these duplicate measurements to reflect within subject scatter. The mean within subject standard deviation for slope was  $0.24 \text{ l} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$ , giving a coefficient of variation of about 9%.

During all experiments, ECG and heart rate were monitored continuously and blood pressure was checked intermittently. Subjects were asked to describe any subjective effects after each drug administration. To provide a route for drug infusion, a 20-gauge catheter was placed in a vein in the foot. An 18-gauge catheter was placed in the arm opposite the tourniquet for sampling of venous blood to determine plasma levels of each drug. Analyses for nalbuphine and morphine were performed with a high-pressure liquid chromatograph (Bioanalytical Systems, Inc.).<sup>8</sup> A modification of this

technique was used for nalbuphine analyses (see appendix).

To observe the effects of a single low drug dose, subjects were studied on each of two separate days (at least 4 days apart), and received blindly by random allocation, either 0.15 mg/kg morphine or 0.15 mg/kg nalbuphine intravenously. Subjects were tested prior to drug administration (control), 30 min after each drug, hourly for four hours, and finally, 10 min after receiving 0.4 mg naloxone intravenously.

The effects of larger cumulative drug doses were evaluated in a multiple dose study. Subjects were studied on two separate days, at least seven days apart, and again received either morphine or nalbuphine in single-blind random sequence. The drugs were administered intravenously as four successive doses, 0.15 mg/kg each (total dose 0.60 mg/kg), at intervals 30–40 minutes apart. Subjects were tested prior to drug administration and after each drug increment. The testing sequence in each subject was started 15 min after each dose, and consisted of blood sampling, measurement of analgesia, and finally,  $\text{CO}_2$  rebreathing. Naloxone, 0.4 mg, was administered intravenously to subjects 15 min after completing measurements with the final analgesic dose. The response to pain was again tested 10 min after this naloxone dose. Additional naloxone doses (0.4 mg, im, and 0.4 mg, iv) were administered prior to the subjects' departure from the laboratory.

Results are expressed as means  $\pm$  SEM. Differences between control and treatment states and between the two drugs were analyzed with Student's *t* test for paired data utilizing Bonferroni's correction<sup>9</sup>;  $P < 0.05$  was considered significant.

## Results

Control values for tolerance to experimental pain prior to nalbuphine ( $8.5 \pm 1 \text{ min}$ ) and morphine ( $9 \pm 0.8 \text{ min}$ ) were increased when both drugs were given as single 0.15-mg/kg doses (fig. 1). Significant increases in tolerance were noted between one-half and two hours after injection. Changes in pain threshold (not pictured) followed a similar pattern of increase from control values of  $2.8 \pm 0.2 \text{ min}$  with nalbuphine, and  $3.0 \pm 0.4 \text{ min}$  with morphine. The analgesic effects of nalbuphine at this dose did not differ significantly from those of morphine ( $P > 0.05$ ). Plasma concentrations of morphine averaged 76 ng/ml one hour after injection, and exhibited a rate of decay corresponding to a half-life of 90 min. Nalbuphine levels at the same point (21 ng/ml) were significantly lower ( $P < 0.01$ ) and showed a slower rate of decay with a half-life of 186 minutes.

The respiratory effects of these single 0.15-mg/kg doses followed a time course similar to the analgesia

(fig. 1, lower half). Neither drug significantly altered the slopes of the ventilatory or occlusion pressure responses to  $\text{CO}_2$ , but each produced a rightward displacement of the same curves. This was reflected by significant decreases in  $\dot{V}_E$  and  $P_{0.1}$  at  $P_{\text{CO}_2}$  of 60 mmHg. Although mean values for  $P_{0.1}$  and  $\dot{V}_E$  were slightly lower after morphine, the differences between the two drugs were not significant. Naloxone administration returned ventilatory parameters and analgesia to control levels.

When the drugs were administered as multiples of the 0.15-mg/kg dose, plasma levels progressively increased (fig. 2). Plasma nalbuphine concentration increased from  $24 \pm 3$  ng/ml with the first dose, to  $62 \pm 4$  ng/ml after the last dose. Morphine levels were significantly higher ( $P < 0.01$ ) after each dose, increasing from  $47 \pm 2$  ng/ml to  $85 \pm 2$  ng/ml.

The respiratory changes resulting from these multiple drug doses are depicted in fig. 3. The slope of the  $\text{CO}_2$  response curve ( $\Delta\dot{V}_E/P_{\text{CO}_2}$ ) did not vary significantly from its control value of  $3.1 \pm 0.3 \text{ l} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$  with incremental doses of nalbuphine. Morphine administration produced a decrease in slope only after the final dose (cumulative total 0.60 mg/kg). The slope at this time was  $2.4 \pm 0.2 \text{ l} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$ , a value significantly lower than all preceding values ( $P < 0.01$ ). The changes in the occlusion pressure response ( $\Delta P_{0.1}/P_{\text{CO}_2}$ ) followed a similar pattern. Control slope ( $0.52 \pm 0.04 \text{ cmH}_2\text{O}/\text{mmHg}$ ) was essentially unchanged after all nalbuphine doses, while the final morphine dose produced a significant decrease ( $P < 0.01$ ) to  $0.40 \pm 0.04 \text{ cmH}_2\text{O}/\text{mmHg}$ . Drug effects on the position of the response curves were more pronounced (fig. 3, right panel). Control  $\dot{V}_{E60}$  for nalbuphine ( $34 \pm 7 \text{ l/min}$ ) and morphine ( $36 \pm 8 \text{ l/min}$ ) decreased significantly ( $P < 0.01$ ) with the initial 0.15-mg/kg dose to  $19 \pm 5 \text{ l/min}$  and  $15 \pm 3 \text{ l/min}$ , respectively. Additional doses of nalbuphine did not further decrease  $\dot{V}_{E60}$  such that the value recorded after the total dose of 0.60 mg/kg ( $18 \pm 6 \text{ l/min}$ ) was not significantly different ( $P > 0.1$ ) from that noted after any of the previous doses. Changes in  $P_{0.160}$  followed a similar pattern. Incremental morphine doses did not elicit this plateau effect, but instead, progressively reduced  $\dot{V}_{E60}$  and  $P_{0.160}$ . Both parameters were significantly lower ( $P < 0.01$ ) after the last two doses compared with nalbuphine.

Respiratory patterns during rebreathing are compared (table 1) between control and after maximum dosage (0.60 mg/kg) of both drugs. Neither morphine nor nalbuphine consistently altered indices of respiratory timing such as  $f$ ,  $T_i$ , and  $T_{\text{tot}}$ . Morphine, however, was associated with a significant decrease ( $P < 0.01$ ) in the ratio of inspiratory time to total respiratory cycle

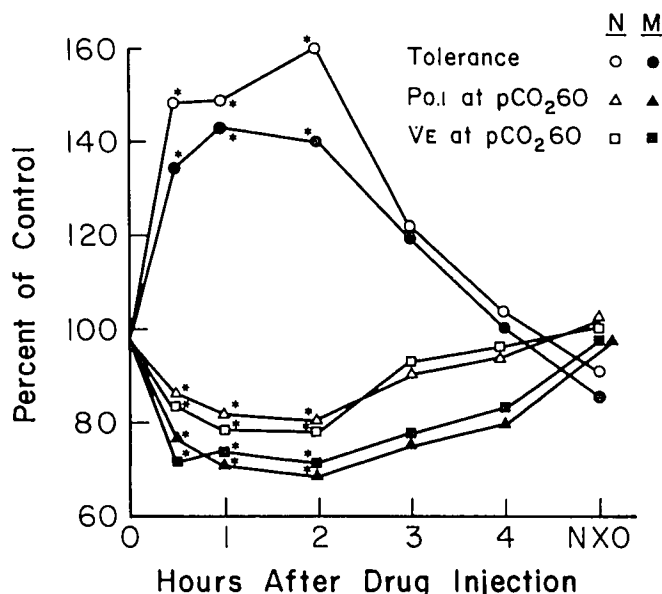


FIG. 1. Time-related changes in tolerance to experimental pain and respiratory depression after single 0.15-mg/kg doses of nalbuphine (N) and morphine (M), and after reversal with 0.4 mg naloxone (NXO). Mean values for six subjects are plotted as per cent of control. Occlusion pressure ( $P_{0.1}$ ) and minute ventilation ( $\dot{V}_E$ ) were measured at  $P_{\text{CO}_2}$  60 mmHg during rebreathing. \* $P < 0.01$  denotes values significantly different from control.

duration ( $T_i/T_{\text{tot}}$ ), which decreased from 0.44 to 0.33. Both drugs significantly reduced  $V_T$  and  $V_T/T_i$  compared with the control ( $P < 0.01$ ). The decreases were greater after morphine compared with nalbuphine ( $P < 0.01$ ).

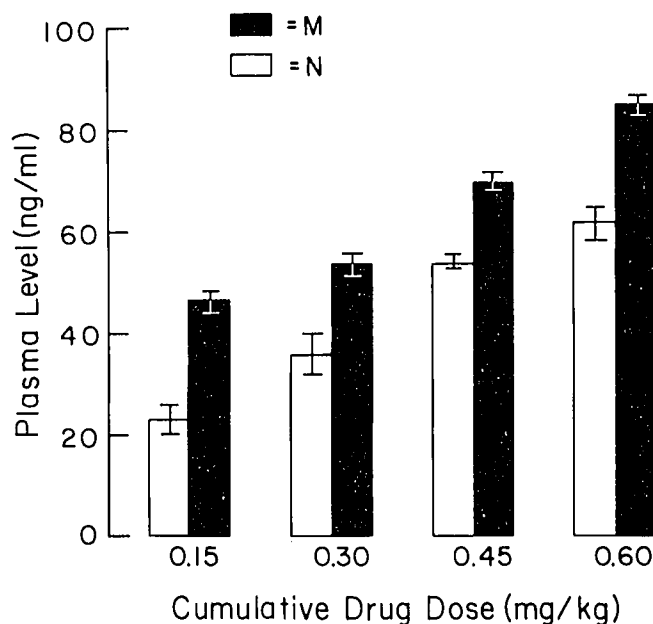


FIG. 2. Plasma levels of nalbuphine (N) and morphine (M) after each of four successive 0.15-mg/kg doses given intravenously. Values are means  $\pm$  SEM for six subjects.

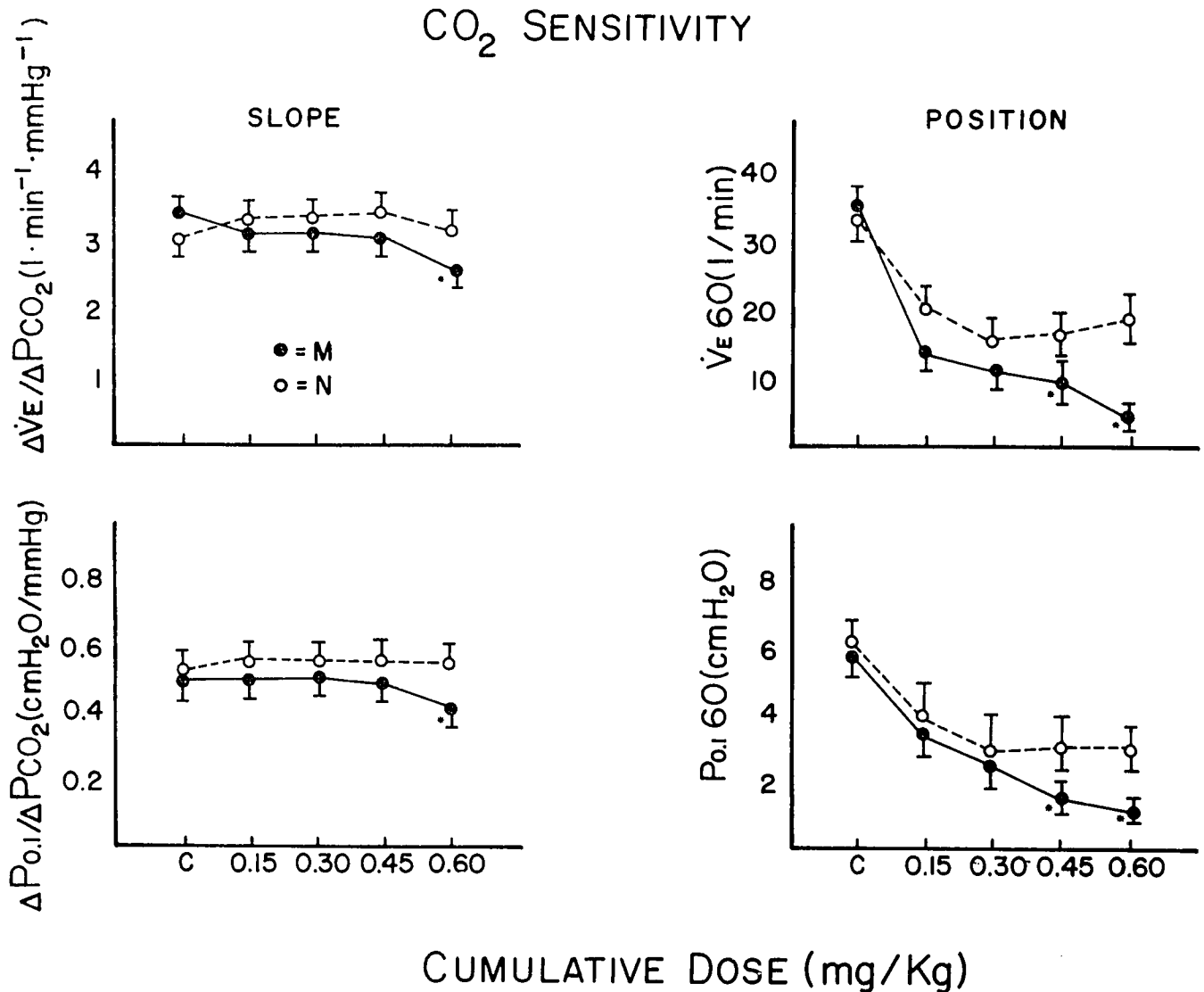


FIG. 3. Changes in CO<sub>2</sub> sensitivity after each of four successive 0.15-mg/kg doses of nalbuphine (N) and morphine (M). Mean values  $\pm$  SEM for six subjects are plotted for slopes of ventilatory ( $\Delta \dot{V}_E / P_{CO_2}$ ) and occlusion pressure ( $\Delta P_{0.1} / P_{CO_2}$ ) responses to CO<sub>2</sub>. Shifts in position of response curves are indicated by minute ventilation ( $\dot{V}_E 60$ ) and occlusion pressure ( $P_{0.1} 60$ ) measured at  $P_{CO_2}$  of 60 mmHg during rebreathing. \* $P < 0.01$  denotes values with morphine significantly different from similar doses of nalbuphine.

Alterations in response to experimental pain with multiple doses of morphine and nalbuphine are shown in figure 4. The initial 0.15-mg/kg dose increased pain threshold  $47 \pm 13\%$  with nalbuphine, compared with  $44 \pm 11\%$  with morphine. Although mean values for threshold increased further above control with subsequent doses of both drugs, the responses were highly variable and not significantly greater than with the first dose. Relative increases in threshold were not significantly different with morphine compared to nalbuphine.

Pain tolerance was increased  $40 \pm 12\%$  above control with the initial nalbuphine dose, compared with  $30 \pm 13\%$  with morphine. Further doses of nalbuphine did

not produce additional tolerance to pain. The  $60 \pm 20\%$  increase after the final dose did not differ significantly from the effects of any of the previous doses. In contrast, each successive dose of morphine produced consistent increases in tolerance which reached a maximum of  $107 \pm 13\%$  above control. Morphine-induced tolerance to pain was significantly greater ( $P < 0.01$ ) after the third and fourth doses compared with nalbuphine. The changes produced by both drugs were promptly reversed by naloxone.

To summarize and contrast the relative analgesic and respiratory effects of the two drugs, pain tolerance expressed as per cent increase above control is plotted against ventilation which is expressed as per cent de-

TABLE 1. Respiratory Patterns during CO<sub>2</sub> Rebreathing

	Nalbuphine		Morphine	
	Control	Dose #4	Control	Dose #4
V <sub>i</sub> (l)	1.88 ± 0.29	1.41 ± 0.20*	2.20 ± 0.36	0.71 ± 0.10*†
T <sub>i</sub> (s)	1.60 ± 0.20	1.70 ± 0.10	1.60 ± 0.20	1.60 ± 0.20
V <sub>i</sub> /T <sub>i</sub> (l/s)	1.26 ± 0.24	0.83 ± 0.07*	1.36 ± 0.22	0.46 ± 0.06*†
T <sub>tot</sub> (s)	3.50 ± 0.40	4.20 ± 0.20	3.70 ± 0.50	4.70 ± 0.40
T <sub>i</sub> /T <sub>tot</sub>	0.44 ± 0.02	0.40 ± 0.03	0.44 ± 0.02	0.33 ± 0.03*
f (breaths/min)	18.00 ± 2.00	14.00 ± 0.70	17.00 ± 2.00	13.00 ± 1.00

\* *P* < 0.01 compared with control.

† *P* < 0.01 compared with nalbuphine.

Values are means ± SEM for parameters measured at end-tidal CO<sub>2</sub> tension of 60 mmHg during rebreathing.

V<sub>i</sub> = tidal volume; T<sub>i</sub> = duration of inspiration; V<sub>i</sub>/T<sub>i</sub> = average inspiratory flow rate; T<sub>tot</sub> = duration of total respiratory cycle; and f = respiratory rate.

crease in  $\dot{V}_{E60}$  (fig. 5). Nalbuphine produced an initial increase in tolerance to pain and decrease in ventilation similar in degree to morphine. Incremental nalbuphine did not produce significant added analgesia or respiratory depression. In contrast, incremental morphine produced progressive ventilatory depression, while tolerance to pain also increased.

All subjects reported a sense of warmth upon injection of morphine, followed by a relaxed sense of well being. With higher doses of morphine, subjects exhibited moderate sedation, and all complained of facial as well as generalized itching. Four of the six subjects also complained of nausea. Nalbuphine produced marked drowsiness and detachment from surroundings in all subjects. One subject (No. 6) become extremely anxious after the last dose, and described unpleasant feelings that something disastrous was about to occur. Naloxone administration promptly reversed these effects, but three subjects experienced transient mild nausea in the immediate post-reversal period.

## Discussion

The results of this study demonstrate that nalbuphine, like morphine, alters the response to experimental pain. The modified submaximal tourniquet test used in this study has been shown to dependably identify analgesia produced by morphine and other analgesics, including aspirin.<sup>5,10</sup> Although experimental pain may differ from that seen clinically, the tourniquet-induced ischemia simulates pathologic pain more closely than other experimental techniques.<sup>11</sup> Threshold and tolerance were increased by drug administration, suggesting that both are reasonable indices of analgesic efficacy. However, subjects often had difficulty giving a dependable identification of the onset (threshold) of minimal pain. This became more evident as increasing sedation occurred with higher doses of the drugs, particularly nalbuphine. Subjects could identify the time at which pain became unbearable (tolerance) with much greater certainty. Our results, therefore, agree with previous

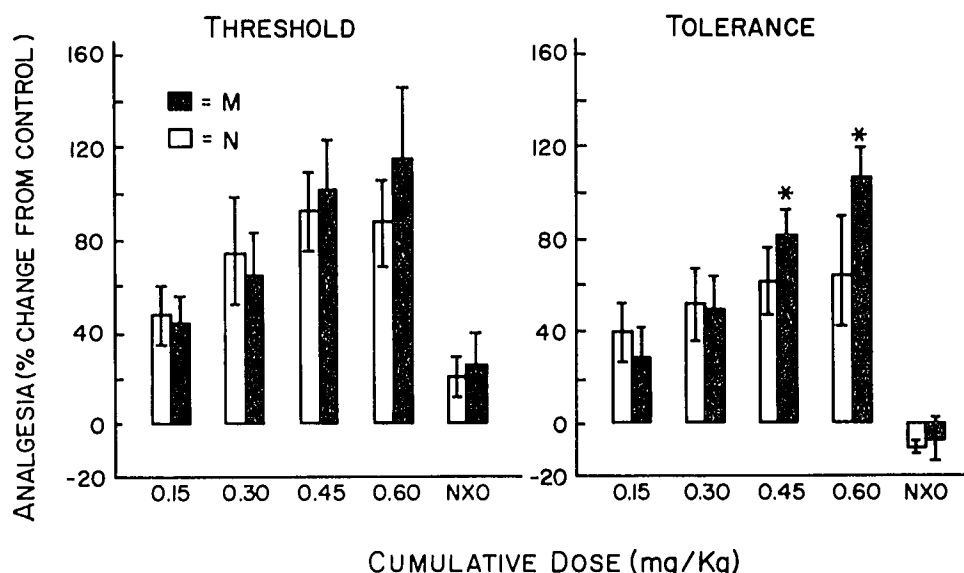


FIG. 4. Altered responses to experimental pain after each of four successive 0.15-mg/kg doses of nalbuphine (N) and morphine (M), and following 0.4 mg naloxone (NXO) intravenously. Values are means ± SEM for six subjects expressed as per cent change from control. \**P* < 0.01 denotes means values for morphine significantly different from similar doses of nalbuphine.

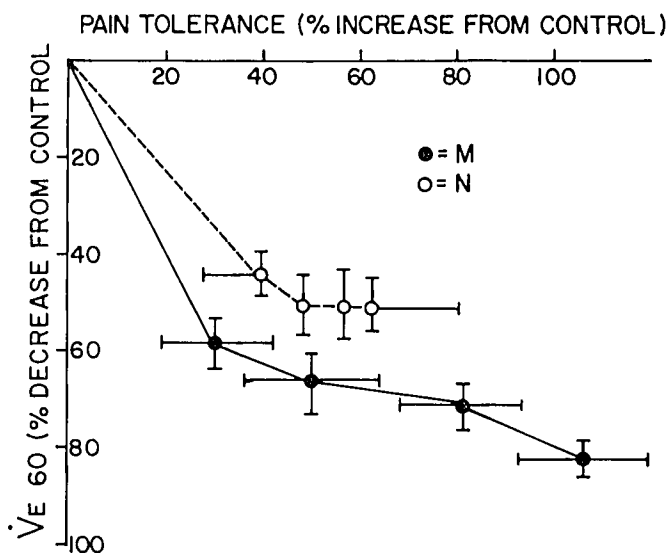


FIG. 5. Changes in pain tolerance are compared with changes in minute ventilation measured at end-tidal  $\text{CO}_2$  tension 60 mmHg during rebreathing ( $\dot{V}_E 60$ ) after each of four successive 0.15-mg/kg doses of nalbuphine (N) and morphine (M). Values are means  $\pm$  SEM for six subjects expressed as per cent change from control.

observations that pain tolerance is a more reproducible index of analgesic effect than pain threshold.<sup>12</sup>

When given as a single 0.15-mg/kg dose, nalbuphine produced analgesia similar in magnitude and duration to equal doses of morphine. Since no placebo was utilized in this study, it may be suggested that these time-related effects reflect a placebo reaction to the intravenous injection. In this study, we observed that control values for pain threshold and especially pain tolerance, were very reproducible in the same subjects on different occasions. A previous study<sup>13</sup> noted this same within-subject consistency, but more importantly, demonstrated that the response to experimental pain was unaffected by injection of a saline placebo. Unlike patients who are seeking relief of pain, volunteer subjects have no incentive to endure pain any longer than it is tolerable. The placebo effect is therefore not likely to be a significant factor in this scheme of measurements.

Pain tolerance was increased 40% by 0.15 mg/kg nalbuphine. Continued administration of the drug to a cumulative dose of 0.60 mg/kg produced only slight but insignificant increments in analgesia. The responses among subjects were highly variable. Subjects 4 and 6 actually demonstrated less analgesic effect with the third and fourth doses, compared with the first two doses. In contrast, continued incremental morphine administration was associated with consistently increasing pain tolerance. After the third and fourth doses, the analgesia

was significantly greater than that resulting from nalbuphine.

The analgesia associated with nalbuphine exhibited a limited maximal effect in our subjects. This effect on experimental pain resembles the limited ability of the drug to reduce anesthetic requirements in animals.<sup>14</sup> Whereas the effects of morphine increased linearly with dose, the anesthetic contribution of nalbuphine was dose-dependent until a plateau contribution equivalent to 0.22 MAC was achieved. A similar reduction of anesthetic requirement equivalent to 0.20 MAC was demonstrated in humans with morphine doses of 10–15 mg or an average dose of 0.17 mg/kg.<sup>15</sup> Comparable doses of nalbuphine in this study (0.15 mg/kg) produced a maximal analgesic effect, and this suggests that the major contribution of nalbuphine to reducing anesthetic requirements is the result of its limited analgesic effect.

Nalbuphine in single 0.15-mg/kg doses affected ventilation to a similar extent as morphine. Neither drug produced significant slope changes in the ventilatory or occlusion pressure responses to  $\text{CO}_2$ , but both produced similar rightward shifts of the response curves indicated by decreased  $\dot{V}_E 60$  and  $P_{0.160}$ . Larger cumulative doses of morphine ( $>0.30$  mg/kg) resulted in further respiratory depression. Both  $\dot{V}_E 60$  and  $P_{0.160}$  progressively decreased, and were ultimately accompanied by decreased slopes of the ventilatory and occlusion pressure response curves. Incremental doses of nalbuphine did not produce additional respiratory depression beyond that associated with the initial 0.15 mg/kg dose.

These data indicate that nalbuphine produced a ceiling effect for respiratory depression at doses above 0.15 mg/kg. Previous work has suggested that such respiratory effects do not occur until higher doses (30 mg/70 kg) are given.<sup>4</sup> The principal reason for this discrepancy may lie in the method which the authors utilized in their study to measure  $\text{CO}_2$  sensitivity. The steady-state  $\text{CO}_2$  response curves required considerable time to complete, such that the interval between successive doses (50–60 min) was longer than in this study (30–40 min) and may have resulted in less of a cumulative effect. This difference is of minor significance since our results show that only at cumulative doses greater than 0.30 mg/kg does morphine produce respiratory depression which clearly exceeds the limited effects of nalbuphine.

The respiratory pattern observed in subjects during  $\text{CO}_2$  rebreathing followed that described by Hey *et al.*<sup>16</sup> with  $\dot{V}_E$  increasing primarily as a consequence of increased  $V_T$ . As each subject's  $V_T$  approached one-half vital capacity, further increments in  $\dot{V}_E$  were achieved by increases in  $f$ . This pattern of  $\text{CO}_2$  response persisted after the high cumulative dose of both drugs, but the

$V_T$  values are significantly lower than in the control state, particularly with morphine (table 1). These reduced  $V_T$  values did not result from a shortened inspiratory time ( $T_i$ ), but rather from a decreased mean inspiratory flow ( $V_T/T_i$ ). Like  $P_{0.1}$ ,  $V_T/T_i$  is a mechanical transform of respiratory center output. Discrepancies between respiratory center output reflected by  $P_{0.1}$  measurements and those of  $V_T/T_i$ ,  $V_T$ , and  $\dot{V}_E$  must arise from changes in respiratory mechanics. By relating  $P_{0.1}$  to  $V_T/T_i$ , an estimate of the impedance or resistance to airflow may be obtained. Relating occlusion pressure to  $V_T$  provides an estimate of the stiffness or elastance of the respiratory system.<sup>17</sup> Both  $V_T$  and  $V_T/T_i$  decreased slightly less than  $P_{0.160}$  after each drug. This strongly suggests that increased airflow resistance and respiratory system elastance did not play a role in the decreased ventilatory responses, or in the differences between nalbuphine and morphine. Further evidence that the drug effects are solely a result of central respiratory depression is provided by the fact that maximum decreases in  $P_{0.160}$  (morphine 20% of control, nalbuphine 44% of control) were similar to reductions in  $\dot{V}_E60$  (morphine 17% of control, nalbuphine 50% of control).

The scheme of drug administration utilized in the multiple dose portion of this study produced incremental plasma levels of each drug which corresponded well to the total dose administered for both nalbuphine ( $r = 0.84$ ) and morphine ( $r = 0.97$ ). The absolute blood levels (fig. 2) were significantly higher ( $P < 0.01$ ) after each dose of morphine compared with nalbuphine, a phenomenon which most likely results from the higher lipid solubility of nalbuphine. The higher morphine levels give rise to the speculation that this is the underlying mechanism whereby the greater analgesia and respiratory depression occur. This explanation does not account for the fact that both respiratory and analgesic effects after the first 0.15-mg/kg dose of nalbuphine were similar to morphine in the presence of plasma levels less than one-half of morphine (fig. 2). Furthermore, plasma levels of the drugs did not correlate well with either per cent increase in pain tolerance ( $r = 0.45$ ) or per cent decrease  $\dot{V}_E60$  ( $r = 0.52$ ). Previous work<sup>18</sup> has also demonstrated this lack of distinct relationship between plasma morphine concentration and the magnitude of ventilatory effects, a finding which also contrasts with predictions that plasma concentration may be a useful index of morphines pharmacologic activity.<sup>19</sup>

In summary, normal subjects receiving intravenous nalbuphine in doses of 0.15 mg/kg experienced respiratory depression and analgesia to experimental pain similar to that produced by an equivalent amount of morphine. Larger cumulative doses of morphine pro-

duced increasing respiratory depression and significantly greater analgesia as the dose was increased. Incremental doses of nalbuphine produced no additional respiratory depression beyond that observed with 0.15 mg/kg. The higher doses of nalbuphine resulted in marked variability in analgesic effect, and the resultant analgesia was not significantly greater than that achieved by 0.15 mg/kg. Unpleasant, psychotomimetic effects, though not prominent, did occur. In most cases marked drowsiness and sedation resulted and may provide an advantageous clinical feature, since they were not associated with profound respiratory depression. Nalbuphine, nevertheless, appeared to have limited maximal effects as an analgesic, which tended to parallel its ceiling effect for respiratory depression.

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## APPENDIX

### *Nalbuphine Analysis*

Plasma samples were prepared by centrifugation and frozen at  $-15^{\circ}\text{C}$ . until the time of analysis. Naloxone, 250 ng, was added to 1 ml of plasma as an internal standard. The sample was de-proteinated with 0.25 N perchloric acid, vortexed, allowed to stand for 3-5 min, centrifuged, and the supernatant collected. The supernatant was adjusted to pH 8 with 1 N sodium hydroxide, and then extracted with 10 ml of a 9:1 mixture of ethyl

acetate and 2-propanol. After centrifugation, the organic top layer was collected and evaporated to dryness with a gentle air stream. The sample residue was then redissolved in 1 ml of methanol and injected into the chromatograph using a 200- $\mu\text{l}$  injection loop. A Bio-phase ODS 5- $\mu\text{m}$  chromatograph column and a BAS LC-4A electrochemical detector were used. The detector cell potential was set at 0.75 volts with the detector in the oxidation mode. This voltage was chosen from a cyclic voltammograph obtained for nalbuphine. The mobile phase was 55% monobasic potassium phosphate (0.01 M) and 45% HPLC grade methanol which had been degassed and filtered through a 0.22- $\mu\text{m}$  filter before use. A flow rate of 0.8 ml/min resulted in retention times of 400 s for naloxone and 507 s for nalbuphine. The plasma concentration of nalbuphine was determined from the ratio of the nalbuphine and naloxone responses in the samples, which contained naloxone as the internal standard.