

Prolonged Antagonism of Opioid Action with Intravenous Nalmefene in Man

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To identify the opioid antagonist activity of nalmefene and to determine its duration in man, six healthy male subjects were pretreated on separate days with a saline placebo, 0.5 mg, 1 mg, or 2 mg nalmefene intravenously in a randomized double-blind fashion. Opioid challenges with fentanyl, 2 $\mu\text{g}/\text{kg}$, then were administered 1, 2, 4, 6, and 8 h afterward. Respiratory depression was monitored by ventilatory and occlusion pressure responses during CO_2 re-breathing, while analgesia to experimental pain was identified with the submaximal effort tourniquet ischemia test. One hour following placebo pretreatment, the initial fentanyl dose produced marked respiratory depression. Minute ventilation and occlusion pressure at a PCO_2 60 mmHg during re-breathing (\dot{V}_{E60} and $P_{o,i60}$) were reduced to 29 and 41% of control, respectively. The slopes of the ventilatory and occlusion pressure responses also decreased significantly to 51 and 55% of control. Respiratory effects were similar with all subsequent fentanyl doses. Pretreatment with 2 mg nalmefene completely prevented the subjective and respiratory effects of fentanyl for the entire 8 h of the experiment. Nalmefene, 1 mg, significantly blunted the fentanyl effects for the same period, but \dot{V}_{E60} values at 6 and 8 h were depressed significantly ($P < 0.05$) to 66 and 61% of control. The antagonist effects of the lowest nalmefene dose, 0.5 mg, persisted for about 4 h, at which time \dot{V}_{E60} was 64% of control. Fentanyl administration produced consistent increases in pain tolerance (44–55% above control) throughout the experiment. Nalmefene pretreatment abolished this analgesic response in a dose-related time course that mirrored the respiratory effects almost exactly. These findings demonstrate that nalmefene is an effective opioid antagonist with a duration of action far in excess of naloxone and more clearly related to dose. (Key words: Analgesics, narcotic: fentanyl. Antagonist, narcotic: nalmefene. Carbon dioxide: ventilatory response; occlusion pressure response. Pain: experimental; measurement. Ventilation: airway occlusion pressure; carbon dioxide response.)

THE ABILITY OF NALOXONE specifically to antagonize narcotic analgesics is relatively short-lived and often characterized by recurrence of respiratory depression. This phenomenon is most dramatic following anesthetic techniques using large doses of opioid,^{1,2} but also has been demonstrated in conscious subjects after smaller analgesic doses of narcotic.^{3,4} Attempts to synthesize naloxone analogues with longer durations of action have resulted in compounds such as naltrexone with a cyclopropylmethyl group substituted for the N-allyl group of naloxone.⁵

More recently, nalmefene, a structural analogue of naltrexone with a methylene group substituted in the number 6 position, has been developed (fig. 1). Pharmacokinetic data in man indicate that plasma concentrations after intravenous nalmefene injection are well maintained and suggest a prolonged duration of action.⁶ However, there are no data in man relating these sustained plasma nalmefene concentrations to its ability to antagonize the effects of narcotic analgesics.

Identification of prolonged antagonist activity is difficult because the actions of most opioid agonists diminish with time when safe clinical doses are given. Thus, the presence of a reversal effect is obscured by the declining agonist effect. This problem can be avoided somewhat by using a continuous infusion of an opioid agonist, but prolonged time-course studies can result in excessive total doses of the agonist. This study, therefore, was designed to test the prolonged duration of nalmefene action by pretreating subjects with one of several doses of the antagonist, and then challenging periodically with an effective, relatively short-acting opioid agonist, fentanyl.

Methods

Six healthy, nonsmoking men (ages 23–28 yr) with normal pulmonary function consented to participate in the study, which was approved by the Human Investigation Committee of the University of Virginia. Subjects fasted overnight and abstained from caffeine or alcohol-containing beverages for at least 12 hours prior to the study. All testing was performed with subjects in the supine position. Analgesia was identified by a modification of the submaximal tourniquet ischemia test, which was used to produce experimental pain.⁷ Exsanguination of the subject's upper arm was accomplished by application of an Esmarch® bandage, and maintained by inflating tourniquet to 250 mmHg. Following 1 min of ischemia, subjects performed submaximal exercise by compressing a hand-held ball once each s for an additional min, and then placed the arm at the side. The pain response was assessed by recording the time from tourniquet inflation to the point at which the pain became unbearable (tolerance). Two such trials were performed prior to drug administration, and the average value served as the control for each day's experiment.

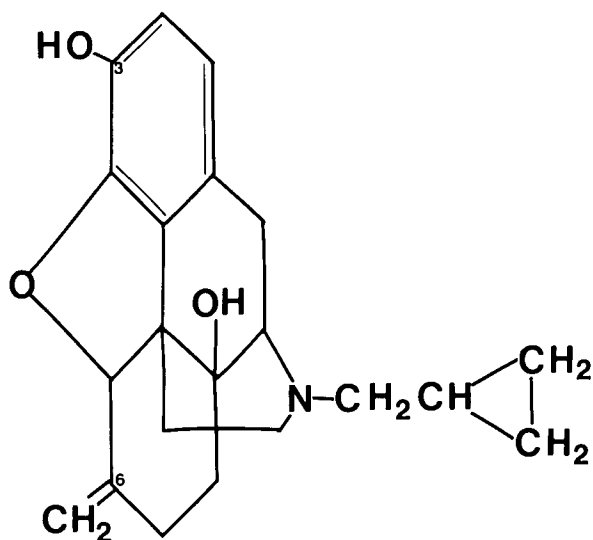
Respiratory-center sensitivity to carbon dioxide was determined by the re-breathing method of Read.⁸ Progressive hyperoxic hypercapnia was produced as subjects

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NALMEFENE

FIG. 1. Chemical formula of nalmefene showing the exocyclic methylene (CH_2) group at the number 6 position.

rebreathed a mixture of 7% CO_2 , 93% O_2 from an electronic spirometer (model 840, Ohio Medical Products), which measured flow and volume. The spirometer was filled with a volume of gas equal to the subjects' forced vital capacity plus 1 l. End-tidal carbon dioxide tension (P_{ETCO_2}) was measured by an infrared analyzer (Beckman® LB-2). Subjects breathed *via* a mouthpiece through a circuit divided into inspiratory and expiratory limbs by two low-resistance, unidirectional valves (Hans Rudolf, Inc.). The circuit resistance was $1.0 \text{ cmH}_2\text{O} \cdot \text{l}^{-1} \cdot \text{s}$ linear to a flow of $4 \text{ l} \cdot \text{s}^{-1}$. During rebreathing runs that lasted 5–6 min, airway occlusion was accomplished at the rate of about one every 20 s by silently closing a valve on the inspiratory side of the circuit for 0.2 to 0.4 s as subjects breathed out through the expiratory limb. This allowed occluded inspirations to begin at functional residual capacity. 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 (Valdine MP 45®, range $\pm 50 \text{ cm H}_2\text{O}$), and recorded at a paper speed of 50 mm/s. Inspiratory (T_i), expiratory (T_e), and total breathing cycle durations (T_{tot}) were measured from the flow signal. Minute ventilation (\dot{V}_E) was calculated from the average of tidal volume (V_T) and frequency (f) for the three breaths preceding each occlusion. Since f is related inversely to total respiratory cycle duration (T_{tot}), it was calculated as the reciprocal of the total cycle duration times 60 (*i.e.*, $f = 1/T_{\text{tot}} \times 60$). Another index of respiratory center sensitivity calculated from the three

breaths preceding each occlusion was the mean inspiratory flow rate (V_T/T_i).

Linear regression equations were used to calculate the slopes relating changes in \dot{V}_E and P_{ETCO_2} (\dot{V}_E/PCO_2) and changes in occlusion pressure to P_{ETCO_2} ($P_{0.1}/PCO_2$). To detect changes in CO_2 sensitivity not reflected by a change in slope, but rather by a shift in position of the response curves, we also recorded changes in \dot{V}_E and $P_{0.1}$ during rebreathing at a fixed increased level of CO_2 ($P_{\text{ETCO}_2} = 60 \text{ mmHg}$). This point was chosen because it was encompassed by the linear portion of the response curves in all subjects so that \dot{V}_E60 and $P_{0.1}60$ could be derived by interpolation rather than extrapolation. Control measurements of CO_2 response were made in duplicate and their average was used to compute control values.

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 arm opposite the tourniquet.

On each of four separate days, subjects received an intravenous injection of saline placebo, 0.5 mg, 1 mg, or 2 mg of nalmefene. These treatments were administered in randomized, double-blind fashion from unidentified ampules provided by the manufacturer (Key Pharmaceuticals). Subjects were tested prior to these pretreatments, and then 10 min after each drug. Opioid challenge was then produced by administering fentanyl, $2 \mu\text{g}/\text{kg}$, at 1, 2, 4, 6, and 8 h after this pretreatment. The testing sequence that consisted of CO_2 rebreathing and measurement of analgesia was begun 5 min after each fentanyl dose. Rebreathing runs lasted 5–6 min and were followed immediately by inflation of the tourniquet to produce experimental pain. Naloxone, 0.4 mg, was administered intravenously to subjects 15 min after completing measurements with the final fentanyl dose. Additional naloxone doses, 0.4 mg im and 0.4 mg iv, were administered before subjects departed from the laboratory.

Results are expressed as mean value \pm SEM. Analysis of variance was performed to test for significant differences among treatment groups. The differences were isolated by the modified t-test according to the method of Bonferroni.⁹ A value of $P < 0.05$ was considered significant.

Results

When subjects were pretreated with placebo, the initial fentanyl dose 1 h later produced nasal itching, mild nausea, drowsiness, and marked respiratory depression in all (table 1). Both \dot{V}_E60 (29% of control) and $P_{0.1}60$ (41% of control) were significantly decreased ($P < 0.01$), as were slopes of the ventilatory and occlusion pressure responses

TABLE 1. Respiratory Depression after Placebo Injection and Challenge with Fentanyl (2 µg/kg i.v.) 1, 2, 4, 6, and 8 H Later

	Control	Placebo	1 H	2 H	4 H	6 H	8 H
\dot{V}_{E60} (l · min ⁻¹)	45.9 (6.3)	48.1 (4.9)	13.4*† (2.3)	10.2* (2.2)	13.6* (2.8)	12.5 (2.2)	12.3 (2.3)
$P_{0.160}$ (cm H ₂ O)	8.0 (1.2)	8.1 (1.3)	3.3*† (0.4)	2.8* (0.4)	3.0* (0.4)	3.6* (0.6)	3.1* (0.7)
\dot{V}_E/PCO_2 (l · min ⁻¹ · mmHg ⁻¹)	3.36 (0.47)	3.81 (0.62)	1.73*† (0.26)	1.94* (0.22)	2.01* (0.21)	2.11* (0.22)	1.64* (0.13)
$P_{0.1}/PCO_2$ (cm H ₂ O · mmHg ⁻¹)	0.58 (0.09)	0.66 (0.11)	0.32*† (0.07)	0.35* (0.06)	0.36* (0.04)	0.39* (0.08)	0.31* (0.06)

Values are mean ± SEM for six subjects.

* $P < 0.01$ denotes significant difference from control.

† $P < 0.01$ denotes significant difference from preceding measurement.

(\dot{V}_E/PCO_2 , $P_{0.1}/PCO_2$), which were 51 and 55% of control, respectively.

The subjective effects and degree of respiratory depression were strikingly similar after each subsequent fentanyl challenge throughout the study (table 1), and were essentially gone prior to each subsequent dose. This consistency of fentanyl effect also is evident in figure 2, which depicts the alterations in respiratory pattern that contributed to the decreased ventilation during CO₂ rebreathing. The mean respiratory rate (*f*) during hypercapnic rebreathing (PCO_2 60 mmHg) decreased significantly ($P < 0.01$) from 17 ± 1 to 12 ± 1 breaths/min after fentanyl. This was accompanied by a marked reduction in V_T from 2.9 ± 0.2 to 1.1 ± 0.2 l. The decreased V_T was not the result of a shortened duration of inspiration (T_i), but rather the result of a decreased mean inspiratory flow (V_T/T_i) from 1.6 ± 0.2 to 0.6 ± 0.1 l · s⁻¹.

Subjective effects of nalmefene pretreatment were indistinguishable from those of placebo in all subjects except subject number 4, who complained of a gagging sensation for about 10 h after receiving the 2-mg dose. The consistent reduction in the slope of the ventilatory (\dot{V}_E/PCO_2) response with fentanyl was blunted significantly for at least 2 h by 0.5 mg nalmefene (fig. 3). This blunting effect of nalmefene increased to 4 h with 1 mg, and persisted for more than 8 h with the 2-mg dose. The time course of nalmefene effects on the slope of the occlusion pressure response ($P_{0.1}/PCO_2$) followed a similar pattern (fig. 4). The time-dose relationships for nalmefene pretreatment are illustrated more dramatically by shifts in the position of the response curves. Control \dot{V}_{E60} was unaffected by fentanyl administration for the entire 8-hour experiment after pretreatment with 2 mg nalmefene (fig. 5). A significant blunting of fentanyl effect was noted with 1 mg nalmefene over the same time period when compared with placebo pretreatment. However, \dot{V}_{E60} at 6 h (66% of control) and 8 h (61% of control) were significantly less ($P < 0.05$) than their baseline values. The antagonist

effects of 0.5 mg nalmefene were manifest for 4 h, at which time \dot{V}_{E60} was 64% of control. The effects of nalmefene pretreatment on $P_{0.160}$ followed the same time course (fig. 6).

Fentanyl administration produced consistent analgesic responses to experimental pain. Control pain tolerance (13 ± 2.5 min) was increased by 44 to 55% throughout the study. Nalmefene pretreatment abolished the analgesic response in a fashion that mirrored the respiratory effects almost exactly (fig. 7). At 8 h after 1 mg nalmefene, fentanyl was able to produce a significant ($P < 0.01$) increase in pain tolerance to 20% above control. When subjects were pretreated with 0.5 mg nalmefene, significant ($P < 0.01$) analgesia to experimental pain was demonstrable at 6 and 8 h, when tolerance was increased by 24 and 28%, respectively. The 2 mg nalmefene dose blocked

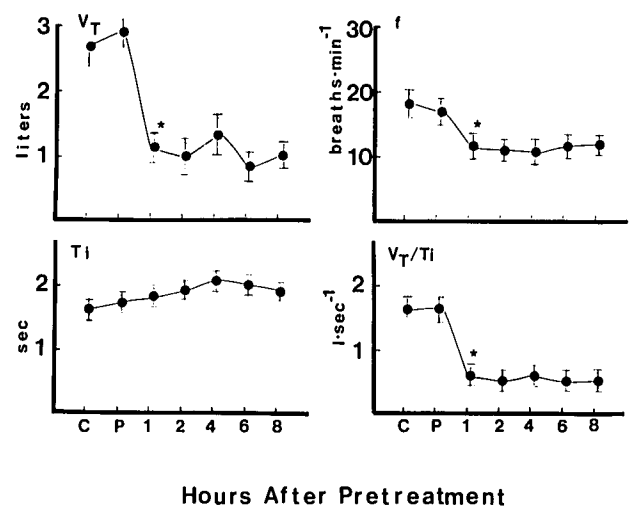


FIG. 2. Tidal volume (V_T), inspiratory time (T_i), respiratory frequency (*f*), and mean inspiratory flow rate (V_T/T_i) measured at PCO_2 60 mmHg during rebreathing. Values are mean ± SEM for six subjects in control state (C), with placebo (P) pretreatment, and after challenge with five doses of fentanyl (2 µg/kg). * $P < 0.01$ denotes significant difference from preceding measurement.

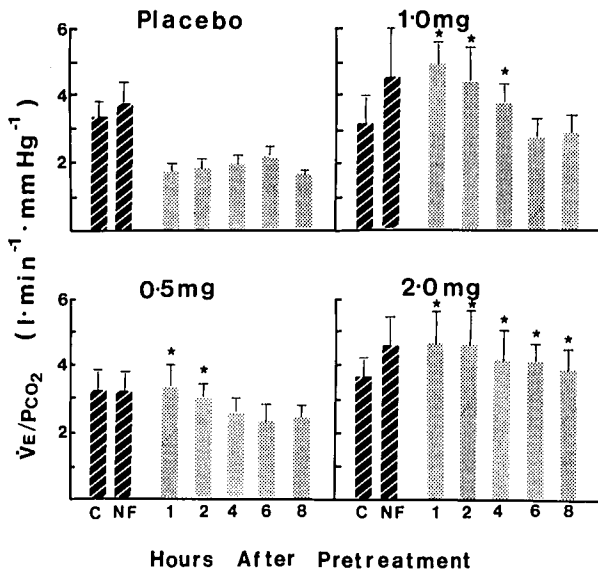


FIG. 3. The slopes of the ventilatory response (\dot{V}_E/PCO_2), with fentanyl challenge ($2 \mu\text{g}/\text{kg}$) 1, 2, 4, 6, and 8 h after pretreatment with placebo, 0.5 mg, 1.0 mg, and 2.0 mg nalmefene (NF). C = control measurements. * $P < 0.05$ indicates significant difference compared to placebo at the same time period after pretreatment.

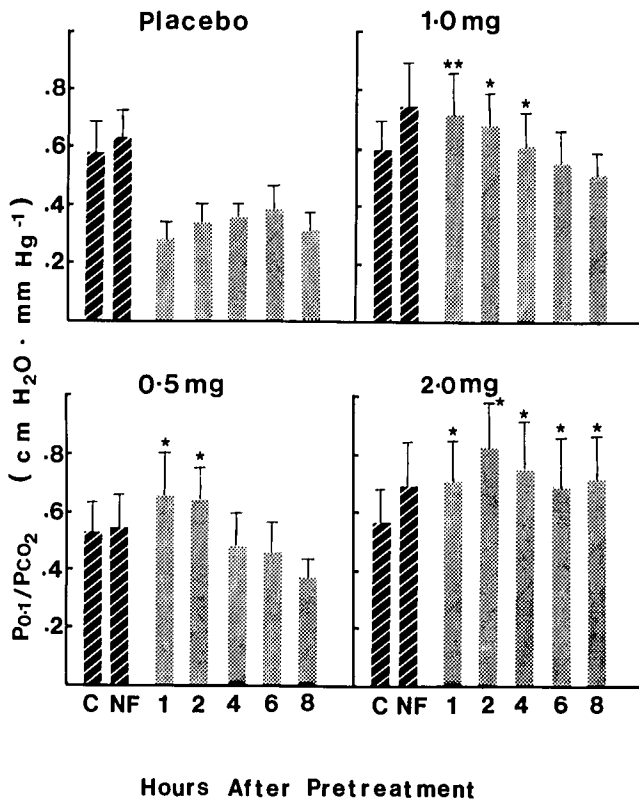


FIG. 4. The slopes of the occlusion pressure response ($P_{0.1}/PCO_2$) with fentanyl challenge ($2 \mu\text{g}/\text{kg}$) 1, 2, 4, 6, and 8 h after pretreatment with placebo, 0.5 mg, 1.0 mg, and 2.0 mg nalmefene (NF). C = control measurements. * $P < 0.05$, ** $P < 0.01$, indicate significant differences compared to placebo at the same time period after pretreatment.

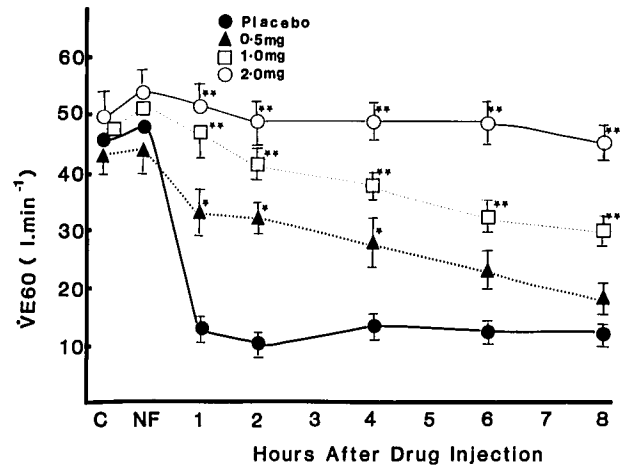


FIG. 5. Respiratory depression reflected by changes in minute ventilation at PCO_2 60 mmHg during rebreathing (\dot{V}_{E60}). Mean values \pm SEM are plotted for six subjects in control state (C), after pretreatment with placebo or each of the three doses of nalmefene (NF), and after fentanyl challenge ($2 \mu\text{g}/\text{kg}$) 1, 2, 4, 6, and 8 h later. * $P < 0.05$, ** $P < 0.01$ denote significant differences from placebo pretreatment.

fentanyl-induced analgesia throughout the experiment. At 1 h after pretreatment with this large dose, pain tolerance was actually decreased significantly ($P < 0.01$) to $81 \pm 7\%$ of control values.

Discussion

This study was designed principally to identify whether the sustained plasma concentrations of nalmefene ob-

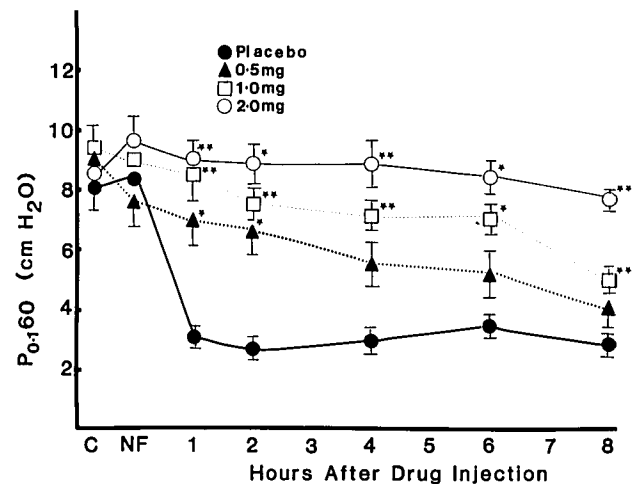


FIG. 6. Respiratory depression indicated by changes in occlusion pressure at PCO_2 60 mmHg during rebreathing ($P_{0.1,60}$). Mean values \pm SEM are plotted for six subjects in control state (C), after pretreatment with placebo or each of three doses of nalmefene (NF), and after fentanyl challenge ($2 \mu\text{g}/\text{kg}$) 1, 2, 4, 6, and 8 h later. * $P < 0.05$, ** $P < 0.01$ denote significant differences compared to placebo pretreatment.

served following intravenous injection⁶ were associated with a prolonged ability to antagonize opioid effects. When similar clinical doses of naloxone and nalmefene are administered, naloxone concentrations in the blood decline about five times as rapidly as those of nalmefene.^{6,10} The clinical antagonist actions of such doses of naloxone, (0.4 mg) are evident for little more than 1 h. The data of Ngai *et al.*¹⁰ suggest that the rather evanescent effects of naloxone are not a function of its short-lived distribution and elimination phases in blood, because the latter are similar to morphine, a decidedly longer-acting drug. It appears more likely that the relatively brief reversal effects are a function of the rapidity with which naloxone concentrations in the CNS decline.

The results of this study clearly demonstrate that nalmefene is a pure opioid antagonist, which is capable of antagonizing the analgesia and respiratory depression associated with opioid administration over a long period. The duration of nalmefene action far exceeds that of naloxone and appears to be longer than that of naltrexone.[‡] The antagonist effects of 2 mg nalmefene are evident for more than 8 h, almost four times as long as the effects of the 0.5-mg dose. Therefore, increasing the dose of nalmefene appears to be effective in prolonging its duration of action. This contrasts sharply with the characteristics of naloxone. Doubling¹ or quadrupling³ the usual 0.4-mg intravenous dose of naloxone seems to have little effect in prolonging its duration of action. Larger increases in naloxone dosage may have effects that relate to mechanisms other than opioid antagonism.

The large 2-mg dose of nalmefene used in this study appeared to have some mild antianalgesic (fig. 7) and respiratory stimulant (figs. 3 and 4) effects in some subjects. Caution must be exercised in using such doses clinically to reverse existing opioid effects, because the ability to reestablish adequate analgesia will be severely limited for an extended period. A nalmefene dose of 0.5 mg with its duration of 2 to 3 h appears to be more appropriate.

The periodic opioid challenge with fentanyl was associated with very prominent subjective effects, analgesia (fig. 7) and respiratory depression (table 1). The magnitude of these respiratory and analgesic effects very closely resemble those produced in a similar group of subjects with cumulative doses of 0.3 mg/kg morphine sulfate.¹¹ The fentanyl dose was chosen in the hopes of achieving measurable respiratory and analgesic effects, but with minimal likelihood of producing cumulative effects with repeat administration. The data of Harper *et al.*¹² suggested that a dose of 2 μ g/kg would represent an ideal compromise. Although subjective effects of drowsiness

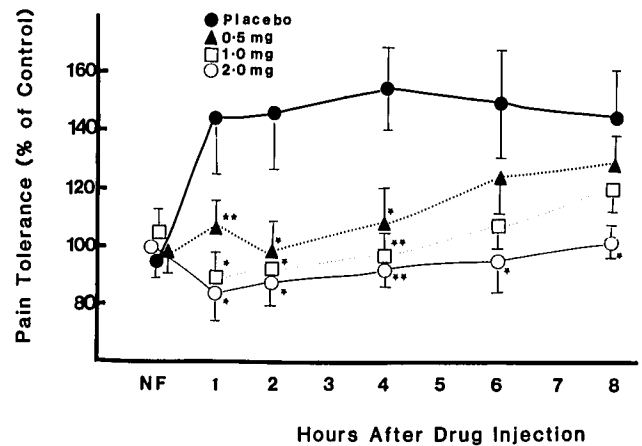


FIG. 7. Changes in tolerance to experimental pain after pretreatment with placebo or each of three doses of nalmefene (NF) and after fentanyl administration (2 μ g/kg) 1, 2, 4, 6, and 8 h later. Values are mean \pm SEM for six subjects expressed as per cent of control. * P < 0.05, ** P < 0.01 denote significant differences compared to placebo pretreatment.

and nausea appeared to be slightly more prominent with fentanyl given at 8 hours, compared with that given in the first hour, the respiratory and analgesic effects did not increase. While this suggests that significant cumulative fentanyl effects were not present, it is also possible that accumulation did occur and was offset by acute tolerance to the drug.

The fentanyl-induced respiratory depression was associated with a pattern of breathing during CO₂ re-breathing that was characterized by a marked reduction in V_T and mean inspiratory flow (V_T/T_I). These were also accompanied by a dramatic decrease in respiratory rate (f), as seen in figure 2. Thus, fentanyl appears to have a profound influence on respiratory timing.

One of the most disturbing phenomena observed with intravenous fentanyl administration is the apparent increase in chest-wall and abdominal rigidity.¹⁵ This can result in an increased respiratory impedance, which includes both respiratory system resistance and compliance. The P_{0.1} represents a mechanical transform of respiratory center output that increases with CO₂ but, unlike \dot{V}_E , is not affected by the mechanical characteristics of the respiratory system.¹⁴ In healthy subjects, \dot{V}_E adequately reflects respiratory-center activity. Any discrepancy between changes in P_{0.1} and \dot{V}_E suggest the possibility of altered respiratory system mechanics. This is a possibility in the case of \dot{V}_E60 (29% of control), which appears to be decreased relatively more after fentanyl administration (table 1) than P_{0.1}60 (41% of control).

Respiratory impedance can be estimated from the ratio of P_{0.1} and mean inspiratory flow.¹⁵ We compared P_{0.1} and V_T/T_I ratios at increased PCO₂ (60 mmHg) during

‡ Smith TC: Comparison of naltrexone and naloxone in man (abstract). ANESTHESIOLOGY 51:S373, 1979.

rebreathing and also the $P_{0.1}$ values associated with the same V_T/T_i , ($1.0 \text{ l} \cdot \text{s}^{-1}$) before and after fentanyl so that pressure and flow components would be similar.¹⁶ In neither case did the pre- and post-fentanyl values differ significantly. Thus, increased respiratory impedance from chest-wall rigidity does not appear to be a significant factor in the marked decreased ventilatory responsiveness observed in our awake subjects following the $2 \mu\text{g}/\text{kg}$ fentanyl challenge in this study.

The prolonged ability of nalmefene to antagonize profound respiratory depression, such as that produced by the fentanyl, indicates that its reversal effects are likely to outlast the duration of most opioids. The fentanyl challenge at 8 h, for example, represents a greater agonist effect than most opioids would exhibit at such a long time after administration. Recurrence of respiratory depression after nalmefene therapy would only appear to be likely if very small doses ($<0.5 \text{ mg}$) are used to reverse large doses of a relatively long-acting opioid, such as methadone.

In conclusion, nalmefene is a pure opioid antagonist devoid of any agonist activity. Nalmefene exhibited a prolonged ability to antagonize significant opioid challenges with fentanyl. The duration of nalmefene action far exceeds that of naloxone and appears to be more clearly dose-related. Even at the lowest dose used in this study (0.5 mg), nalmefene produced opioid antagonism lasting three to four times that of naloxone. Nalmefene, therefore, appears capable of producing a more sustained reversal that is likely to outlast the return of residual opioid effects.

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