ANTAGONISM OF MORPHINE-INDUCED RESPIRATORY DEPRESSION WITH NALMEFENE

K. M. KONIECZKO, J. G. JONES, M. P. BARROWCLIFFE, C. JORDAN AND D. G. ALTMAN

The only pure opioid antagonist available currently for clinical use is naloxone. Its duration of activity is short [1] compared with that of most routinely used opioids [2].

The need for a longer acting antagonist has been highlighted recently by the use of extradural and intrathecal opioids [3]. Unpredictable late ventilatory depression produced by extradural morphine is antagonized selectively by naloxone [4, 5], leaving analgesia intact, but recurs as naloxone activity diminishes. Prolonged opioid antagonism would also be valuable in the intensive care unit when treating opioid overdose or when weaning patients from ventilatory support which has required prolonged opioid sedation.

Nalmefene (17 N-methylcyclopropyl 3-14 dihydroxy 4-5 epoxy morphinan 6 methylene, produced by Schering-Plough Pharmaceuticals) is a new pure opioid antagonist. It is a water soluble naltrexone derivative with pharmacokinetics that suggest a longer duration of action than that of naloxone. The mean terminal $\beta$ elimination half-life of nalmefene is 8.5 h [6], compared with 1–2.5 h [7, 8] for naloxone. Nalmefene is also more effective than naloxone at inhibiting agonist binding at the central opioid receptor site in the rat [9]. These characteristics and its oral bioavailability are attributed to the exomethylene group found at position 6 of the nalmefene molecule (fig. 1), which blocks one site of metabolism. Nalmefene is metabolized in the liver and excreted in urine as the glucuronide [6].

In clinical studies using healthy volunteers, doses of up to 300 mg by mouth and 24 mg i.v. have been tolerated well, with only mild subjective effects and with no evidence of opioid agonist activity.

We have studied the degree and duration of nalmefene-induced antagonism of respiratory depression produced by i.m. morphine and compared it with high and low doses of naloxone, and a placebo. Both high and equiefficacious doses of
NALMEFENE AND NALOXONE.

**FIG. 1.** Molecular structure of nalmefene and naloxone.

Naloxone were included in the study, to counter possible criticism that the prolonged duration of activity of nalmefene could be attributed solely to its increased potency.

**SUBJECTS AND METHODS**

Six healthy male volunteers (ages 29–48 yr, weights 61–90 kg) participated in the study, which was approved by the Harrow District Ethics Committee.

Each subject was studied on four separate days with intervals of at least 1 week. The subjects received morphine 10 mg/70 kg i.m. on each occasion, followed 1 h later by nalmefene 0.4 mg/70 kg, naloxone 1.6 mg/70 kg, naloxone 0.4 mg/70 kg or saline placebo i.v. The test drugs were administered in a double-blind design study in a random sequence. The subjects were allowed light breakfast without tea or coffee, and then fasted throughout the day except for water. Hydration was maintained by an i.v. infusion of 1 litre of 4% Dextrose and 0.18% saline solution, which also allowed the test drugs to be administered without the subject's knowledge. All the subjects were studied in the supine position and, except for the experimental procedure, were undisturbed and lay quietly for the whole 8-h period of the study.

Measured variables included resting end-tidal \( P_{\text{co}_2} \), rate of ventilation and the ventilatory response to hypercapnia. The results were obtained during a cycle of testing which lasted approximately 15 min, throughout which the subject wore a noseclip and breathed through a mouthpiece connected to a low resistance circuit. First, with the subject breathing room air via a non-rebreathing valve, the end-tidal carbon dioxide tension \( (P_{\text{e}}\text{co}_2) \) and rate of ventilation were measured over a period of 7 min using a Hewlett-Packard (Model 42710) infra-red analyser. The mean values during each 1-min interval were derived electronically. Subsequently, the ventilatory response to hypercapnia was determined using a modified Read re-breathing method [10, 11]. Subjects breathed 50% oxygen through a low resistance valve for 3 min before being connected to a rebreathing system primed with a gas mixture containing 6.5% carbon dioxide and 50% oxygen in nitrogen. Rebreathing continued until the carbon dioxide concentration increased to 8.5% or until ventilation increased to 40 litre min\(^{-1}\), whichever occurred first. The gas mixture was contained in an electronic Ohio spirometer which provided an output proportional to volume, and this signal was processed to derive continuous minute ventilation. Minute volume \((V\text{e})\) was plotted instantaneously against \( P_{\text{e}}\text{co}_2 \) on a Bryans X-Y recorder.

Three such test sequences were recorded before the administration of i.m. morphine. Testing was recommenced 20 min later and repeated at 20-min intervals for 2.5 h and then every 30 min. Test drugs were injected i.v. 1 h after opioid treatment and subjects were monitored for the subsequent 6 h.

As the reproducibility of respiratory measurements within days is greater than that between days, measurements were assessed relative to baseline values for each study day [12]. Baseline values were obtained from the mean of the last two measurements made before injection of morphine. The values of ventilatory rate and \( P_{\text{e}}\text{co}_2 \), at each time point were obtained from the average of the data obtained over 7 min.

The slopes of the ventilatory response curves were determined by drawing a line of best fit through the linear portion of each curve. These lines were extrapolated to the ventilation at \( P_{\text{e}}\text{co}_2 \) 8 kPa to determine \( V\text{e}8 \). Slope and \( V\text{e}8 \) data were log transformed because the distribution of slopes of ventilatory response to hypercapnia is skewed and log normal [13, 14]. For these two variables, change from baseline was obtained by subtraction after taking logarithms.

Data for the 14 time points following injection of the test drug were analysed by “two-way repeated measures” analysis of variance. To simplify further statistical analysis, data were averaged within three time periods following injection of test drug: the first 1.5 h when the activity of a conventional dose of naloxone would be present and waning, the subsequent 3 h when nalmefene activity is expected to be dominant, and the final 1.5 h to assess possible recurrence of opioid activity.
FIG. 2. Time course of changes in minute ventilation at an end-tidal $PCO_2$ of 8 kPa ($\dot{V}bE_8$). At zero time morphine was given, and 1 h later one of the three morphine antagonists (■ = nalmefene 0.4 mg/70 kg; ○ = naloxone 1.6 mg/70 kg; □ = naloxone 0.4 mg/70 kg) or saline placebo (●).

**TABLE I. Log $\dot{V}bE_8$.** Mean values of change from baseline after drug. SEM 1 = SE of each mean in that column; SEM 2 = SE of the difference between any pair of means in the column

<table>
<thead>
<tr>
<th>Drug</th>
<th>0–1.5</th>
<th>1.5–4.5</th>
<th>4.5–6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-0.428</td>
<td>-0.359</td>
<td>-0.246</td>
</tr>
<tr>
<td>Naloxone 0.4 mg/70 kg</td>
<td>-0.305</td>
<td>-0.440</td>
<td>-0.396</td>
</tr>
<tr>
<td>Naloxone 1.6 mg/70 kg</td>
<td>-0.151</td>
<td>-0.343</td>
<td>-0.264</td>
</tr>
<tr>
<td>Nalmefene 0.4 mg/70 kg</td>
<td>-0.119</td>
<td>-0.139</td>
<td>-0.026</td>
</tr>
<tr>
<td>SEM 1</td>
<td>0.067</td>
<td>0.062</td>
<td>0.065</td>
</tr>
<tr>
<td>SEM 2</td>
<td>0.095</td>
<td>0.088</td>
<td>0.092</td>
</tr>
<tr>
<td>$P$ values (*significant)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nalmefene v. placebo</td>
<td>0.009*</td>
<td>0.03*</td>
<td>0.04*</td>
</tr>
<tr>
<td>Nalmefene v. naloxone 0.4 mg</td>
<td>0.08</td>
<td>0.006*</td>
<td>0.003*</td>
</tr>
<tr>
<td>Nalmefene v. naloxone 1.6 mg</td>
<td>0.74</td>
<td>0.04*</td>
<td>0.03*</td>
</tr>
</tbody>
</table>

**RESULTS**

Two-way analysis of variance, both before and after division into three time periods, showed significant difference between the four treatments for $PE'CO_2$, log slope and $\dot{V}bE_8$, and demonstrated that the differences varied over time. Rate of ventilation showed no significant difference between any of the drug regimens at any time.

Further analysis comparing the treatments during each time period was undertaken by carrying out paired $t$ tests using the residual standard deviations obtained from the analysis of variance. Statistical significance was assigned at $P \leq 0.05$.

**Fig. 3.** Changes in end-tidal carbon dioxide partial pressure.
LONG ACTING OPIOID ANTAGONISM

TABLE II. $P_{\text{CO}_2}$ Mean values (kPa) of change from baseline after drug

<table>
<thead>
<tr>
<th>Drug</th>
<th>Time after drug (h)</th>
<th>0–1.5</th>
<th>1.5–4.5</th>
<th>4.5–6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td>0.36</td>
<td>0.40</td>
<td>0.37</td>
</tr>
<tr>
<td>Naloxone 0.4 mg/70 kg</td>
<td></td>
<td>0.17</td>
<td>0.39</td>
<td>0.35</td>
</tr>
<tr>
<td>Naloxone 1.6 mg/70 kg</td>
<td></td>
<td>0.05</td>
<td>0.30</td>
<td>0.20</td>
</tr>
<tr>
<td>Nalmefene 0.4 mg/70 kg</td>
<td></td>
<td>0.09</td>
<td>0.25</td>
<td>0.16</td>
</tr>
<tr>
<td>SEM 1</td>
<td></td>
<td>0.08</td>
<td>0.05</td>
<td>0.08</td>
</tr>
<tr>
<td>SEM 2</td>
<td></td>
<td>0.11</td>
<td>0.07</td>
<td>0.11</td>
</tr>
</tbody>
</table>

$P$ values (*significant)
Nalmefene v. placebo      | 0.03* | 0.02* | 0.07  |
Nalmefene v. naloxone 0.4 mg | 0.48  | 0.03* | 0.10  |
Nalmefene v. naloxone 1.6 mg | 0.76  | 0.35  | 0.70  |

Log ventilation at end-tidal $P_{\text{CO}_2}$ 8 kPa (NE8)

Graphical display of averaged data (fig. 2) shows immediate recovery from morphine suppression with nalmefene treatment. Recovery was sustained over the 6-h period studied. Initial recovery with the high and low dose naloxone treatments was followed by a rapid decline and both differed significantly from nalmefene over the final 1.5–6 h period (table I).

Resting end-tidal $P_{\text{CO}_2}$

All three drug treatments were effective initially (fig. 3). Nalmefene was not significantly different from high dose naloxone at any time studied. Low dose naloxone differed significantly from nalmefene only over the middle 3 h (table II). There were no significant differences among any of the treatments, including placebo, after 4.5 h.

Log slope of ventilatory response to hypercapnia

Nalmefene treatment restored the slope of the response curve to baseline values for 6 h (fig. 4). Nalmefene was significantly different from low dose naloxone throughout the period studied (table III).

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![Graphical display of averaged data](image)

Fig. 4. Changes in slope of ventilatory response to carbon dioxide.

TABLE III. Log slope. Mean values of change from baseline after drug

<table>
<thead>
<tr>
<th>Drug</th>
<th>Time after drug (h)</th>
<th>0–1</th>
<th>1.5–4.5</th>
<th>4.5–6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td>-0.292</td>
<td>-0.217</td>
<td>-0.102</td>
</tr>
<tr>
<td>Naloxone 0.4 mg/70 kg</td>
<td></td>
<td>-0.255</td>
<td>-0.316</td>
<td>-0.246</td>
</tr>
<tr>
<td>Naloxone 1.6 mg/70 kg</td>
<td></td>
<td>-0.119</td>
<td>-0.239</td>
<td>-0.196</td>
</tr>
<tr>
<td>Nalmefene 0.4 mg/70 kg</td>
<td></td>
<td>-0.028</td>
<td>-0.024</td>
<td>0.036</td>
</tr>
<tr>
<td>SEM 1</td>
<td></td>
<td>0.065</td>
<td>0.087</td>
<td>0.077</td>
</tr>
<tr>
<td>SEM 2</td>
<td></td>
<td>0.092</td>
<td>0.123</td>
<td>0.108</td>
</tr>
</tbody>
</table>

$P$ values (*significant)
Nalmefene v. placebo      | 0.02* | 0.15  | 0.23   |
Nalmefene v. naloxone 0.4 mg | 0.03* | 0.04* | 0.03*  |
Nalmefene v. naloxone 1.6 mg | 0.35  | 0.11  | 0.06   |
**Side-effects**

Three of the subjects complained of paraesthesiae in the mid-thoracic region following the administration of nalmefene. One had a similar complaint following high dose naloxone. The administration of low dose naloxone was unaccompanied by side effects.

**DISCUSSION**

This study showed that, after the i.m. administration of morphine there was depression of ventilation and reduced sensitivity to carbon dioxide which lasted for 7 h. The subsequent administration of nalmefene produced a significantly greater change in $V_e$ during the final two time periods, that is from 1.5 to 6 h, than did either dose of naloxone. These results were not seen for $P_{E'] CO_2}$, for which there appeared to be no difference between nalmefene and high dose naloxone, and nalmefene differed from low dose naloxone only in the middle time period (1.5–4.5 h).

The different effects of these two opioid antagonists on $P_{E'] CO_2}$ and $V_e$ following morphine may be clinically significant and imply that impaired respiratory control may not be reflected completely in resting $P_{E'] CO_2}$ measurements. This impairment is revealed by a carbon dioxide challenge which only nalmefene antagonized throughout the 6-h period of the study.

The change in log slope of ventilatory response to hypercapnia following morphine-induced respiratory depression (fig. 4), confirmed the hypothesis that nalmefene produces prolonged opioid antagonism. The suggestion of some degree of respiratory stimulation by nalmefene above baseline was not confirmed by statistical testing (table III).

Rate of ventilation failed to show any significant change with any drug regimen, lending weight to the belief that ventilatory rate is not related closely to the degree of respiratory depression.

Towards the end of the study period the effect of morphine on ventilation waned and, for this reason, the differences between the groups tended to disappear.

Our results are in keeping with a rather different study by Gal and DiFazio [15], who pretreated subjects either with a placebo or with nalmefene 0.5 mg, 1 mg and 2 mg and then challenged them with the synthetic opioid fentanyl 2 µg kg$^{-1}$ at intervals for up to 8 h. Their results showed that antagonism persisted for 4 h with the 0.5-mg dose and up to 8 h with larger doses. They also observed a mild respiratory stimulant effect of nalmefene in some subjects before the administration of fentanyl.

Their study has a number of limitations in terms of relevance to clinical practice in that pretreatment with opioid antagonists is rarely used clinically. Furthermore, all the doses of nalmefene in their study caused pharmacological effects that exceeded those produced by the conventional dose of naloxone used in most clinical practice.

One of the problems in the design of our study was to determine the dose of nalmefene that would be equivalent in potency to the standard dose of naloxone 0.4 mg/70 kg body weight. In terms of receptor binding, nalmefene is more effective than naloxone at inhibiting agonist binding at central kappa and delta sites, whilst at central $\mu$ sites nalmefene is almost four times as potent as naloxone [9]. In terms of reversing the effects of morphine on tail flick in rats, nalmefene is twice as potent as naloxone (Manufacturers' Information for Physicians, 5th Revision 1984). On this basis we assumed that nalmefene was two to four times more potent than naloxone; because nalmefene 0.5 mg was the smallest dose that had been studied previously we decided to compare no more than this dose (in fact nalmefene 0.4 mg) with multiples of the conventional dose of naloxone.

These results are consistent with the properties of the drug [6] in that nalmefene 0.4 mg/70 kg has more potent opioid antagonist activity than both conventional and high-dose naloxone and its duration of activity exceeds 4 h. In this regard, nalmefene 0.4 mg appeared to be comparable to naloxone 1.6 mg during the 0–1.5 h time period, but with a longer duration of action. It would be of considerable interest to study the degree of duration of antagonist activity produced by nalmefene 0.1 mg.

**REFERENCES**


