EFFECT OF NALBUPHINE HYDROCHLORIDE ON THE VENTILATORY AND OCCLUSION PRESSURE RESPONSES TO CARBON DIOXIDE IN VOLUNTEERS

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Opioid analgesics decrease respiratory responses to carbon dioxide. Pure agonists, such as morphine, depress ventilation in a dose-related manner [1, 2] while those with partial antagonist activity such as nalorphine [3], pentazocine [4], butorphanol [5] and nalbuphine [6] show an Effect maximum \( E'_{\text{max}} \) for respiratory depression at small clinical doses.

Respiratory depression by anaesthetics and opioids has been attributed to other mechanisms such as altered mechanical factors in the respiratory system [7, 8] in addition to a reduction in central neural drive. Discrimination between these two mechanisms may be determined by measuring airway occlusion pressure \( P_{0,i} \) which allows a more direct index of neural activity and is less dependent on changes in impedance of the respiratory system [9].

The present study was designed to measure both ventilation \( \dot{V}_t \) and \( P_{0,i} \) responses to carbon dioxide and to assess the relative contribution of central and mechanical factors in the ventilatory depression associated with clinical doses [10] of nalbuphine. We also studied the ease of antagonism of the ventilatory depression with naloxone.

Subjects and Methods

Six healthy non-smoking male volunteers aged 19–34 yr gave written consent for the study, which was approved by the local Ethics Committee. No subject was taking medication or had taken drinks containing caffeine for 12 h before the study. Each subject was studied at the same time.

Summary

We studied the effect of nalbuphine on the ventilatory and occlusion pressure responses to carbon dioxide rebreathing in six healthy male volunteers (mean age 25.5 yr) in a single-blind laboratory study. On four separate days volunteers were assigned randomly to receive either placebo (0.9% sodium chloride) or three i.v. doses of nalbuphine (15, 30 and 60 mg 70 kg\(^{-1}\)), followed 90 min later by naloxone 0.4 mg 70 kg\(^{-1}\). Duplicate rebreathing tests were performed and the mean intercept at \( PE_{CO_2} \) 7 kPa and the slopes of the linear relationship between inspiratory minute ventilation \( \dot{V}_t \) or occlusion pressure \( P_{0,i} \) with \( PE_{CO_2} \) were measured. Nalbuphine significantly decreased the mean intercept of the \( \dot{V}_t \) \( (P < 0.01) \) and \( P_{0,i} \) \( (P < 0.05) \) responses, but caused no changes in the slopes. No significant difference between the doses was noted, suggesting that an Effect maximum \( E'_{\text{max}} \) for respiratory depression was reached with a dose of approximately 15 mg 70 kg\(^{-1}\). Naloxone was less effective in antagonizing the depression in \( \dot{V}_t \) at the higher dose of nalbuphine. Similar \( P_{0,i} \) values were associated with the same inspiratory flow rate (1 litre s\(^{-1}\)) before and after drug treatment, suggesting that nalbuphine acts centrally to depress ventilation. Sedation increased significantly following each dose of nalbuphine \( (P < 0.001) \). No demonstrable difference between the doses was shown, suggesting an Effect maximum \( E'_{\text{max}} \) for sedation was reached at about 15 mg 70 kg\(^{-1}\). Administration of nalbuphine was associated with pain at the injection site, dizziness, dreaming, nausea and vomiting. Cardiovascular stability was maintained in all subjects.
time of day, 2–3 h after a non-fatty breakfast. Vital capacity and forced expiratory volume in 1 s were measured with the subject standing. A slow i.v. infusion of sodium chloride 150 mmol litre\(^{-1}\) was started.

No subject had previous experience of the rebreathing method. A practice rebreathing was allowed to familiarize each subject with the apparatus. At the same time of day, at least 4 days apart, subjects received either placebo (0.9 % sodium chloride) or three randomly assigned doses of nalbuphine (15, 30 and 60 mg 70 kg\(^{-1}\)), administered i.v. over 5 min. (These doses are referred to subsequently as 15-, 30- and 60-mg doses.) Naloxone 0.4 mg 70 kg\(^{-1}\) was given i.v. 90 min after each dose of nalbuphine. The subject was unaware of the dose or the timing of the drugs administered.

Duplicate rebreathing tests were performed with the subject in the lying and then the sitting position. A standard sitting position was achieved using a padded polystyrene back-rest moulded for each subject. Rebreathing was commenced at –30 min (control), 30 min (30 min after placebo or nalbuphine), 90 min (immediately after i.v. naloxone 0.4 mg 70 kg\(^{-1}\)) and 150 min (1 h after naloxone). Each rebreathing test was completed in approximately 3–4 min. Sufficient time (usually 2–3 min) was allowed for \(P_{E_{\text{CO}_2}}\) to return to the pre-rebreathing value before the next rebreathing test was started.

The ventilatory response to carbon dioxide was determined by a modified Read method [11]. Subjects wore a noseclip and rebreathed from a 5 litre bag filled with 6 % carbon dioxide in oxygen, using a mouth piece via a large bore three-way tap and an open occlusion valve. The rebreathing bag was surrounded by a rigid container connected to a spirometer (Wedge, Med Science 570). Volume calibration of the spirometer was achieved electronically. The three-way tap allowed subjects either to breathe air or to rebreathe from the bag. The inspiratory and expiratory resistances of the apparatus were 0.02 kPa litre\(^{-1}\) s at a flow rate of 30 litre s\(^{-1}\). Gas was sampled close to the mouth and returned to the bag. The gas was analysed with a rapid response carbon dioxide analyser (Engstrom Eliza) to allow a continuous record of carbon dioxide at the mouth and thus measurement of end-tidal partial pressure (\(P_{E_{\text{CO}_2}}\)). Two mixtures of carbon dioxide (6.0 and 8.5 %) in nitrogen were used to calibrate the carbon dioxide analyser.

Airway pressure (\(P_{aw}\)), carbon dioxide concentration and inspired and expired volume and flow signals were recorded on a six-channel UV recorder (Bell and Howell 5-137). Measurements were taken from the recording with a digitizer (resolution to 0.1 mm; Terminal Display System Limited LC-12) linked to a microcomputer (BBC B plus). Measurements were taken from the rebreathing records after the increase in \(P_{E_{\text{CO}_2}}\) has become linear with time. Measurements of \(T_i\), \(T_e\), \(V_t\) and \(P_{E_{\text{CO}_2}}\) were taken from the individual breaths on the trace preceding airway occlusion. \(T_i\) and \(T_e\) were measured from the flow record. \(V_t\) was calculated as \(V_t \times 60/(T_i + T_e)\) and was not corrected to BTPS. Mean inspiratory flow rate was calculated as \(V_t/T_i\).

A pneumatic device was used to hold the occlusion valve open during normal inspiration. At random times during rebreathing and without the knowledge of the subject, it was inactivated during expiration so that inspiratory flow was prevented during the next inspiratory effort. The valve was reopened 200–300 ms later. The sub-atmospheric \(P_{aw}\) developed during the occluded inspiratory attempt was measured by a transducer (calibrated with a water manometer) connected to the mouthpiece (Furness Controls Ltd, FCO 40; range ± 250 mm H\(_2\)O) and recorded on an FM tape recorder (Thermionic). The \(P_{aw}\) signals were later replayed from the tape recording to the UV recorder at a speed of 10 cm s\(^{-1}\) to permit the measurement of \(P_{9,1}\) for 100 ms after \(P_{aw}\) had become less than –0.1 kPa, rather than after the pressure became less than atmospheric [12]. During rebreathing, airway occlusions (six to 10) were performed at random intervals separated by six to 10 normal breaths.

Serum concentrations of nalbuphine were measured by high pressure liquid chromatography to confirm that satisfactory concentrations were achieved at the time the ventilatory studies were performed. Venous blood samples were taken at 60 min before and 30 and 60 min after administration of the placebo or nalbuphine. The assay was sensitive to 1 ng ml\(^{-1}\) and specific for nalbuphine, with no cross reaction with metabolites. The coefficient of variation was < 2 % for nalbuphine concentrations > 6 ng ml\(^{-1}\). Nalbuphine concentrations in serum and plasma are identical (Aitkenhead AR and Achola KJ, personal communication) and in this paper the term ‘‘plasma” has been used to describe the serum concentration.
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Sedation was assessed with a linear analogue scale (horizontal 10-cm scale from alert to drowsy) at 30 min before and 30 and 150 min after administration of nalbuphine. Systolic and diastolic arterial pressures and heart rate were recorded at 15-min intervals (Dinamap). Other side effects of nalbuphine administration were recorded.

The change in \( V_t \) with increasing \( P_{E'CO₂} \) was calculated by least squares linear regression. The relationship was assessed both from \( V_t \) when \( P_{E'CO₂} \) was 7 kPa and from the slope of the relationship \( (V_t/P_{E'CO₂}) \). Although the relationship between \( P_{O₂} \) and \( P_{E'CO₂} \) was not linear, the relationship between \( \log_2 P_{O₂} \) and \( P_{E'CO₂} \) was, and consequently linear regression relationships between \( \log_2 P_{O₂} \) and \( P_{E'CO₂} \) were used to characterize the \( P_{O₂} \) responses.

In order to assess any change in relationship between \( P_{O₂} \) and \( V_t/Ti \), the regression relationship between \( V_t/Ti \) and \( P_{E'CO₂} \) was used to determine the \( P_{E'CO₂} \) associated with a \( V_t/Ti \) of 1 litre s⁻¹. The relationship between \( \log_2 P_{O₂} \) and \( P_{E'CO₂} \) was used to estimate the \( P_{O₂} \) value at this \( P_{E'CO₂} \). This value was therefore the \( P_{O₂} \) value associated with a \( V_t/Ti \) of 1 litre s⁻¹. In this way, \( P_{O₂} \) values associated with the same flows, before and after drug administration, were compared. This is more appropriate in the assessment of \( P_{O₂}/(V_t/Ti) \) relationship than simple comparison of \( P_{O₂} \) values at the same \( P_{E'CO₂} \), as the \( V_t/Ti \) of a subject at a given \( P_{E'CO₂} \) would be altered by drug administration, and the relationship between \( P_{O₂} \) and \( V_t/Ti \) may not be assumed to be linear.

Mean values for the duplicate measurements were calculated, and these values were used subsequently in statistical analysis. Because the slopes of responses to carbon dioxide are not distributed normally [13], these values were transformed by taking natural logarithms before statistical analysis. For descriptive purposes, mean values for all subjects, in each position and at each measurement time, were calculated and are illustrated in the figures.

Statistical comparisons of changes in the intercept and in the log slope, before and after each drug administration, before and after administration of naloxone, and immediately after and 1 h after naloxone, were made using a paired \( t \) test. Comparison between the effects of different doses of nalbuphine was made using analysis of variance. Sedation scores were compared before and after drug administration with the Wilcoxon test, and between doses with the Mann–Whitney \( U \) test [14].

RESULTS

Details of the subjects are given in table I. All subjects successfully completed the study. However, immediately following nalbuphine administration, severe nausea prevented two subjects from completing one of their rebreathing tests in the sitting position.

Ventilatory response to carbon dioxide

A greater \( V_t \) was recorded with the volunteers rebreathing in the sitting position (fig. 1). However, the pattern of change in \( V_t \) following administration of nalbuphine or naloxone was similar in both positions. The intercepts of the relationship at \( P_{E'CO₂} \) 7 kPa were similar throughout the placebo day and for the control values on each drug day. Following each dose of nalbuphine, the intercept was reduced significantly, but no significant difference between the doses could be shown.

In comparison with the uniform depressant effect of the different doses of nalbuphine, naloxone had different effects in lying and sitting subjects (fig. 1). In lying subjects, naloxone 15 mg and 30 mg significantly increased the intercept, but antagonism was incomplete. In sitting sub-

<table>
<thead>
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<th>Subject</th>
<th>Age (yr)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>FEV/FVC (litre)</th>
<th>Weight (% of ideal)</th>
<th>Expected weight (kg)</th>
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<td>67</td>
<td>4.65/7.30</td>
<td>93</td>
<td>72.1</td>
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<tr>
<td>JB</td>
<td>24</td>
<td>173</td>
<td>73</td>
<td>4.60/5.15</td>
<td>108</td>
<td>67.6</td>
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<tr>
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Fig. 1. Mean (SD) intercept at $P_{E\text{CO}_2}$ 7 kPa for $\dot{V}_t$ (litre min$^{-1}$) against $P_{E\text{CO}_2}$ (kPa), in the lying (L) and sitting (S) positions for the nalbuphine "treatment days" (placebo; nalbuphine 15, 30 and 60 mg 70 kg$^{-1}$) at the control time, following nalbuphine, naloxone and 1 h later. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Fig. 2. Mean (SD) intercept at $P_{E\text{CO}_2}$ 7 kPa for the log $P_{a\text{O}_2}$ (Pa) against $P_{E\text{CO}_2}$ (kPa), in the lying (L) and sitting (S) positions for the nalbuphine "treatment days" (placebo; nalbuphine 15, 30 and 60 mg 70 kg$^{-1}$) at the control time, following nalbuphine, naloxone and 1 h later. *$P < 0.05$; **$P < 0.01$.

Oclusion pressures

The intercepts throughout the placebo day and the control values on each drug day were similar (fig. 2). Compared with control, each dose of

| TABLE II. Mean (SD) log slope (litre min$^{-1}$ kPa$^{-1}$) of the relationship of $\dot{V}_t$ (litre min$^{-1}$) with $P_{E\text{CO}_2}$ (kPa) in lying and sitting subjects. *$P < 0.05$ |
|-----------------|-------|-------|-------|
|                 | Placebo | 15 mg | 30 mg | 60 mg |
| Lying           |        |       |       |       |
| Control         | 2.96 (0.30) | 2.87 (0.28) | 2.86 (0.23) | 2.82 (0.15) |
| Nalbuphine      | 2.81 (0.39) | 2.59 (0.46) | 2.53 (0.67) | 2.47 (0.60) |
| Naloxone        | 2.81 (0.40) | 2.74 (0.37) | 2.74 (0.30) | 2.60 (0.20) |
| 1 h later       | 2.86 (0.37) | 2.73 (0.36) | 2.61 (0.20) | 2.63 (0.24) |
| Sitting         |        |       |       |       |
| Control         | 2.74 (0.24) | 2.92 (0.23) | 2.89 (0.23) | 2.72 (0.18) |
| Nalbuphine      | 2.80 (0.35) | 2.70 (0.33) | 2.65 (0.36)* | 2.69 (0.26) |
| Naloxone        | 2.81 (0.33) | 2.72 (0.39) | 2.68 (0.31) | 2.54 (0.22) |
| 1 h later       | 2.85 (0.36) | 2.75 (0.35) | 2.66 (0.24) | 2.62 (0.24) |
nalbuphine significantly decreased the intercept in the lying and sitting subjects. We could not demonstrate any significant difference in the reduction of \( P_{o1} \) caused by any of the doses of nalbuphine. The decrease in intercept caused by 15 mg was antagonized by naloxone, but antagonism was incomplete. The decrease in intercept caused by 30 and 60 mg was not influenced significantly by administration of naloxone.

The mean log slope of the relationship of log \( P_{o1} \) to \( P_{\text{E}CO_2} \) did not change significantly following nalbuphine or naloxone, except following 60 mg in the sitting subjects (table III).

The administration of nalbuphine or naloxone caused no significant changes in mean \( P_{o1} \) at the same \( V_t/T_i \) (table IV).

**Plasma nalbuphine concentrations**

Mean plasma nalbuphine concentrations after placebo and the three different doses are shown in figure 3. There was a linear relationship between the dose and mean plasma concentration at 30 min \( r = 0.96 \). A small quantity of nalbuphine was detected in one sample on the placebo day (JB). This was considered to be a contaminant, as there was no evidence that nalbuphine had been administered inadvertently.

**Side effects**

Sedation increased significantly following administration of each dose of nalbuphine (fig. 4); no significant difference between the doses could be demonstrated. The effect of naloxone on sedation was not formally tested, but all the subjects were observed to be more alert following naloxone, and after 20 min appeared less sedated.

The degree of nausea and vomiting was not related to the dose of nalbuphine. Nausea and vomiting occurred on 10 occasions in 18 subject exposures to nalbuphine, mainly when the subject attempted to sit up. Only one subject (TT) did not complain of nausea or vomiting at some time during the study. In two subjects (JM, JH) nausea and vomiting was severe enough to interrupt the study briefly and the subjects had to remain supine for a few minutes to recover. One subject (JM), who vomited once during the study period, had a small uncomplicated haematemesis 3 h after...
the end of the study. Naloxone did not appear to have an influence on the frequency of nausea or vomiting. Vivid dreams were experienced by 50% of the subjects, and dizziness and pain at the injection site were reported by four subjects. The systolic and diastolic arterial pressures and heart rates remained stable throughout the study.

**DISCUSSION**

This study was undertaken to determine the effect of nalbuphine on $V_t$ and $P_{0.1}$ responses to carbon dioxide, and to analyse possible changes in the relationship between $P_{0.1}$ and $V_t/T_t$. We hoped to determine whether nalbuphine had purely central or central and peripheral effects.

$P_{0.1}$ was measured from when Paw had decreased to $-0.1$ kPa. This method avoided the difficulty with variation in the onset of the occlusion pressure wave [15] caused by changes in upper airway compliance [16]. Although $V_t/T_t$ increases linearly with $P_{E_{CO_2}}$, $P_{0.1}$ does not, and hence the relationship between $V_t/T_t$ and $P_{0.1}$ alters as $P_{E_{CO_2}}$ increases, and the “effective impedance” of the system increases with increasing inspiratory flow. Consequently we compared $P_{0.1}$ values that were associated with identical inspiratory flow rates (1 litre s$^{-1}$), so that the pressure component related to flow would be similar. We used the same inspiratory flow rate, rather than the same $V_t$, as $V_t$ may be affected by changes in relative duration of inspiration ($T_i/T_t$), despite a constant mean $V_t/T_t$.

Our subjects were unaware of the drug administered, in contrast with previous studies [2, 6, 17]. It was felt less important for the observer to be blinded, as the majority of the assessments were objective. The assessment of sedation was the only subjective measurement, but this was not a major interest of the study.

The results suggest that an Effect maximum ($E_{max}$) for ventilatory depression occurred with nalbuphine 15 mg/70 kg or less. With the carbon dioxide rebreathing [2, 17] and the steady-
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state methods [6, 18] the $E'$max for respiratory depression has been reached with doses of nalbuphine 10.5–30 mg/70 kg. Knoch and colleagues [18] and Romagnoli and Keats [6] administered nalbuphine by different routes. These differences may have accounted for the variations in doses associated with maximal respiratory depression. Although the route and pattern of administration were different, it is of interest that all these investigators [2, 6, 17, 18] and the present study found no further respiratory depression after the lowest dose of nalbuphine had been given. The respiratory depression caused by the three different doses of nalbuphine in this study was equivalent to that observed after morphine 10.5 mg/70 kg [2].

$V_t$ and ventilatory response to carbon dioxide were greater in the sitting than the supine subjects, an observation that is consistent with previous reports [19–21].

Opioid analgesics change the timing of the ventilatory cycle and co-ordination of the muscles of ventilation so that the generation of chest wall movement is altered. Opioids may also change other mechanical factors in the ventilatory system. Thus even if central neural drive were constant, ventilation could change if the effective impedance of the respiratory system were affected. The method proposed by Grunstein, Younes and Milic-Emili [22] has allowed separation of central and mechanical factors. It was proposed that the ventilatory muscles did not shorten during occlusion and that occlusion did not change respiratory neurone discharge [7, 9]. $P_{0.1}$ has been used as a measure of inspiratory muscle force to assess whether ventilation is reduced by a decrease in available force ($P_{0.1}$) or by an increase in respiratory impedance ($P_{0.1}$/ventilation). Using this method, respiratory depression associated with anaesthesia [7], opioid administration [8] and drug overdose [23] has been attributed to an increase in effective impedance. Changes in impedance have also been observed during exercise [24], but not during sleep [25]. However, this approach may be too simple [26]. Direct measurement of muscle fibre length in intact dogs showed that, during airway occlusion, diaphragmatic contraction was not isometric [27]. This observation does not support the premise that neural activation resulted in a muscle force that was not influenced by the force/length and force/velocity relationships of the muscle concerned.

The decrease in $P_{0.1}$ at a given $P_{E' \text{CO}_2}$, in this study suggests that nalbuphine has a direct central respiratory depressant effect. However, for identical inspiratory flow rates, $P_{0.1}$ remained unchanged before and after administration of nalbuphine. This supports previous findings that nalbuphine has no effect on the impedance characteristics of the lung or chest wall that could influence the translation of inspiratory force into ventilation [2,18].

In this study the changes in $P_{0.1}$ were not altered significantly by the subject’s position. This is a surprising observation, as other assessments of ventilatory mechanics have shown considerable changes with position [19, 28–30]. The pattern of ventilatory muscle activity also changes with position and the relationship between neural activation and mechanical output of the diaphragm is altered [31]. However, a previous study of $P_{0.1}$ has shown that this index did not alter with posture, despite changes in FRC [32]. These findings and those of others [26] suggest that $P_{0.1}$ does not permit an exact assessment of the altered respiratory impedance. In particular, changes in the time course of the inspiratory activity within a single breath may conceal alterations in the relationship of muscle activity to lung volume changes [26].

Sedation is a recognized feature of nalbuphine treatment [33, 34] and we confirmed that sedation increased significantly following each dose of nalbuphine. However, we could not determine a significant difference between the doses, suggesting that an $E'$max for sedation may also have been reached.

Changes in respiratory depression with time, following similar single doses of nalbuphine, have been reported by Gal and colleagues [2] and Romagnoli and Keats [6]. They reported maximal respiratory depression between 60 and 120 min and 20 and 40 min, respectively. Because the present study utilized a rebreathing technique similar to that of Gal and colleagues [2], it was decided to administer naloxone 90 min after each dose of nalbuphine. However, no rebreathing study was performed immediately before the administration of naloxone, and the maximal effect of the nalbuphine dose may have passed before naloxone was given. However, after naloxone administration $V_t$ at 7 kPa was still significantly less than control (fig. 1), suggesting that nalbuphine was still active at this time and had not been completely antagonized by naloxone.
Naloxone had no effect on the ventilatory response during the placebo study, confirming earlier findings [35, 36]. Previous studies have reported either complete [2] or incomplete [6] antagonism of the respiratory depressant effects of nalbuphine with naloxone. In the present study naloxone appeared to antagonize the respiratory depression induced by the smallest dose of nalbuphine in the lying subjects. It was clinically significant that the antagonism was incomplete, which supports previous studies [6]. At the higher doses of nalbuphine, and in sitting subjects, no significant antagonism occurred with naloxone even though the ventilatory depression was similar at each dose. This may have been because, in sitting subjects, the depression of ventilation caused by nalbuphine was less marked. A larger dose of naloxone may have been effective.

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REFERENCES


