A DOSE-RESPONSE STUDY WITH NALBUPHINE HYDROCHLORIDE FOR PAIN IN PATIENTS AFTER UPPER ABDOMINAL SURGERY

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In the treatment of pain after surgery, a balance has to exist between the efficacy of an analgesic and its adverse effects. If the partial agonist-antagonist, nalbuphine hydrochloride, is effective in the treatment of severe pain, it may offer advantages over full agonists, since it causes less respiratory depression at higher doses (Romagnoli and Keats, 1980; Gal, DiFazio and Moscicki, 1982). However, partial agonists such as nalbuphine may reach a maximum analgesic effect (Gal, DiFazio and Moscicki, 1982; Eisele and Steffey 1984; Kay and Krishnan, 1986). Indeed, it has been suggested that nalbuphine-induced analgesia may be reversed at higher doses (Welch et al., 1980; Welch and Feldman, 1981). Infusion studies, in which stable plasma concentrations can be used to predict the concentration associated with pharmacodynamic action, have been advocated to test whether the high doses of agonist-antagonist opioids do provide improved analgesia (Eisele and Steffey, 1984).

This study aimed to assess the relationship between incremental increases in steady-state plasma nalbuphine concentrations and pain relief, sedation and the safety of nalbuphine—in patients after upper abdominal surgery.

PATIENTS AND METHODS

Six male patients (ASA grade I or II) were studied. They were aged between 19 and 60 yr and about to undergo highly selective vagotomy for peptic ulceration. Patients gave consent to the study, which included the reassurance that they could withdraw from the study or request alternative analgesia at any time without prejudice. The study was approved by the local ethics advisory committee.

The day before surgery patients answered questions about symptoms that could result from the administration of an analgesic. The same questions were repeated at the end of the study for comparison. The linear analogue method for measuring pain and sedation was explained.

SUMMARY

Six male patients were studied on the morning following upper abdominal surgery for highly selective vagotomy. Nalbuphine hydrochloride was infused i.v. at different rates that increased progressively in each hour over a 4-h period. In the last 15 min of each hour, the plasma nalbuphine concentrations were almost steady (73-68, 71-82, 116-113 and 201-208 ng ml⁻¹). Patients and an observer made hourly assessments of pain and sedation. Although the changes in the pain and sedation scores were not significant, the patients' mean pain scores increased when the mean plasma nalbuphine concentrations were greater (> 82 ng ml⁻¹), which suggested that nalbuphine analgesia had been reversed. Nalbuphine caused sedation and possibly induced amnesia which could invalidate retrospective assessment since the patients' assessment of analgesic efficacy at the end of the study was good. No cardiovascular depression or significant decrease in the ventilatory rate was recorded.

Anaesthesia and the period before the dose-response study

Patients received temazepam 20 mg orally 1-2 h before surgery. Anaesthesia was induced with...
thiopentone 5–7 mg kg\(^{-1}\) i.v. and tracheal intubation was facilitated with suxamethonium 1.5 mg kg\(^{-1}\). Anaesthesia was maintained with 66% nitrous oxide and enflurane in oxygen. Nalbuphine 20 mg i.v. was given during surgery. Neuromuscular blockade was achieved with alcuronium and antagonized, on completion of surgery, with neostigmine 2.5 mg (plus atropine 1.2 mg). About 15 min after the induction of anaesthesia, an i.v. infusion of nalbuphine 2 mg kg\(^{-1}\)/24 h in 5% dextrose was started, from a clockwork infusion pump (Handley), modified for 24-h delivery.

In the recovery room, patients received nalbuphine 10 mg i.v. at 5-min intervals until analgesia was achieved. In the ward, the ventilatory rate was counted over 1 min and recorded hourly. Each patient could be given nalbuphine 10 mg i.m. every 2 h, if required for pain, in addition to the infusion.

**Nalbuphine dose–response infusion**

At 06.00 h (−60 min) on the morning following the day of the operation, the overnight nalbuphine infusion (2 mg kg\(^{-1}\)/24 h) was discontinued. A second nalbuphine infusion (dose–response infusion) was commenced 1 h later (time zero) using an electronic digital syringe pump (Vickers, Treonić IP4, model No. 118). Patients were unaware of the change in nalbuphine infusion or of the subsequent changes in dose.

The initial dose of nalbuphine during the first 1 h was 1 mg kg\(^{-1}\)/24 h (fig. 3A). For the first 6 min of the second hour, the infusion rate was increased to 10 mg kg\(^{-1}\)/24 h (loading dose) and then reduced to 2 mg kg\(^{-1}\)/24 h for the remaining 54 min. In the third hour, the infusion rates for the 6- and 54-min periods of the previous hour were doubled, and then doubled again in the fourth hour. The intention of this procedure was to reach a stable nalbuphine plasma concentration at the end of each hour of infusion (times 60, 120, 180 and 240 min) which was related in a logarithmic manner to the preceding values. The mean total dose of nalbuphine administered during the 4-h dose–response infusion was 61.8 mg (range 48.0–72.2 mg).

**Nalbuphine assay**

Venous blood samples (10 ml) were taken at the following times: zero, 45, 60, 105, 120, 165, 180, 225, 240 and 300 min. The samples were taken 15 min apart to indicate how well plasma steady-state concentrations had been achieved during that 1 h of the infusion. Nalbuphine serum concentrations (ng ml\(^{-1}\)) were estimated by high pressure liquid chromatography. 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\(^{-1}\).

**Patient and observer assessments of pain and sedation**

Patients were confined to bed for the period of the dose–response infusion. Routine nursing care was given, but conversation and reassurance were kept to a minimum so as not to influence the assessments. The assessments were performed by one observer (G.C.P.) who remained with each patient throughout the study.

Patients marked a horizontal (100-mm) linear analogue scale (LAS) to assess the degree of pain (between “no pain” and “worst pain”) and sedation (between “alert” and “drowsy”) at −60 min, zero and at the end of each hour at 60, 120, 180, 240, 300 and 360 min. At the same times, the observer assessed patients’ pain with a scale related to movement (Prince Henry Pain Scale, PHPS: 0 = no pain on coughing; 1 = pain on coughing, but not on deep breathing; 2 = pain on deep breathing, but not at rest; 3 = some pain at rest, slight; 4 = pain at rest, severe (Torda and Pybus, 1984)) and sedation with a 4-point scale (1 = awake and normal; 2 = drowsy; 3 = sleepy, needs to be spoken to; 4 = sound asleep). The effect of decreasing nalbuphine plasma concentrations was determined by assessing pain and sedation for 2 h after the end of the dose–response infusion.

Patients gave an assessment of the effectiveness and tolerance of their analgesic treatment (4 = excellent, 3 = good, 2 = fair, 1 = poor) following surgery at 360 min.

**Cardiovascular and ventilatory assessments**

Arterial pressure was measured by the Riva-Rocci method and recorded every 0.5 h along with heart rate until 2 h after the infusion (360 min). Ventilatory rate was counted over 1 min and recorded every 0.5 h.
Chest physiotherapy was performed on those patients who had evidence of sputum retention. Patients were examined for signs of chest infection at 360 min. The criteria for chest infection were: pyrexia (temperature > 37 °C), spontaneous coughing, expectoration of purulent sputum and any abnormality detected on auscultation of the lungs. Chest infection was diagnosed if three or all of these features were present.

**Statistics**

The results were expressed as mean (SD). Statistical analysis was by the Wilcoxon rank sum test.

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**RESULTS**

Each operation was performed by the same surgeon, through a midline upper abdominal incision. The physical characteristics of patients are summarized in table I. Five patients were taking either regular cimetidine (Nos 2 and 3) or ranitidine (Nos 4, 5 and 6).

**Period before the dose-response study**

The mean total dose of nalbuphine administered from operation to 06.00 h (mean 18.8 h) was 183.6 (55.5) mg (range 113.3–245.0 mg). The cumulative doses of nalbuphine, administered to each patient, are illustrated in figure 1. Three patients (Nos 4, 5 and 6) required frequent administration of nalbuphine for severe pain on recovery from anaesthesia. One (No. 6) required nalbuphine 60 mg i.v. over a period of 30 min. On the ward, another patient (No. 3) continued to have pain after nalbuphine i.m. (total 20 mg) within 2 h of surgery and required i.v. injections of nalbuphine (total 80 mg) over a period of 45 min. These doses of nalbuphine caused profound sedation. No cardiovascular depression or significant change in the ventilatory rate was recorded during this period. No patient requested alternative analgesia or withdrawal from the study.

**Nalbuphine dose–response study: plasma concentrations**

The nalbuphine plasma concentration profiles for each patient were similar (fig. 2). Three patients (Nos 4, 5 and 6) required nalbuphine 10 mg i.m. for pain, within 10 min of stopping the first infusion at −60 min, but plasma concentrations in these patients at the start of the dose–response infusion were not greater than in the other patients. The initial plasma concentrations (time zero) showed a wide variation (range 37–145 ng ml⁻¹). The mean nalbuphine plasma concentration decreased over the first 60 min, but increased again at 120 min with values similar to the initial mean plasma concentration (table II, fig. 3B). This was consistent with stopping the overnight infusion (2 mg kg⁻¹/24 h) for 60 min and starting the dose–response infusion at a slower rate (1 mg kg⁻¹/24 h). The mean plasma concentration then increased from 120 min to the end of the infusion in a log linear manner (r = 0.86) (fig. 3B). In the last 15 min of each hour, the mean plasma concentrations were 73–68, 71–82, 116–113 and 201–208 ng ml⁻¹ which, as a percentage of the concentration at the end of each hour, represented a change of only 7.3, 13.4, 2.7 and 3.3% within the last 15 min.

The plasma nalbuphine concentration from one patient (No. 4) at 240 min was unexpectedly low (58 ng ml⁻¹) (fig. 2). The reason for this is not clear, but the infusion tubing may have become disconnected in the final hour of the infusion. As
Fig. 2. Individual plasma nalbuphine concentration profiles (closed symbols and continuous lines) related to the subjective pain scores (open symbols, interrupted lines). The patient numbers 1 to 6 correspond to the text.

**TABLE II.** Mean (SD) values for plasma nalbuphine concentration (ng ml⁻¹), patient pain and sedation (LAS), and observer pain (PHPS) and sedation scores during the dose-response study. *Patient No. 4 omitted from 240 min; **patient No. 6 omitted from 360 min

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>-60</th>
<th>zero</th>
<th>60</th>
<th>120</th>
<th>180</th>
<th>240*</th>
<th>300</th>
<th>360**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nalbuphine concn (ng ml⁻¹)</td>
<td>72(22)</td>
<td>54(31)</td>
<td>82(45)</td>
<td>113(33)</td>
<td>208(59)</td>
<td>93(52)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain LAS</td>
<td>1.8(0.4)</td>
<td>2.3(0.8)</td>
<td>2.6(1.1)</td>
<td>3.0(0)</td>
<td>2.2(0.8)</td>
<td>2.0(0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedation LAS</td>
<td>1.8(0.4)</td>
<td>2.3(0.8)</td>
<td>2.6(1.1)</td>
<td>3.0(0)</td>
<td>2.2(0.8)</td>
<td>2.0(0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PHPS</td>
<td>3.5(0.6)</td>
<td>3.3(0.8)</td>
<td>2.8(0.8)</td>
<td>3.0(0.9)</td>
<td>2.6(1.1)</td>
<td>2.2(1.5)</td>
<td>1.8(1.1)</td>
<td></td>
</tr>
<tr>
<td>Sedation score</td>
<td>3.5(0.6)</td>
<td>3.3(0.8)</td>
<td>2.8(0.8)</td>
<td>3.0(0.9)</td>
<td>2.6(1.1)</td>
<td>2.2(1.5)</td>
<td>1.8(1.1)</td>
<td></td>
</tr>
</tbody>
</table>

a steady state concentration had not been achieved in the final hour, the plasma nalbuphine concentrations from this patient were not included in the mean plasma concentrations at 225 and 240 min. The response of this patient to the decrease in the plasma nalbuphine concentration is discussed.

**Patient pain scores (LAS)**

No significant change in pain scores was demonstrated. However, some of the trends observed were of interest. At the start of the study (−60 min), patients recorded high pain scores (mean 72) (table II, fig. 3c). In the subsequent hour, when no drug was being infused, each patient recorded a decrease in pain score (fig. 2). The mean pain scores showed a tendency to increase at the greater plasma nalbuphine concentrations.

Patient No. 4 was not included in the mean pain score at 240 min as a steady plasma nalbuphine concentration had not been reached in the final 1 h of the infusion. In this patient the decrease in the plasma concentration (from 123 to 58 ng ml⁻¹) at 180 min and 240 min coincided with a marked decrease in the pain score (73 to 37) (fig. 2) and PHPS (4 to 1). This fortuitous event supports the conclusion that pain relief may be greater at
lower nalbuphine plasma concentrations (< 100 ng ml⁻¹).

Observer pain scores (PHPS)

There were no significant changes in the observer pain scores. The mean score was greatest (3.5) at -60 min (table II, fig. 3d), in accordance with the high patient mean pain LAS at the same time. At the start of the dose-response infusion, the mean pain score decreased (3.3) and remained constant over the next 3 h of the infusion (3.3, 2.8 and 3.0). The mean score decreased (2.6) at 240 min (fig. 3d).

Sedation scores

No significant change in the sedation scores was demonstrable (table II). Marked sedation was present throughout the study. The patients’ mean sedation score was greatest at 60 and 240 min (fig. 4).

The observer recorded high sedation scores at the start of the study which increased during the dose-response infusion, reaching a maximum at 240 min (fig. 4). Each patient was able to be aroused, when spoken to, at the time of maximum sedation. The effect of sedation on the patients’ ability to complete the pain and sedation LAS was difficult to assess. No patient failed or needed help to complete the LAS.

Assessments after the dose-response infusion

As part of their routine mobilization regimen, patients were sat out of bed 30 min after the end of the dose-response infusion (except patient No. 6), and this change of posture may have influenced the assessments of pain and sedation. The mean patient and observer pain scores decreased 1 h after completion of the infusion (49 and 2.2, respectively) which coincided with a decrease in the mean plasma nalbuphine concentration (fig. 3). Patient No. 6 was excluded from the final assessments of pain and sedation, at 360 min, as alternative analgesia was given on request at 310 min. The remaining patient (36) and observer (1.8) mean pain scores showed a further decrease at 360 min.

The mean patient sedation score decreased (42) 1 h after the end of the dose-response infusion and increased (63) 1 h later at 360 min (fig. 4). The observer sedation scores continued to decrease in the 2 h after the end of the dose-response infusion (2.2 and 2.0).

Cardiovascular and ventilatory assessments

The systolic and diastolic arterial pressures and heart rate remained stable throughout the dose-response infusion study (mean range (SD): systolic 144–154 (14–20) mm Hg; diastolic 85–91 (4–19) mm Hg; heart rate 80–90 (8–15) beat min⁻¹).
Five patients (Nos 1–5) required physiotherapy, during the dose–response infusion; this was performed shortly after an assessment. Patients were more comfortable following physiotherapy as their need to cough was reduced. Patient No. 6 had no cough, so physiotherapy was delayed until alternative analgesia had been given at 310 min. Four patients (Nos 1, 2, 4 and 5) were cigarette smokers and were assessed as having a chest infection.

No depression of the ventilatory rate was observed with nalbuphine (mean range 17–20 b.p.m.).

Patient assessment of efficacy, tolerance and side effects

Five patients gave their assessment of the efficacy and tolerance of the treatment given for pain from operation to completion of the study at 360 min. One patient (No. 6) gave his assessment at 310 min before receiving alternative analgesia. In contrast to the pain scores, these retrospective assessments were equally divided between excellent (Nos 4 and 5), good (Nos 1 and 2) and fair (Nos 3 and 6).

The tolerance scores were: good (Nos 1, 5 and 6), fair (Nos 3 and 4) and poor (No. 2), which were related to the number of adverse effects reported: 1 (No. 1), 3 (No. 5), 4 (No. 6), 6 (Nos 3 and 4) and 10 (No. 2). The adverse effects were not limited to analgesic side effects (drowsiness, dry mouth, sweating, dizziness, difficulty in remembering, sore throat, nausea, feeling hot, blurred vision, hearing problems, excessive thirst, urinary problems, limb stiffness and depression).

DISCUSSION

The number of patients in this study was small. However, it was considered ethically unacceptable to continue the study as it became clear from other studies that nalbuphine provided inadequate analgesia in a high proportion of patients who had undergone abdominal surgery (Kay and Krishnan, 1986; Pugh et al., 1987).

Dose–response study

The number of patients in this study was small. However, it was considered ethically unacceptable to continue the study as it became clear from other studies that nalbuphine provided inadequate analgesia in a high proportion of patients who had undergone abdominal surgery (Kay and Krishnan, 1986; Pugh et al., 1987).

Period before the dose–response study

Nalbuphine was the only analgesic administered to patients before the dose–response study. Half the patients required frequent administration of nalbuphine for severe pain on recovery from anaesthesia. No patient requested to be withdrawn from the trial or asked for alternative analgesia.

The observer considered withdrawing three patients, but allowed them to continue in the study when additional nalbuphine caused increased sedation and the patients appeared to “settle”. Although the larger doses of nalbuphine appeared to increase sedation without a commensurate increase in analgesia, no formal testing of pain and sedation was performed. The mean total dose of nalbuphine administered between surgery and the dose–response study represented more than three times the dose of nalbuphine given to patients, following cholecystectomy, by Bahar, Rosen and Vickers (1985). The difference may reflect the greater pain experienced after vertical upper abdominal incisions. Greater doses of nalbuphine have been administered to patients following abdominal surgery, in whom analgesia was unsatisfactory in a large proportion (Kay and Krishnan, 1986).
increased at the higher nalbuphine plasma concentrations—a feature which supports the clinical impression gained by Welch and Feldman (1981). The mechanism of action of nalbuphine at the receptor is not understood clearly. An inverse response curve for analgesia has been discussed (Jasinski, 1983) and may explain the pharmacodynamic effects of nalbuphine in terms of either a two-receptor theory or a form of acute tolerance. The two-receptor theory attempts to explain the reduction of analgesia at higher doses, by suggesting that the drug acts at a second receptor, which produces physiological antagonism to the first. If there is a drug concentration-receptor occupancy relationship, as the plasma concentration decreases again, analgesia should return along the same path (Hull, 1983). Our results suggested that analgesia improved as the plasma nalbuphine concentration decreased.

Analgesic studies (Bullingham, 1983 from drug company data) have suggested that a plasma nalbuphine concentration of 20 ng ml\(^{-1}\) exerts a significant pharmacological effect. In the present study a mean plasma nalbuphine concentration greater than 82 ng ml\(^{-1}\) was associated with a greater patient pain score, and supports the findings of Welch and colleagues (1980). Kay and Krishnan (1986) have suggested that the efficacy of nalbuphine analgesia runs parallel to its respiratory effects, and that a maximum degree of analgesia is obtained, probably at a dose somewhere between 0.3 and 0.5 mg kg\(^{-1}\). Gal, DiFazio and Moscicki (1982) administered nalbuphine i.v. to six healthy volunteers who were subjected to experimental pain. The mean pain tolerance reached a maximum at the lowest plasma concentration (24 ng ml\(^{-1}\)) and in two of the subjects pain increased at the greater plasma concentration (62 ng ml\(^{-1}\)).

Sedation is a recognized feature of treatment with nalbuphine (Forrest, 1971; Beaver and Feise, 1978) and was marked throughout this study. The observer rated pain as least at the highest plasma concentration, when the greatest degree of sedation was present. The patients, however, recorded increased pain associated with the greater plasma nalbuphine concentrations, at a time when they felt sleepy. The difference between the patient and observer pain scores, at the greatest plasma nalbuphine concentration, may possibly have been because the observer was unable to distinguish analgesia from sedation. Three patients would have been withdrawn from this study, if sedation had not given the impression that they were “settled”. One patient recorded high pain scores throughout the study, but did not request additional or alternative analgesia until 1 h after the nalbuphine infusion had been discontinued, when his sedation had decreased.

Amnesia following the administration of nalbuphine has not been widely reported, but was noted by Kay and Krishnan (1986) in a study with large doses of nalbuphine in patients following abdominal surgery. Patients in our study complained of severe pain and recorded high pain scores on a number of occasions, yet at the end of the study, four of the six patients indicated that their analgesia since operation had been good or excellent. This apparent paradox may be explained if the patients had forgotten the severe pain earlier or had been influenced by the improved level of pain relief at the time of the assessment. One patient complained of nausea which required i.m. medication on two occasions, but failed to remember this when questioned at the end of the study. An amnesic effect is supported by our observations in a separate study with nalbuphine for pain after operation. Patients who had been withdrawn because of inadequate analgesia, despite large doses of nalbuphine, failed to remember the severe pain in the immediate postoperative period when questioned the following day (Pugh et al., 1987). Analgesics which cause amnesia may give misleading results if studies depend on retrospective assessments. This supports the criticism of single 24-h assessments of analgesia (Kay, 1985; Smith, 1985).

Cardiovascular stability was observed, as in earlier studies (Fahmy, 1980; Lake et al., 1982). The ventilatory rate did not alter as the nalbuphine plasma concentration increased, suggesting that respiratory depression was not a major feature of the use of nalbuphine (Romagnoli and Keats, 1980; Gal, DiFazio and Moscicki, 1982). Sedation and dry mouth were the most commonly reported side-effects; no serious side-effects were observed.

Nalbuphine may not possess a strong positive dose-response relationship. This study suggests that, if satisfactory analgesia is not obtained in some patients with low doses of nalbuphine, improvement may not necessarily occur with additional doses. Heavy sedation is a feature of high doses of nalbuphine and this hampers the assessment of analgesia.
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