Nalbuphine versus meperidine for post-operative analgesia: A double-blind comparison using the patient controlled analgesic technique

John S. Sprigge MB BCHIR FFARCS,
Paul E. Otton MD FRCP(C)

A double-blind study was undertaken to compare nalbuphine, a synthetic partial agonist opiate, with meperidine in providing analgesia in patients following abdominal surgery, using the patient controlled analgesic technique. Both drugs showed a wide variation in demand requirements, but they were equally effective in relieving pain as assessed by the linear analogue technique. Neither drug caused a reduction of respiratory rate. The patient-controlled analgesic technique gave analgesia of good quality and it aided the comparison of the two drugs. However, some of the patients found the technique difficult to manage, and it is expensive and time-consuming. Until further experience is gained with this device its use should be confined to a constant care unit.

Key words

PAIN: postoperative; ANALGESIA: patient demand; ANALGESICS: nalbuphine, meperidine.

The management of postoperative pain with traditional narcotic analgesic regimes is associated with an unacceptably high failure rate¹ and at best has represented a cautious compromise between adequate analgesia and the risk of complications, particularly that of respiratory depression.²

Recently the development of patient controlled analgesia therapy (PACAT), using narcotic analgesics administered by a special intravenous infusor, has provided greater analgesic success with enthusiastic patient acceptance.^{1,3} There remains, however, a lack of data on the incidence of side effects including respiratory complications, or the relative safety of the technique when used outside of special care nursing units.⁴

As respiratory depression represents the major morbidity cost of narcotic analgesia any protection offered against this complication could further enhance the safety and extend the use of patient controlled analgesia. In this regard the synthetic mixed agonist-antagonist opiate nalbuphine⁵ with an analgesic potency, at moderate dosage levels, roughly equivalent to morphine⁶⁻⁸ has also been shown to have a limited depression of respiration.^{6,9,10} This early ceiling plateau effect of nalbuphine on respiratory depression, if attendant with satisfactory analgesia, would be a particularly useful and inherently safer agent for use in patient controlled analgesia therapy. Accordingly the present trial was established to survey the analgesic efficacy of nalbuphine as compared to the standard narcotic analgesic meperidine using the Cardiff

From the Department of Anaesthesia, Royal Victoria Hospital, Montreal, Quebec.

Address correspondence to: Dr. P.E. Otton, Anaesthetist-in-Chief, Royal Victoria Hospital, 687 Pine Avenue West, Montreal, Que., H3A 1A1.

Supported in part by a grant from DuPont Pharmaceuticals, Montreal, Canada.

TABLE I Clinical details of patients

	Nalbuphine	Meperidine
No. of Patients	9	9
Sex	F 9	M 1 F 8
Age (years)	39 $\pm$ 11	44 $\pm$ 8
Weight (kg)	57 $\pm$ 9	63 $\pm$ 14
Operations	Cholecystectomy 3 Hysterectomy 6	Cholecystectomy 1 Hysterectomy 7 Tuboplasty 1

Palliator*¹¹ for postoperative patient controlled analgesia.

Methods

With ethical committee permission and informed consent, 18 patients undergoing elective abdominal surgery acted as subjects. Their clinical details are shown in Table I. All patients were in good health.

The anaesthetic technique consisted of premedication with oral diazepam 20 mg, induction with thiopentone 4 mg·kg⁻¹ preoxygenation with curare 3 mg, suxamethonium 1 mg·kg⁻¹ for intubation, and curare 0.3 mg·kg⁻¹ to maintain satisfactory muscle relaxation. Ventilation was with nitrous oxide 70 per cent, oxygen 30 per cent and halothane, administered via a modified T-piece circuit at rates and flows to maintain normocarbia. At the end of surgery, muscle relaxation was reversed with neostigmine 2.5 mg and atropine 1.2 mg, and the patients were extubated and returned to the recovery unit where they remained for the duration of the study.

In the preoperative period, one of us (J.S.S.), explained the purpose of the study to the patients and they were made familiar with the Cardiff Palliator patient controlled infusion pump and the linear analgesic technique of assessing pain.¹² The patients were randomly assigned, in a manner blind to both the patient and observer, to receive a postoperative course of one or other of the analgesic solutions.

When the patients recovered consciousness they were asked, by the same observer who conducted the preoperative interview, to indicate their pain on the linear analogue. They were further reminded

*Cardiff Palliator - Pyc Dynamics Ltd., England.

FIGURE 1 Linear analogue scores in cm (mean $\pm$ SD) versus time in hours. Linear analogue 10 cm = severe pain; 0 cm = no pain. Nalbuphine (●) and meperidine (○).

how to use the Cardiff Palliator when in pain and were encouraged to use it throughout the study. Assistance with the use of the Palliator was available if the patients were unable to use it by themselves. Triggering the Palliator caused a bolus of nalbuphine 3 mg or meperidine 20 mg, in 2 ml saline, to be administered intravenously over two minutes. The machine was refractory to further demands within 15 minutes of the last demand. The times at which analgesia was administered were recorded, and at hourly intervals the linear analogue score for pain was measured. Also the respiratory rate, pulse and blood pressure were recorded at hourly intervals. Side effects such as drowsiness, nausea, vomiting and dysphoria were noted.

Results

Nalbuphine and meperidine were equally effective in relieving pain, as assessed by the linear analogue scores. Pain scores fell from initial means of 8.9 (nalbuphine) 8.8 (meperidine), to 4.5 (nalbuphine) 6.6 (meperidine) at 2 hours, and 3.5 (nalbuphine) 5.6 (meperidine) at 4 hours (Figure 1). Although it

TABLE II Drug requirements for the two drugs in the 4-hour study period

	Nalbuphine	Meperidine
Average number of demands $\pm$ SD	5.6 $\pm$ 3	5.7 $\pm$ 1.3
Range in Number of demands	2-11	3-8

FIGURE 2 Number of drug demands per hour versus time in hours.

would appear that nalbuphine gives analgesia of more rapid onset and better quality, statistical analysis (Wilcoxon signed rank test), at each time period showed no significant difference between the pain scores for the two drug groups. Nalbuphine 3 mg appeared to be equipotent with meperidine 20 mg.

There was a wide range in demand requirements for the two drugs (Table II), but there was no significant difference between the average number of demands. The drug demands were highest in the first hour (Figure 2). Neither drug produced respiratory depression as monitored by respiratory rate. The pulse and blood pressure recordings remained stable during the study period. Two patients felt nauseated postoperatively, not apparently associated with administration of the drug. However, in another two patients, nausea followed immediately after administration of the drug, in both cases meperidine.

All patients were drowsy postoperatively, and most remained so during the study but no patient experienced dysphoria. Unfortunately, because of drowsiness and lack of co-ordination none of the patients was able to use the Palliator for initial analgesia; furthermore, the inability to self demand a dose persisted in seven patients after three hours, and in three patients up to four hours postanaesthesia, but this lack of compliance was unrelated to the analgesic drug selected.

Discussion

The use of narcotic analgesics carries the risks of respiratory depression, nausea, dysphoria and addiction. The partial agonist narcotics have been introduced to try to solve this problem, but none is more free of these risks than the pure agonists such as morphine or meperidine. However, it has been reported that nalbuphine, in contrast to traditional agonist narcotics, exhibits a ceiling effect for respiratory depression^{6,9,10} although it is still unclear whether this benefit may be at the expense of analgesia.^{6,8}

The experimental design of this study randomly assigned nine patients each to the two drug groups and collectively they selected a total of 101 separate analgesic demands consisting of 50 nalbuphine and 51 meperidine doses. Although the size of each group is relatively small the total comparative pain assessment sample involved some 50 doses of each drug and as each of these doses was consistent in either improving the pain score or in sustaining an already satisfactory level of analgesia, the total sample size was considered sufficient to discriminate between any gross differences in the analgesic effectiveness of the two drugs. Furthermore placebo overlay, particularly inherent in analgesia studies requiring attentive observer presence,¹³ undoubtedly existed but any bias in this direction should have been corrected by the double blinded allocation of drugs. Ethical considerations obviated the inclusion of a placebo substitute.

Under these study conditions bolus doses of nalbuphine 3 mg appeared to give analgesia as potent as that of meperidine 20 mg, which is in approximate agreement with previous assessments of potency.⁶⁻⁸ Nalbuphine did not appear to cause respiratory depression, but neither did meperidine. As the patients in this study were all healthy it should not be assumed that the drugs would not cause respiratory depression if administered in larger doses or to sicker patients. Furthermore, the administration of narcotic analgesics by intravenous infusion regimes may be associated with respiratory depression,² and this may occur also even when partial agonists are used.¹⁴ However, it would seem reasonable to expect that the limited respiratory depressant effect of nalbuphine^{6,10} may make it an inherently safer drug for use with patient triggered infusion pumps.

Unfortunately, both groups of patients were drowsy during the study period and it was felt that this was probably due as much to the general anaesthetic hangover as to the narcotic. However, it has been previously noted that when narcotic infusions are continued into the second and third postoperative days sedation is less marked.¹⁵ Nalbuphine did not appear to cause nausea or dysphoria and in this regard it may be superior to the partial agonist, buprenorphine, although its duration may not be as long.¹¹

Previous studies have shown how wide are the variations in individual requirements for postoperative analgesia. This study confirmed these findings, and again demonstrated how well a patient-controlled technique can satisfy the broad variability in analgesia requirements.^{3,11,12,14-16} Furthermore, the patient demand technique is a simple but valuable objective method for comparative studies of analgesic drugs.

Like others, we found that not all patients were able to master the technique.¹⁶ In this study, all patients had to be assisted with their initial dose and after four hours, three patients were still too unco-ordinated to satisfy their own demands. In addition, the need for close patient supervision with the possible risk of respiratory depression due to overdose probably confines the use of the Palliator to a high dependency unit. In this regard further controlled studies are required to quantify the potential protection against respiratory depression offered by nalbuphine before a more liberal use of this drug for self-administered techniques can be advocated.

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Résumé

On a effectué une étude à double insu comparant la nalbuphine, un opiacé synthétique partiellement agoniste à la mépéridine comme agent analgésique à la suite de chirurgie abdominale. Le patient s'administrait lui-même le médicament. Pour les deux médicaments, on a observé une grande variabilité dans les doses administrées mais l'efficacité analgésique appréciée sur une échelle linéaire était la même pour les deux drogues. Aucune des deux n'a réduit la fréquence respiratoire. Cette technique d'auto-administration assurait une analgésie de bonne qualité et permettait de comparer les deux médicaments. Cependant, certains malades ont trouvé la technique difficile à maîtriser, technique dont il faut reconnaître qu'elle entraîne des dépenses de temps et d'argent. Pour le moment, cet appareil doit être réservé pour utilisation sous surveillance constante.