A comparison of nalbuphine and meperidine in treatment of postoperative pain

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The analgesic efficacy and side effect profile of nalbuphine 20 mg IV and of nalbuphine 40 mg IV were compared to those of meperidine 75 mg IM in the immediate postoperative period. Pain intensity, pain relief, additional analgesic requirements and the overall acceptability of the treatment were recorded for 150 patients. No significant differences were found between the groups for any of the efficacy variables. Peak analgesic effects occurred at 15 minutes in both nalbuphine groups and at 30 minutes in the meperidine group. The mean time to additional analgesic medication was approximately 207 minutes in each group. The incidence of nausea and vomiting with meperidine was 22 per cent (95 per cent confidence interval 10 to 34 per cent) and with nalbuphine 20 mg the incidence was two per cent (95%CI −2 to 6 per cent). This difference was significant ($p < 0.01$). The difference between nalbuphine 40 mg (10 per cent, 95%CI 1 to 19 per cent) and meperidine, was not considered statistically significant ($p = 0.17$).

The analgesic efficacy of nalbuphine 20 mg was indistinguishable from that of nalbuphine 40 mg and from that of meperidine 75 mg. The significantly lower incidence of nausea and vomiting with nalbuphine is a major advantage for a recovery room analgesic.

Nalbuphine is an opioid kappa-agonist, mu-antagonist, 0.8 to 0.9 times as potent as morphine.[1] The drug has definite advantages over the more commonly used narcotic analgesics: a ceiling respiratory depression,[2–4] little effect on the cardiovascular system[5–7] and a lower incidence of nausea and vomiting.[1]

Our clinical impression was that the maximal single dose of 20 mg recommended by the manufacturers was not always sufficient. Our experience suggested that a dose of 40 mg of nalbuphine was often required to provide analgesia equivalent to that of 10 mg of morphine or 50 mg of meperidine, which are the standard postoperative analgesic doses used in our recovery room. We therefore designed a double-blind controlled trial. The objective was to compare the relative efficacy and safety of nalbuphine 20 mg IV, nalbuphine 40 mg IV, and meperidine 75 mg IM.

We chose meperidine as the active control because of the penury of published studies comparing its postoperative use with that of nalbuphine and because of its broad usage. The dose of meperidine was increased to 75 mg since only patients with moderate to severe pain would be included. Nalbuphine was administered intravenously since we could find no satisfactory data on its intramuscular absorption.

Key words
NARCOTIC ANALGESICS: meperidine; nalbuphine;
PAIN: postoperative.

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Supported by a grant from Du Pont Pharmaceuticals.

Methods

Following approval by the ethics committee, we began reviewing the charts of patients scheduled for eligible surgeries. All inclusion criteria were met by 273 patients. Two hundred and forty-six (90 per cent) agreed to participate and signed the consent form. Of these, 150 (61 per cent) required analgesic medication in the recovery room, and were included in the study.

All patients were ASA physical status I or II. All were scheduled to undergo abdominal or orthopaedic surgery expected to cause moderate to severe postoperative pain. The patients were interviewed prior to surgery and informed consent was obtained. The anaesthetic technique, including pre-medication, was standardized: thiopentone 3–5 $mg \cdot kg^{-1}$; fentanyl 1.5 $\mu g \cdot kg^{-1}$; pancuronium 0.025–0.030 $mg \cdot kg^{-1}$; succinylcholine 1–2 $mg \cdot kg^{-1}$; N_2O 70 per cent/O_2; enflurane, as required.

A single observer followed the patient from admission to the recovery room until discharge to a ward. We did not influence the time at which the postoperative analgesic was given. As soon as the patient, upon questioning by the recovery room staff, requested an analgesic, the observer rated the patient's pain and the study drug was administered. The study medication was prepackaged and num-

TABLE I Demographic data

	Meperidine 75 mg	*Nalbuphine 20 mg*	*Nalbuphine 40 mg*	*p*
Number of patients	50	50	50	
Age mean ± SD	42 ± 11	40 ± 11	40 ± 11	ns
Females	31	41	42	0.02
Hysterectomy	21	20	27	ns
Other abdominal	19	25	18	ns
Orthopaedic	10	5	5	ns
Duration of surgery (min) mean ± SD	117 ± 55	126 ± 56	119 ± 37	ns

bered according to a computer-generated randomization schedule. In order to maintain double-blind conditions, patients received both an IM and an IV injection, only one of which was active medication.

Pain relief (PAR) and pain intensity (PI) were assessed 15, 30, 60 and 120 minutes after the medication was administered. After questioning the patient, the observer rated PI by circling a number from 0 to 10, where 0 = no pain; 1–2 = mild; 3–5 = moderate; 6–8 = moderately severe; 9–10 = severe pain. PAR was rated by the observer on a 5-point ordinal scale: none (1), slight (2), moderate (3), good (4), complete (5). PAR scores were summed over the 120-minute period to yield a total pain relief score (TOTPAR). Baseline PI scores were subtracted from each subsequent score to derive a pain intensity difference (PID). These differences were then added to give a summed pain intensity difference score (SPID). We also recorded the time from administration of the postoperative study drug until the next analgesic.

Vital signs were recorded at 0, 15, 30, 60 and 120 minutes. The patients were observed closely for side-effects throughout their stay in the recovery room.

Following the patient's return to the ward, the observer interviewed the patient and then assessed the overall acceptability of the treatment on a 5-point ordinal scale (poor, fair, good, very good, excellent). This assessment took into consideration both the efficacy of and tolerance to the medication.

Patients were followed for two hours after the administration of the study analgesic. If at any time prior to the end of the observation period, patients required additional analgesic medication, pain intensity and pain relief were immediately assessed and further evaluations discontinued. This last score was attributed to the remaining evaluation periods.

Pain intensity (PI), pain intensity differences (PID) and pain relief scores (PAR) were analyzed by repeated measures analysis of variance. SPID, TOTPAR, the time to additional analgesics and appropriate demographic data were compared by analysis of variance. Categorical demographic data and the incidence of side effects were compared by χ^2 analysis. Finally, the overall evaluation scores were compared by Kruskal-Wallis one-way analysis of variance.

Results

Table I summarizes the demographic data. There were no significant differences among the three groups other than the distribution of sexes. In spite of randomizing, there were significantly fewer females in the meperidine group ($p < 0.02$).

Compared to baseline pain intensity (PI_0), all treatments significantly reduced pain by 15 minutes ($t = 15$; $p < 0.001$) (Figure 1). the maximum analgesic effect was seen at this time with both nalbuphine groups. The mean pain intensity at 15 minutes (PI_{15}) in the nalbuphine 20 mg group was 1.2 ($CI_{95\%}$ 0.6 to 1.8); in the nalbuphine 40 mg group it was 1.6 ($CI_{95\%}$ 0.9 to 2.3). The corresponding PID_{15}s were 6.9 ($CI_{95\%}$ 6.3 to 7.5) and 6.2 ($CI_{95\%}$ 5.5 to 6.9). The intramuscularly administered meperidine had its peak effect at 30 minutes, when PI_{30} was 1.4 ($CI_{95\%}$ 0.8 to 2.0) and PID_{30} was 6.5 ($CI_{95\%}$ 5.9 to 7.1). Pain intensity remained significantly below baseline values for the duration of the observation period. Between-group analysis (ANOVA) could not detect significant differences in pain intensity, pain intensity differences or in pain relief, at any time. The summed pain intensity differences (SPID) and total pain relief scores (TOTPAR) were not significantly different (Table II).

There were no significant differences in the percentage

TABLE II End-point variables (95% confidence intervals)

	Meperidine 75 mg	*Nalbuphine 20 mg*	*Nalbuphine 40 mg*	*p*
SPID	41 (36 to 46)	46 (41 to 51)	43 (37 to 49)	ns
TOTPAR	30 (28 to 32)	31 (28 to 34)	30 (26 to 34)	ns
Time to next analgesic (min)	205 (178 to 232)	210 (176 to 244)	206 (169 to 243)	ns
Overall assessment of good, very good or excellent	78 (66 to 90)	78 (66 to 90)	78 (66 to 90)	ns

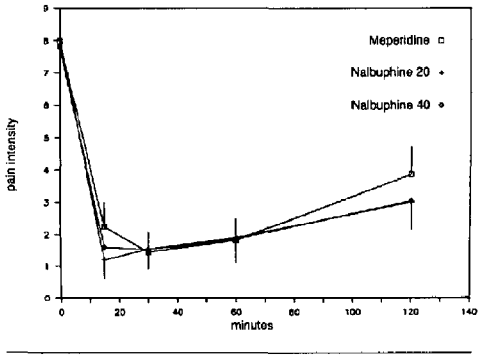

FIGURE 1 Mean pain intensity (95 per cent confidence intervals) as a function of time. Curves from the two nalbuphine groups are nearly superimposed from 30 minutes on.

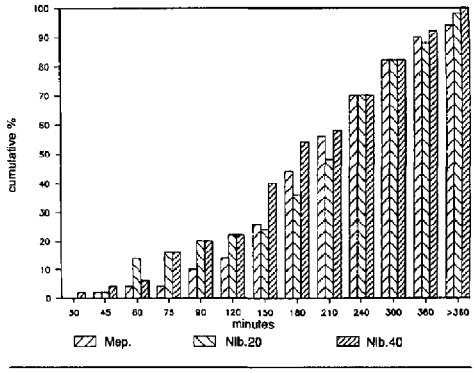

FIGURE 2 The cumulative percentage of patients requiring additional analgesic medication in each group. Mep. = meperidine 75 mg IM; Nlb.20 = nalbuphine 20 mg IV; Nlb.40 = nalbuphine 40 mg IV.

of patients reporting good or complete relief at any time (Table III). At 15 minutes, 62 per cent of meperidine-treated patients and 78 per cent of patients in both nalbuphine groups, had good or complete pain relief. By 30 minutes, 82 per cent of the meperidine group had reported good or complete pain relief compared to 78 per cent in each of the other groups.

Only one patient, in the nalbuphine 40 g group, required additional analgesic medication during the first 30 minutes (Figure 2). By 180 minutes, an analgesic had been administered to 44 per cent of the meperidine group, 36 per cent of the nalbuphine 20 mg group, and 54 per cent of the nalbuphine 40 mg group ($p > 0.05$). By 240 minutes, 70 per cent of patients in each group had taken an analgesic. Overall, 97 per cent of the patients received at least one additional dose of analgesic in the 12 hours following the study drug. The mean time to the next analgesic was 207 minutes and did not differ between groups (Table II).

The observer, after a follow-up interview with the patient, rated the overall acceptability of the analgesic treatment as good, very good or excellent in an identical number of patients in each group: 39/50 (78 per cent) (Table II).

There were no reports of excessive sedation in any group. There were no clinically important increases or decreases in blood pressure during the period of evaluation. No patient had a systolic below 90 mmHg or a diastolic below 50 mmHg at any time.

The only side effects reported were nausea and vomiting. These occurred more often with meperidine (22 per cent, $CI_{95\%}$ 10 to 34 per cent) than with nalbuphine 20 mg (two per cent, $CI_{95\%}$ −2 to 6 per cent). This difference is significant ($\chi^2 = 7.67$; $p < 0.01$). the difference between meperidine and nalbuphine 40 mg (10%, $CI_{95\%}$ 1 to 19%) was not considered statistically significant ($\chi^2 = 1.86$; $p = 0.17$).

Discussion

This controlled double-blind study has shown that nalbuphine 20 mg is an effective analgesic, indistinguishable from meperidine 75 mg and with a very low incidence of side effects. The efficacy results are comparable to those obtained following Caesarean section, where nalbuphine 0.2 mg·kg^{-1} was found to be equivalent to meperidine 0.75 mg·kg^{-1} for the relief of postoperative pain.[8] In a small study (18 patients) using a patient-controlled analgesic device, 3 mg of nalbuphine appeared equivalent to 20 mg of meperidine.[9] The validity of this latter

TABLE III Percentage of patients reporting good or complete pain relief (95% confidence intervals)

	Meperidine 75 mg	*Nalbuphine 20 mg*	*Nalbuphine 40 mg*	*p*
15 minutes	62 (49 to 75)	78 (66 to 90)	78 (66 to 90)	ns
30 minutes	82 (71 to 93)	78 (66 to 90)	78 (66 to 90)	ns
60 minutes	76 (64 to 88)	74 (62 to 86)	74 (62 to 86)	ns
120 minutes	46 (32 to 60)	54 (40 to 68)	54 (40 to 68)	ns

comparison is questionable since some patients were unable to use the device due to drowsiness or lack of coordination; and because the device was programmed to limit the number of doses delivered in a one-hour period.

The apparent lack of difference between 20 and 40 mg of nalbuphine may have one of three explanations. Firstly, in the type of postoperative pain studied, it is conceivable that the best pain relief possible was reached with 20 mg of nalbuphine. The mean 15-minute pain intensity score was 1.2 on a ten-point scale. Perhaps it is unrealistic to expect any analgesic to reduce the mean pain intensity to less than 1.2. Also, the fact that none of the 50 patients required additional analgesia during the first 30 minutes suggests that, at least for this period, better pain relief might be difficult to achieve.

Secondly, the number of patient studied may have been too few to provide the statistical power to find a significant difference. The number of patients studied was high enough to have a greater than 90 per cent chance of detecting a two-fold difference in efficacy between the two nalbuphine treatments. However, if the true difference in efficacy between the nalbuphine doses was only 20 per cent, then the study would have had less than a 60 per cent chance of concluding that there was a significant difference.

The last of the three possible explanations is that nalbuphine may have a ceiling analgesic effect in these types of pain. Nalbuphine has been shown to have a plateau in its respiratory depressant effect[2–4] as well as in its ability to reduce anaesthetic requirements in animals.[2,10] In the tourniquet-induced ischaemia test, nalbuphine appeared to reach a plateau analgesic effect at 0.15 $mg \cdot kg^{-1}$.[11]

In conclusion, our initial clinical impression regarding the relative potency of nalbuphine proved to be unfounded. Under controlled conditions, nalbuphine 20 mg was found to be indistinguishable from meperidine 75 mg in this immediate postoperative population. The significantly lower incidence of nausea and vomiting is an important attribute especially in the recovery room setting.

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Résumé

On a comparé l'efficacité analgésique et les effets secondaires de 20 mg et de 40 mg de nalbuphine IV à ceux de 75 mg de mépéridine IM dans la période postopératoire immédiate. On a enregistré l'intensité de la douleur, le soulagement de la douleur, les exigences analgésiques supplémentaires et l'évaluation globale du traitement chez 150 patients. On a trouvé aucune différence significative de l'efficacité entre les groupes. L'analgésie maximum s'est produite à 15 minutes dans les deux groupes recevant de la nalbuphine et à 30 minutes dans le groupe recevant de la mépéridine. Le temps moyen pour une dose analgésique supplémentaire était d'environ 207 minutes dans chaque groupe. L'incidence de nausées et de vomissements après l'administration de 20 mg de nalbuphine était de deux pour cent (intervalle de confiance −2 à 6 pour cent) tandis que l'incidence après l'administration de 75 mg de mépéridine était de 22 pour cent ($IC_{95\%}$ 10 à 34 pour cent). Cette différence était significative ($p < 0.01$). L'incidence après 40 mg de nalbuphine était de dix pour cent ($IC_{95\%}$ 1 à 19 pour cent; $p > 0.05$). L'efficacité analgésique de 20 mg de nalbuphine est indiscernable de celle de 40 mg de nalbuphine et de 75 mg de mépéridine. L'incidence, significativement plus faible, de nausées et vomissements avec la nalbuphine est un atout important pour un analgésique administré en salle de réveil.