Antinociceptive effect of a novel long-acting nalbuphine preparation

K. S. Liu¹ ², O. Y. P. Hu³, S. T. Ho⁴, J. I. Tzeng¹, Y. W. Chen¹ and J. J. Wang¹*

¹Department of Medical Research, Chi-Mei Medical Center, Tainan, Taiwan. ²Department of Chemistry, National Cheng Kung University, Tainan, Taiwan. ³Department of Research and Education, National Defense Medical Center, Taipei, Taiwan. ⁴Department of Anesthesiology, Tri-Service General Hospital, Taipei, Taiwan

*Corresponding author. E-mail: 400002@mail.chimei.org.tw

Background. A long-acting analgesic may be particularly desirable in patients suffering from long-lasting pain. The aim of the study was to evaluate the antinociceptive effect of a novel nalbuphine preparation and to determine its duration of action.

Methods. The antinociceptive effects of i.m. nalbuphine HCl in saline and nalbuphine base in sesame oil were evaluated in rats. The in vitro drug-releasing profiles of nalbuphine HCl and base in different preparations were also evaluated.

Results. We found that i.m. nalbuphine HCl 25, 50 and 100 µmol kg⁻¹ produced dose-related antinociceptive effects with a duration of action of 1.5, 2 and 3 h, respectively. I.M. nalbuphine base 100, 200 and 400 µmol kg⁻¹ also produced dose-related antinociceptive effects but with longer durations of action: 27, 49 and 55 h, respectively. In vitro studies demonstrated that nalbuphine base in sesame oil had the slowest drug-releasing profile of the different preparations.

Conclusions. I.M. injection of an oil formulation of nalbuphine base produced a long-lasting antinociceptive effect.


Keywords: analgesics opioid, nalbuphine; nerve, long-acting antinociception

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A long-lasting analgesic effect (i.e. a single dose with a 3–6-day duration of action) may be particularly desirable in patients suffering from long-lasting pain (e.g. postoperative pain, burn pain, post-traumatic pain, etc.) However, clinically available analgesics do not have such a long-lasting effect. Nalbuphine, (−)-17-(cyclobutyl-methyl)-4, 5α-epoxymorphan-3,6α,14-triol, is a morphine-like drug. It has agonist activity at κ-opioid receptors and antagonist activity at μ-opioid receptors.¹⁻³ As an analgesic, it is almost as potent as morphine and has been widely used in the treatment of clinical pain.¹⁻⁷ Its main advantages over morphine are a ceiling effect on respiratory depression, low tolerance liability and a lack of significant withdrawal symptoms.¹⁻³ It is available as injection for i.m. and i.v. administration, with recommended doses of 10–20 mg (25–50 µmol).²⁻⁷ However, nalbuphine is a short-acting drug with a duration of action of 3–5 h after i.v. or i.m. injection.²⁻⁷ In our laboratory, an oil formulation of nalbuphine base was made.

The aim of the study was to evaluate whether this form had a long-lasting effect.

Methods

Two studies were carried out. In the first study the antinociceptive effects of i.m. nalbuphine HCl in saline and nalbuphine base in sesame oil were evaluated in rats. In the second study, the in vitro drug-releasing profiles of nalbuphine HCl and base in different preparations were evaluated.

Study 1

Male Sprague–Dawley rats, obtained from the National Science Council, Taiwan, weighing 175–225 g, were used.

This work was done in the Chi-Mei Medical Center, Tainan, Taiwan.
They were housed in groups of three for at least 1 week in a climate-controlled room maintained at 21°C with approximately 50% relative humidity. Lighting was on a 12-h light/dark cycle (lights on at 6.00 a.m.), with food and water available ad libitum up to the time of testing. All tests were performed in accordance with the recommendations and policies of the International Association for the Study of Pain and the protocol was approved by the Animal Investigation Committee of Chi-Mei Medical Center.

Nalbuphine HCl was purchased from Du Pont Merck (DE, USA). Nalbuphine base was obtained by precipitation. In brief, after addition of a saturated solution of Na₂CO₃ drop by drop into a nalbuphine HCl solution, nalbuphine base was precipitated. The precipitate was then filtered and washed several times with cold deionized water to remove excess Na₂CO₃. Nalbuphine base was obtained by drying the white residue and was then prepared in injectable sesame oil (Sigma, MO, USA) suspension. Nalbuphine HCl was prepared in water.

A paw pressure test was used to determine the antinociceptive effect of i.m. nalbuphine HCl and nalbuphine base. Briefly, the nociceptive threshold was measured by applying increasing pressure to the right hind paw using a TSE analgesia system (Randall-Selitto; Technical & Scientific Equipment GmbH, Bad Homburg, Germany). The nociceptive threshold (expressed in grams) was taken as the point that the rat made a vigorous attempt to remove the paw. A cut-off of 500 g was used.

Two dose–response studies were done (n=6 for each treatment). In the first we evaluated the antinociceptive effect of i.m. nalbuphine HCl at doses of 25, 50 and 100 µmol kg⁻¹. The vehicle (saline) was used as control. In the second, we evaluated the antinociceptive effect of i.m. nalbuphine base at doses of 100, 200, and 400 µmol kg⁻¹. The vehicle (sesame oil) was used as control. All drugs were injected into the left hind leg (biceps femoris and semitendinosus). Each rat received only one injection of 0.3 ml.

An in vitro dialysis study was performed. A dialysis bag with a cut-off of 12 000–14 000 molecular weight (Union Carbide, IL, USA) was used. Before the test, phosphate buffer was prepared using monobasic potassium phosphate 1.9 g, dibasic sodium phosphate 8.1 g and sodium chloride 4.1 g dissolved in 1 litre of water to make an isotonic solution with a pH of 7.4. Nalbuphine HCl (100 µmol) or base (100 µmol) in 1 ml oil vehicle or phosphate buffer was put in the dialysis bag at the start of testing. Then, each of the different formulations (n=6 for each formulation) were put individually into a 200 ml flask containing 150 ml phosphate buffer and stirred at 500 rpm using a magnetic stirrer. The release of nalbuphine from each preparation (in the dialysis bag) into the phosphate buffer solution was measured. A UV spectrophotometer (UV-160, Shimadzu, Kyoto, Japan) was used to detect the nalbuphine concentration in the phosphate buffer outside the dialysis bag.

Statistical analysis
In Study 1 (the in vivo dose–response studies), the antinociceptive effects of nalbuphine HCl or base were compared with baseline values in the vehicle group using Student’s t-test. In the in vitro study (Study 2), we used...
repeated-measures ANOVA to compare the differences between the four groups. Bonferroni correction was applied for post hoc comparisons in a pair-wise manner. A P value less than 0.05 was considered significant.

Results

Study 1

Nalbuphine HCl produced a dose-related antinociceptive effect after i.m. injection (Fig. 1). The duration of action of nalbuphine HCl 25, 50 and 100 µmol kg⁻¹ was 1.5, 2 and 3 h, respectively (Fig. 1). A fourfold increase in dose produced a twofold (3 h/1.5 h) increase in duration of action. I.M. injection of nalbuphine base also produced a dose-related antinociceptive effect but with longer duration of action (Fig. 2): 27, 49 and 55 h at doses of 100, 200 and 400 µmol kg⁻¹, respectively. A fourfold increase in dose produced a twofold (55 h/27 h) increase in duration of action. On an equimolar basis, i.m. injection of nalbuphine base 100 µmol kg⁻¹ in sesame oil produced a longer duration of action (27 h) than nalbuphine HCl in saline (3 h).

Study 2

The in vitro drug-releasing profiles of nalbuphine HCl or base in different preparations are shown in Figure 3. The results demonstrated that any two groups in the study were significantly different. The preparations of drugs in sesame oil had slower drug-releasing profiles than those prepared in phosphate buffer. Nalbuphine base in sesame oil had the slowest drug-releasing profile.

Discussion

We found that i.m. injection of a novel nalbuphine preparation in rats produced a long-lasting effect, which was far longer than that of a traditional preparation of nalbuphine. An in vitro study also demonstrated that this novel nalbuphine preparation had a slow drug-releasing profile which supported this long-acting effect.

Opioid analgesics (e.g. morphine, meperidine and fentanyl) are frequently used for the management of clinical pain. These drugs interact with specific opioid receptors (i.e. µ receptors) in the central nervous system and exhibit potent analgesic activities. However, all these opioid analgesics have similar disadvantages. For long-term use, addiction is the most unwanted problem. Severe respiratory depression can also occur in some patients.

Opioid agonist–antagonist analgesics have been used clinically for the management of pain. These are typically nalbuphine and butorphanol and exhibit dual agonist and antagonist activity at opioid receptors. For instance, nalbuphine has antagonist activity at µ-opioid receptors and agonist activity at κ-opioid receptors. As a result of these pharmacological characteristics, the incidence of addiction and respiratory depression associated with their use is lower than with the pure opioid agonists. Equivalent doses of nalbuphine and butorphanol to morphine 10 mg are 10 mg and 2 mg, respectively. Among these drugs, nalbuphine is widely used clinically and it can be administered i.v. and i.m. but it is a short-acting drug. Extending the duration of action would make nalbuphine more valuable in clinical practice. A novel formulation of nalbuphine was made in our laboratory. In the present study, we found that this form had a long-lasting effect.

Pharmacologically, pure opioid agonists are not considered to be good candidates for the preparation of long-acting formulations because of safety considerations. Pure opioid agonists such as morphine and fentanyl can cause severe respiratory depression in high doses, without a ceiling effect. It is a problem if a large amount of drug is accidentally released from the formulation into the blood stream. In contrast, mixed opioid agonist–antagonists are relatively safer and have a ceiling effect on respiratory depression.

Pharmacologically, the duration of action of a drug may be controlled by the chemical form (base or salt) of the drug, the physical state of the injection (suspension or solution) and the vehicle (oleaginous or aqueous solution) used. Drugs in base form are more oil soluble whereas drugs in salt form are more water soluble. Drugs have a longer duration of action in oleaginous solution than in aqueous solution. In order to obtain a longer duration of action, nalbuphine base was suspended in an oleaginous vehicle (sesame oil). Indeed, we found that the duration of action of this novel formulation was much longer. Moreover, we found that, among different preparations, nalbuphine base in sesame oil had the slowest drug-releasing profile.
oil had the slowest drug-releasing profile, supporting the long duration action of this formulation in rats.

In our preparation, slow release of nalbuphine base from sesame oil is considered to be the mechanism of its long duration of action. However, at equimolar doses, short-acting formulations should produce a more potent effect (the magnitude of action) than a long-acting formulation. Following a higher dose, the potency of a long-acting formulation will be increased, as demonstrated in our study (Figs 1 and 2).

Although a syringe or patient-controlled analgesia pump may be used to produce sustained analgesia in patients who require it, a single i.m. injection of a long-acting preparation has advantages over these methods: it reduces healthcare personnel time, it reduces the use of related medical products and it enhances patient convenience and compliance in daily activity.

The safety of i.m. vegetable oils such as peanut, cotton seed and sesame oils is well documented. Several clinically available long-acting drugs are formulated in these preparations and injected i.m. for example estradiol valerate, fluphenazine decanoate, fluphenazine enanthate, progesterone, testosterone cypionate and testosterone enanthate. Most of these long-acting preparations are formulated in sesame oil and injected and this was used in our study.

In clinical practice, nalbuphine HCl 25 μmol (10 mg) i.m. provides an adult with 3–5 h analgesia (4 h average). In our study, i.m. injection of nalbuphine HCl 25 μmol kg⁻¹ in rats had a 1.5 h duration of action. According to the ratio (2.7) obtained in humans and rats (4 h/1.5 h), we estimate that i.m. injection of nalbuphine base 100, 200 or 400 μmol in humans will have a duration of action of 3, 5.5 or 6.2 days.

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**References**