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INJECTABLE SUSPENSIONS FOR PROLONGED RELEASE NALBUPHINE

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SUMMARY

There is a need for parenteral opioid analgesics with longer durations of action. Suspensions of nalbuphine were formulated by buffering the HCl salt to pH 9-9.2 in the presence of the commonly used suspending agents, methylcellulose, sodium carboxymethylcellulose, and PEG. Each of these suspensions prolonged nalbuphine release, relative to a nalbuphine HCl solution, after intramuscular administration to rats. Peak plasma concentrations were lower, and the half-life was increased more than 2-fold. The methylcellulose suspension had the smallest particle size and gave the highest plasma nalbuphine concentrations. This was also evaluated in dogs, and as in rats, the half-life was approximately doubled. These suspensions can be lyophilized and readily resuspended, and do not appear to be irritating. This is a simple, practical approach to a prolonged release injectable.

INTRODUCTION

Nalbuphine HCl (Nubain®, DuPont Pharmaceuticals) is a narcotic agonist/antagonist available as an injectable for relief of moderate and severe pain. The duration of analgesia is usually 4 to 5 hours after 10 mg i.m. doses,

and approximately 2.5 hours after i.v. injection.[1] The average terminal half-lives after 10 mg and 20 mg i.v. and i.m. injections ranged from 2.2 to 2.5 hours, and there was no difference between i.v. and i.m.[2] Oral bioavailability is low; in healthy volunteers the average bioavailability was 16-17%.[3] An oral dosage form is not yet available in the U.S. The continuous suppression of chronic pain with this agent therefore requires frequent injections. A rational approach to improving chronic pain therapy with nalbuphine is the development of a long-acting parenteral formulation.

Several approaches have been used to prolong the release of narcotic analgesics and antagonists. For example, these include naloxone esters[4], an implantable solid lipid matrix containing buprenorphine HCl[5], insoluble naltrexone salt-metal complexes[6], and insoluble naloxone salts suspended in oil[7]. Although these formulations provide prolonged release, they utilize drug substances or excipients which have not been approved by FDA. A simpler approach to formulating a prolonged release parenteral product, utilizing nalbuphine HCl and commonly used polymeric suspending agents, is presented here.

MATERIALS AND METHODS

Solubility Determinations

The pH dependency of the equilibrium solubility of nalbuphine was determined. Excess nalbuphine HCl was tumble-mixed in appropriate buffers of varying pH for 48 hours at 23°. After filtering, the pH of the filtrate was determined and the nalbuphine concentrations were measured using HPLC. The chromatography was as described below, and uv absorbance detection at 284 nm was used.

TABLE 1

Composition and Properties of Nalbuphine Suspensions in pH 9-9.2 PO_4 Buffer.

Formulation	Composition	Particle Size (μm) Mean	SD	Viscosity (cps)
A	1% Methylcellulose [a] 12.5 mg/ml Nalbuphine HCl	12.2	6.9	45.41
B	0.5% Na Carboxymethylcellulose [b] 12.5 mg/ml Nalbuphine HCl	59.8	9.4	4.78
C	2.7% PEG 3350 [c] 12.5 mg/ml Nalbuphine HCl	38.9	7.7	1.56

[a] Methocel™, A4M Premium, Dow Chemical Co.

[b] Fluka BioChemika, low viscosity

[c] Fisher Scientific

Formulation

Starting with nalbuphine HCl and using suspending agents approved for parenteral use, the nalbuphine suspensions listed in Table 1 were prepared. The suspending agent was first dissolved or dispersed in 0.1 M monobasic sodium phosphate (pH 4-5). Nalbuphine HCl was then added and the pH was adjusted to 9-9.2 by adding NaOH with continuous stirring. The viscosity of each suspension at room temperature was determined with a rotational viscometer. Particle size distribution measurements were made using a particle size distribution analyzer (HIAC/ROYCO, model 4300) after diluting with degassed water to 40000 particle counts per 20 ml.

Pharmacokinetic Studies

The nalbuphine suspensions were shaken thoroughly and then administered i.m. in the thigh of the hind legs of male Sprague-Dawley rats

weighing 250-350 g. All rats were anesthetized with ether prior to injection. Each suspension contained the equivalent of 12.5 mg/ml nalbuphine HCl, and the dosing volume was 1 ml/kg. Control rats received 1 ml/kg of a 12.5 mg/ml aqueous solution of nalbuphine HCl. Serial blood samples (0.3-0.4 ml) were withdrawn by cutting the tip of the tail, and were collected into heparinized test tubes. Plasma was separated.

Three male beagle dogs were administered, in a cross-over study, suspension A, containing the equivalent of 8 mg/ml of nalbuphine HCl at a dose of 2 mg/kg (0.25 ml/kg), and a nalbuphine HCl solution containing 8 mg/ml at a dose of 2 mg/kg (0.25 ml/kg). Doses were injected into the thigh muscle of a hind leg. Blood was collected by jugular venipuncture and anticoagulated with EDTA. Plasma was stored frozen.

Plasma Nalbuphine Assay

An HPLC method similar to that previously described by Lo et al.[8] was used. Naltrexone (DuPont) was added to 0.2 ml rat plasma or 0.5 ml dog plasma as an internal standard. A volume of pH 9 carbonate buffer equal to the plasma volume was added. Plasma was then doubly extracted into 4 ml of a toluene/ethyl acetate/isopropanol (70/29/1) mixture and back-extracted into 0.2 ml of 0.3 M phosphoric acid, which was injected onto an HPLC. The mobile phase contained 13-14% acetonitrile and 0.2% tetrahydrofuran in 0.27 M phosphate buffer (pH 3-4). A 25 cm octylsilane column (Zorbax®, DuPont) was used. Electrochemical detection at an oxidation potential of +0.98 v was employed. Calibration was by nalbuphine/naltrexone peak area ratios.

RESULTS AND DISCUSSION

The aim of this study was to formulate an aqueous suspension, starting with nalbuphine HCl and precipitated as nalbuphine base, which when injected

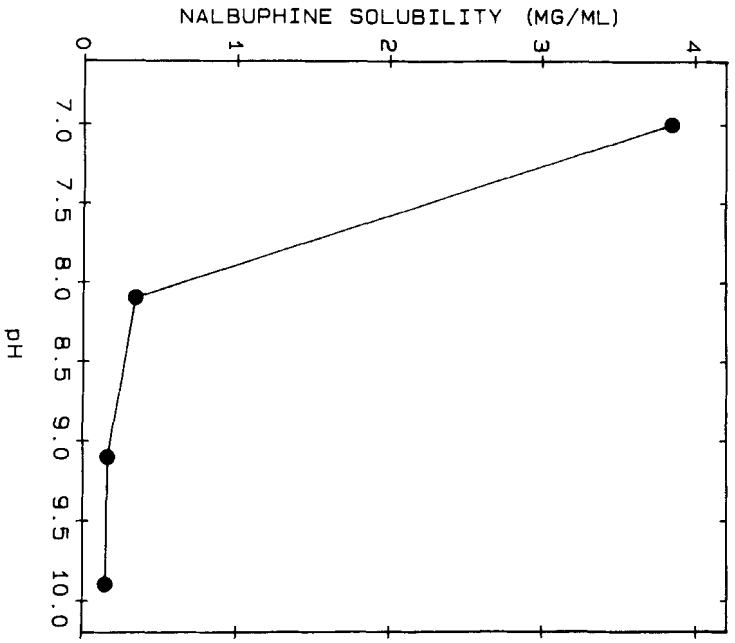

FIGURE 1

Nalbuphine pH/solubility profile.

would provide prolonged plasma nalbuphine concentrations (i.e., dissolution rate-limited absorption). A modified Noyes-Whitney equation can be used to illustrate the factors controlling the dissolution rate.

$$\frac{dX}{dt} = \frac{DSC^s}{h}$$

dX/dt represents the amount of drug dissolved per unit time, D is a diffusion coefficient, S is the surface area of the dissolving particles, h is the thickness of the stagnant diffusion layer adjacent to the particles, and C^s is the drug solubility in the diffusion layer. As this equation shows, the dissolution rate is proportional to drug solubility. The solubility of nalbuphine HCl in the appropriate buffers was determined as a function of pH. Results are shown in

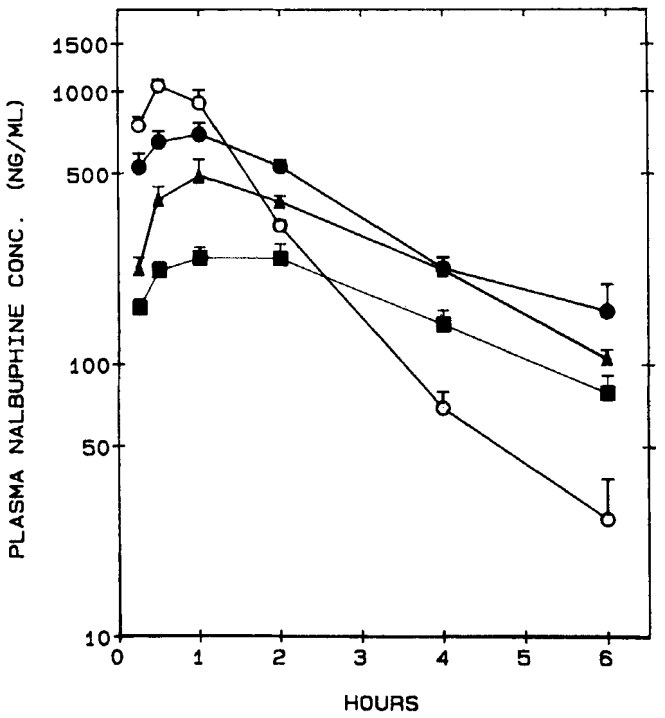

FIGURE 2
Nalbuphine disposition in rats dosed i.m. with a solution (○) or suspensions containing methylcellulose (●), Na carboxymethylcellulose (▲), or PEG (■).

Figure 1. The pH of minimum nalbuphine solubility and minimum potential for irritation or pain upon injection was 9-9.2. Formulations A, B, and C (see Table 1), in which nalbuphine HCl was dissolved and precipitated as the free base in suspension form at pH 9-9.2, were prepared. Viscosity and particle size were determined because these could influence, respectively, h and S from the above equation.

A, B, and C were administered i.m. to rats and nalbuphine disposition was characterized. The plasma concentration vs. time profiles after these three formulations or i.m. injection of a nalbuphine HCl solution are shown in Figure

TABLE 2

Pharmacokinetic Parameters (Mean ± SE) Describing Nalbuphine Disposition in Rats after Solution or Suspension Injections Intramuscularly.

	Solution	Methylcellulose Suspension	Na CMC [a] Suspension	PEG Suspension
Cmax (ng/ml)	1133 ± 52	776 ± 67	547 ± 73	261 ± 26
t max (hr)	0.6 ± 0.1	1.0 ± 0.2	1.0 ± 0.2	1.3 ± 0.2
t 1/2 (hr)	1.21 ± 0.24	1.90 ± 0.21	2.35 ± 0.24	3.23 ± 0.66
$AUC_{0-\infty}$ ($ng \cdot hr \cdot ml^{-1}$)	2029 ± 116	2619 ± 183	2101 ± 63	1467 ± 174
N	4	12	7	8

[a] Sodium carboxymethylcellulose

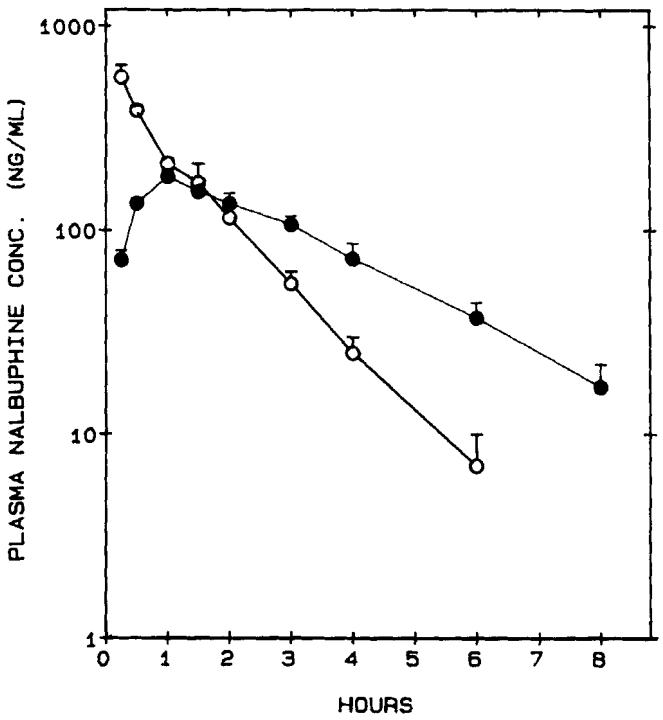

FIGURE 3
Disposition of nalbuphine in dogs administered a solution (○) or methylcellulose suspension (●).

2. Some pharmacokinetic parameters describing nalbuphine disposition are given in Table 2. Maximum plasma nalbuphine concentrations (Cmax) were significantly lower after each suspension than after the solution. Also with each suspension, the terminal half-life was prolonged, demonstrating the prolonged release characteristics of these formulations. Of the suspensions, methylcellulose (A) provided the highest Cmax and AUC. This is consistent with it having the smallest particle size, as shown in Table 1, and presumably also the greatest initial surface area available for dissolution. Viscosity of the suspension did not appear to directly influence nalbuphine pharmacokinetics, since it might

TABLE 3

Nalbuphine Pharmacokinetics in Dogs (Mean ± SE of 3 Dogs Crossed-over).

	Solution	Methylcellulose Suspension
Cmax (ng/ml)	565 ± 82	187 ± 13
t max (hr)	0.3 ± 0.1	1.2 ± 0.1
t 1/2 (hr)	0.99 ± 0.05	1.98 ± 0.25
$AUC_{0-\infty}$ ($ng \cdot hr \cdot ml^{-1}$)	675 ± 86	696 ± 76

have been expected that the most viscous formulation would be absorbed slowest. Even though the methylcellulose suspension was the most viscous, it was easily injected through a 23 gauge needle.

The methylcellulose suspension was also administered to dogs and compared with a nalbuphine HCl solution. Plasma nalbuphine concentrations are shown in Figure 3, and the pharmacokinetic parameters are given in Table 3. As in rats, Cmax was significantly lower and the time of the maximum plasma nalbuphine concentration was delayed. The terminal half-life was prolonged 2-fold when administered as the suspension. The AUCs were not significantly different. The AUC and t1/2 after the i.m. solution were similar to values previously reported after i.v. injection in dogs[9].

Formulations for prolonged release i.m. nalbuphine have been prepared starting with nalbuphine HCl. These can be lyophilized for prolonged storage, and resuspend in water easily. To obtain a preliminary indication of the irritation potential of these formulations, the injection site in rats was dissected and examined 24 hours after the i.m. injection. There were no visible signs of inflammation.

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REFERENCES

1. R. R. Miller, *Am. J. Hosp. Pharm.*, 37, 942 (1980).
2. M. W. Lo, F. H. Lee, W. L. Schary, and C. C. Whitney, Jr., *Eur. J. Clin. Pharmacol.*, 33, 297 (1987).
3. M.-W. Lo, W. L. Schary, and C. C. Whitney, Jr., *J. Clin. Pharmacol.*, 27, 866 (1987).
4. C. Linder and J. Fishman, *J. Med. Chem.*, 16, 553 (1973).
5. R. B. Pontani and A. L. Misra, *Pharmacol. Bioch. Behav.*, 18, 471 (1983).
6. T. R. Macgregor, M. A. Drum, S. E. Harrigan, J. N. Wiley, and R. H. Reuning, *J. Pharm. Pharmacol.*, 35, 38 (1983).
7. L. Lachman, R. H. Reiner, E. Shami, and W. Spector, U. S. Patent # 3676557 (1972).
8. M.-W. Lo, G. P. Juergens, and C. C. Whitney, Jr., *Res. Commun. Chem. Path. Pharmacol.*, 43, 159 (1984).
9. B. J. Aungst, G. Lam, and E. Shefter, *Biopharm. Drug Disp.*, 6, 413 (1985).