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The pharmacokinetics of oral and intravenous nalbuphine in healthy volunteers

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The pharmacokinetics of nalbuphine were studied in 10 healthy volunteers on two separate occasions following administration by either the intravenous (20 mg) or oral (60 mg) route. After administration, serum concentrations of nalbuphine were measured for 12 h using a high pressure liquid chromatography assay, and pharmacokinetic parameters were derived using a three compartment model. After i.v. administration, elimination half-life was 222 (111–460) min (mean and range) and total body clearance was 1.5 (0.8–2.3) 1 min^{-1}. C_{max} after oral administration was 21.4 (6.0–36.2) ng ml^{-1} and t_{max} was 46.6 (15.3–89.0) min. Bioavailability of the oral preparation was 11.8 (6.1–20.1)%.

Keywords nalbuphine intravenous oral pharmacokinetics

Introduction

Nalbuphine is a semi-synthetic opioid of the phenanthrene series which is related structurally to the agonist oxymorphone and the antagonist naloxone. It is currently available as a parenteral preparation and an oral preparation has been manufactured which is not yet commercially available in Europe. At low doses (< 0.5 mg kg^{-1}), nalbuphine exhibits an analgesic potency which is approximately two-thirds that of morphine (Bahar *et al.*, 1985; Beaver & Feise, 1978) when used to control postoperative pain in patients. A similar relative potency for nalbuphine has been found when it is used as a supplement to volatile anaesthetic agents (Murphy & Hug, 1982; DiFazio *et al.*, 1981). At higher doses (> 1 mg kg^{-1}) the analgesic and anaesthetic effects of nalbuphine appear to 'plateau'. This 'plateau' or 'ceiling' effect also seems to occur in respect of the respiratory depression produced by nalbuphine (Romagnoli & Keats, 1980). Nalbuphine has also been reported as having a decreased tendency to produce nausea, vomiting, psychotomimetic effects, tolerance and addiction when compared with morphine (Jasinski & Mansky, 1972; Stambaugh, 1982; Beaver *et al.*, 1981). Such a profile makes parenteral nalbuphine a potentially advantageous drug for use in the control of moderate postoperative pain. Nalbuphine also seems to be effective as a premedication agent preceding general (Pinnock *et al.*, 1985) or local (Klein, 1983) anaesthesia and the oral preparation might have an application as a premedicant and in the management of chronic pain.

Nalbuphine may also have a potential use as an antagonist to reverse respiratory depression following high-dose fentanyl anaesthesia in order to facilitate early extubation after bypass surgery (Ramsey *et al.*, 1985; Moldenhauer *et al.*, 1985) but results remain inconclusive due to the lack of selectivity in its antagonism.

Although nalbuphine has been approved for clinical use, pharmacokinetic data on the drug remain very limited. The present study was designed to calculate pharmacokinetic parameters for nalbuphine in normal subjects following intravenous and oral administration of the drug.

Methods

Ten subjects (six female) of mean age 26.5 years (range 23–36 years) and mean body weight 68.0 kg (range 45.5–106.5 kg) were studied on two separate occasions 2 weeks apart. After an

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overnight fast, nalbuphine was administered either i.v. (20 mg in 10 ml saline 0.9% over 30s) or orally (two 30 mg tablets), and then venous blood was sampled over a 24 h period. The order of administration was randomised. Following i.v. injection, blood samples were taken at 1, 2, 5, 10, 15, 20, 30, 45, 60, 90 and 120 min after administration, and thereafter at 2 hourly intervals. Blood sampling following oral administration was the same except that the 1 and 2 min samples were omitted. The samples were placed in plain glass containers and centrifuged immediately. The serum was separated and stored at –70°C for subsequent analysis of serum nalbuphine concentrations using high pressure liquid chromatography (h.p.l.c.) with electrochemical detection.

The following extraction procedure was used to process each serum sample. One ml of serum was placed in a stoppered centrifuge tube and 0.5–1 g of sodium chloride added to act as an emulsifying agent. Naltrexone was used as an internal standard and 100 μl of 100 ng ml^{-1} solution together with 1 ml of borate buffer (pH = 9.2) were added to each sample. This mixture was shaken mechanically for 10 min with 10 ml of dichloromethane as the extraction agent, and then centrifuged briefly at 3000 rev min^{-1}. The aqueous layer was discarded; the organic layer was transferred to a conical centrifuge tube and evaporated to dryness in a Buchler vortex evaporater. The residue was finally dissolved in 200 μl of 50–60% methanol ready for injection on to the chromatography column.

The extracted samples were placed on a Talbot AS1–3 autosampler and injected onto the column using a Rheodyne injection valve with a 100 μl injection loop. The chromatography column was packed with microbondapak C18 (Millipore UK Ltd). The column was 25 cm in length, and the internal diameter was 4.9 mm. The electrochemical detection system (Bioanalytical Systems) consisted of a TL–5 reaction cell and LC4A amperometric detector set to a working voltage of 0.76V. A Laboratory Data Control 301 computing integrator displayed the detector output. The mobile phase was a mixture of 30% methanol with 70% phosphate buffer (sodium dihydrogen phosphate), the pH being adjusted to 3.6 with phosphoric acid. Peak separation was improved by adding 2.0 ml of 1-heptane sulphonic acid 0.1 M solution to each 1 l of the mobile phase to act as an ion pairing reagent. Optimum results were obtained with a mobile phase flow rate of 1.0 ml min^{-1} using an Altex 101A double piston pump.

Retention times for the nalbuphine and naltrexone peaks were obtained using an aqueous standard in 50% methanol which contained 100 μl of nalbuphine (100 ng ml^{-1}) and 100 μl of naltrexone (100 ng ml^{-1}). A calibration curve was plotted using a standard solution obtained by spiking serum with nalbuphine (2–40 ng ml^{-1}) and 100 μl naltrexone (100 ng ml^{-1}).

Analyses were performed in duplicate. Serum concentration-time data were analysed using non-linear least squares regression analysis with variable weighting using weighting factors of 1, $1/C_t$, and $1/C_t^2$, where C_t = concentration at time t. Selection of the most appropriate model and choice of weighting, and calculation of derived pharmacokinetic variables, were made using standard methods (Wagner, 1975; Hull, 1979). The significance of differences between groups was evaluated using the Wilcoxon rank sum test for non-parametric data.

Results

The extraction procedure gave a recovery of 75%. The naltrexone and nalbuphine peaks were easily identifiable, with retention times of 6.6 and 10.9 min respectively. The calibration curve obtained was linear over the working range, with a coefficient of variation ranging from 6.7% at 2 ng ml^{-1} to 1.3% at 40 ng ml^{-1}.

Only the first 12 h of serum concentration data were used, as after this time the serum concentration levels fell below the lower limit of sensitivity of the assay (1 ng ml^{-1}). Figure 1 shows the averaged decay curves following oral and intravenous administration. A three compartment model provided the best fit for the data for all subjects following intravenous administration. Values for the pharmacokinetic parameters associated with intravenous administration are shown in Table 1a.

Following first order absorption of the oral preparation, there was distribution into two compartments. The pharmacokinetic data following oral administration are summarised in Table 1b. The mean bioavailability was 11.8%. The mean maximum concentration of nalbuphine achieved (C_{max}) was 21.4 ng ml^{-1} which occurred at a mean time (t_{max}) of 46 min after administration.

Discussion

The recovery of 75% by the extraction procedure is comparable with that obtained by Keegan & Kay (1984) although somewhat less than that obtained by Lake *et al.* (1982) or Lo *et al.* (1984). However, the clarity of the

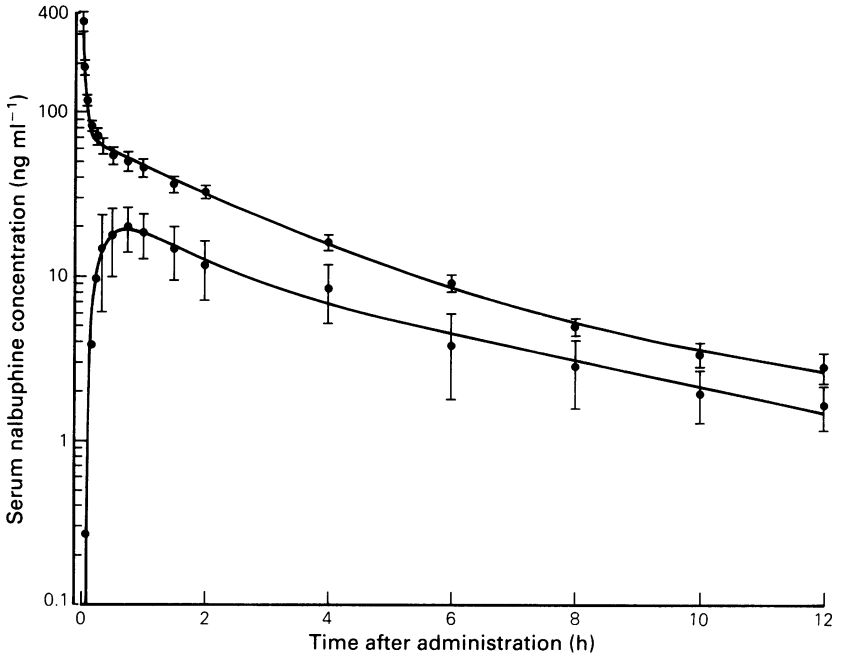

Figure 1 Average decay curves for serum concentration of nalbuphine following intravenous administration of 20 mg (upper curve) and oral administration of 60 mg (lower curve) to 10 volunteers. Bars represent s.e. mean.

Table 1a Mean (range) pharmacokinetic parameters for the disposition of i.v. nalbuphine 20 mg in 10 normal subjects (see appendix for key to abbreviations)

	Mean	*Range*
P (ng ml^{-1})	558.6	44.2–1605.3
A (ng ml^{-1})	69.0	14.2–130.3
B (ng ml^{-1})	30.2	6.1–60.0
π (min^{-1})	0.6	0.1–1.3
α (min^{-1})	0.05	0.01–0.13
β (min^{-1})	0.004	0.002–0.006
$t_{\frac{1}{2}}^{\pi}$(min)	2.3	0.5–5.5
$t_{\frac{1}{2}\lambda_1}$ (min)	53.9	5.3–107.1
$t_{\frac{1}{2}\lambda_2}$ (min)	222.2	111.0–459.9
V (l)	468.3	209.0–1004.6
V_{ss} (l)	315.5	161.7–498.2
CL (l min^{-1})	1.50	0.82–2.29
AUC (ng ml^{-1} h)	216.9	132.1–367.2

Table 1b Mean (range) pharmacokinetic parameters calculated for the disposition of oral nalbuphine 60 mg in 10 normal subjects (see appendix for key to abbreviations)

	Mean	*Range*
k_a (min)	13.0	2.1–27.7
$t_{\frac{1}{2}\lambda_1}$ (min)	46.0	10.6–111.7
$t_{\frac{1}{2}\lambda_2}$ (min)	278.8	164.3–499.6
C_{max} (ng ml^{-1})	21.4	6.0–36.2
t_{max} (min)	46.6	15.3–89.0
AUC (ng ml^{-1} h)	78.6	30.9–136.0
Bioavailability (%)	11.8	6.1–20.1

chromatograms was very good with an absence of interference peaks and good separation of the nalbuphine and naltrexone peaks. The calibration procedure demonstrated that the accuracy and reproducibility of the assay were acceptable and comparable with those obtained by other workers.

The mean elimination half-life ($t_{\frac{1}{2}\lambda_2}$) of nalbuphine after i.v. administration was 222 min. This compares with a value of 2 h in a single male subject reported by Lo *et al.* (1984). Sear *et al.* (1987) found the elimination half-life to be 135 min in anaesthetised patients who had distribution volumes rather lower than those found in the present study. This is not surprising in view of the haemodynamic and body water changes associated with anaesthesia and surgery. Lake *et al.* (1982) found postoperative elimination half-lives of 3 h and 3.5 h respectively in seven patients undergoing mitral valve replacement and fourteen patients receiving coronary artery bypass grafts.

Total body clearance was 1.50 l min^{-1} for all subjects and is in agreement with the value obtained by Hanigan & Ryan (personal communication) of 1.95 l min^{-1} in male subjects, but higher than the value obtained by Lo *et al.* (1984) (1.42 l min^{-1}). In common with most opioids, clearance is high and is likely to be affected by changes in hepatic blood flow. This is confirmed

by the lower clearance (approximately one-third less) reported by Sear *et al.* (1987) in anaesthetised patients.

As is common with high clearance drugs, the bioavailability of the oral preparation was low. This has been found previously in animal studies with nalbuphine (Aungst *et al.*, 1985) and the value obtained in the present study is in close agreement with that found by Hanigan & Ryan (12.4%, personal communication). The wide interindividual variation in the values obtained for C_{max} implies that care should be taken to titrate oral dosage of nalbuphine against individual response to the drug.

Appendix

After i.v. injection, the decay in plasma nalbuphine concentration was fitted best by a tri-exponential equation using the method of residuals (Gibaldi & Perrier, 1975a) to obtain estimated parameters, and an iterative computer program was used to find the best fit curve using non-linear least squares regression analysis. The tri-exponential equation used was that representing a three-compartment mamillary pharmacokinetic model:

$$C_t = \mathrm{P.exp}^{-\pi t} + \mathrm{A.exp}^{-\lambda_1 t} + \mathrm{B.exp}^{-\lambda_2 t}$$

where C_t = concentration of nalbuphine in serum at time t; P,A,B = extrapolated zero intercepts computed from least squares regression analysis of the data; $\pi, \lambda_1, \lambda_2$ = the first-order rate constants.

The total apparent volume of distribution (V), the total volume of distribution at steady state (V_{ss}), and the total body clearance (CL) were calculated from standard formulae (Hull, 1979). V is a proportionality constant relating the amount of drug in the body to the plasma concentration at any time during the elimination phase. It is dependent on the value of k_{10}, and is only an approximate index of total distribution volume. V_{ss} is the sum of the individual compartmental volumes ($V_1 + V_2 + V_3$) (Klotz, 1976)

After oral administration, there was first-order absorption followed by distribution into two compartments, represented by the equation:

$$C_t = -\mathrm{P.exp}^{-k_a t} + \mathrm{A.exp}^{-\lambda_1 t} + \mathrm{B.exp}^{-\lambda_2 t}$$

where k_a = absorption rate constant.

Maximum serum concentration (C_{max}) and time to achieve maximum concentration (t_{max}) were calculated using methods described by Gibaldi & Perrier (1975b).

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