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Intranasal absorption of buprenorphine — in vivo bioavailability study in sheep

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Abstract

The bioavailability of buprenorphine, HCl (BPP) in sheep after nasal administration of two formulations has been studied. 0.9 mg BPP in 150 μl was administered nasally and compared to 0.6 mg i.v. The test solutions were formulated with 30% polyethylene glycol 300 (PEG 300) and 5% dextrose, respectively. The bioavailability for PEG 300 was 70% (S.D. ± 27%, $n = 6$), whereas the bioavailability for 5% dextrose was 89% (S.D. ± 23%, $n = 6$). A two-compartment model with initial and terminal serum half-lives of 10 and 23 min, respectively, may describe the pharmacokinetics. The rate of absorption for both nasal formulations was very fast ($t_{max} = 10$ min). The C_{max} was 37 ng/ml (S.D. ± 17) and 48 (S.D. ± 10) for PEG 300 and dextrose, respectively. No significant difference was found between the two formulations, but PEG 300 has advantages in relation to freezing point depression and solubility, which may be considered if further studies are going to be initiated. The high nasal bioavailability and short time to maximal plasma concentration suggests that it is possible to make a clinically relevant nasal formulation of BPP for the treatment of pain.

Keywords: Nasal; Buprenorphine; Bioavailability; Sheep; Polyethylene glycol 300

1. Introduction

Buprenorphine (BPP), a derivative of the morphine alkaloid thebaine, has long-acting and potent analgesic effect. An intravenous dose of 0.3 mg BPP is equivalent to 10 mg of morphine. The compound has partial agonistic properties on opioid receptors by having agonistic effect on the μ-type and antagonistic on the κ-type (Leander, 1988). Because of these effects, BPP has been under evaluation in the treatment of, e.g. heroin addiction (Kuhlman et al., 1998). However, pain is the main indication for the morphine derivative, especially in acute treatment and pre-anaesthesia.

In human plasma, BPP is highly (96%) bound to proteins and has a terminal half-life between 1.2 and 7.2 h (Martindale, 1999). BPP is extensively metabolised when given orally, due to the

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first pass metabolism, resulting in only 15% bioavailability (McQuay and Moore, 1995).

Beside intravenous formulations, a sublingual tablet is commercially available which has the advantage, relative to an oral formulation, of reducing the first pass metabolism. However, the t_{max}, even after sublingual application of BPP in a 30% ethanol solution is higher than 1 h (Mendelson et al., 1997; Martindale, 1999), which is not desirable when the response is supposed to be immediate. Additionally, some publications indicate huge variations in the bioavailability following sublingual administration of BPP (Bullingham et al., 1982; Kuhlman et al., 1996), which would result in difficulties in the dose regimen of the drug. The variable sublingual retention may be the reason for the variable bioavailability as the swallowed fraction of the dose is exposed to first pass metabolism. Based on the low and variable bioavailability and the lag-time associated with oral formulation and partly sublingual application, an alternative route of administration, such as intranasal, would be of interest.

In 1989, Eriksen et al. performed a clinical trial of nasally administered BPP (0.3 mg/dose) in an aqueous formulation containing 5% dextrose. The bioavailability, t_{max} and C_{max} were 48%, 30 min, 1.77 ng/ml, respectively. As t_{max} is relatively long for the dextrose formulation, an alternative vehicle may be utilised. PEG 300 has excellent solubilising properties as well as relatively low irritating or toxic effects (Bechgaard et al., 1999) and may provide a fast absorption rate (Gizurarson et al., 1999; Nielsen et al., 2000).

Shyu et al. (1993) has evaluated butorphanol, a BPP analog, and found bioavailabilities of 70, 19, and 29% after nasal, sublingual and buccal administrations, respectively. The t_{max} after nasal administration was significantly lower than after the other non-invasive application forms.

The purpose of the present study was to estimate the nasal bioavailability of BPP, when administered intranasally to sheep in a clinical relevant dose, formulated in 30% PEG 300 and comparing it to a 5% dextrose formulation already explored in humans.

2. Materials and method

2.1. Chemicals

Buprenorphine hydrochloride was obtained from Sigma Chemical Company (St. Louis, MO) and injectable BPP was commercially available as Temgesic®, from Reckitt & Colman Pharmaceuticals (Hull, UK). Polyethylene glycole 300 was obtained from Union Carbide Chemicals and Plastics Company Inc. (Danbury) and dextrose from Merck (Darmstadt, Germany).

2.2. Preparations

Stock solutions containing 30% PEG 300 and 5% dextrose were prepared. Buprenorphine, HCl (BPP) was added to a concentration of 6 mg/ml and filled into the nasal device. The pH was adjusted to 5.5 with 0.1 N NaOH.

2.3. In vivo study

Six Icelandic sheep, 1–2 years old, weighing 35–40 kg, and obtained from Keldur, Institute of Experimental Pathology, University of Iceland (Reykjavik, Iceland), were used in a modified cross-over study ($n = 6$, i.v. $n = 3$) with a wash out period of at least 4 days. They were kept together in a stable during the study. They received food and water ad libitum. During each of the 3 study days, two sheep were selected, each receiving one out of following nasal formulations: 0.9 mg BPP in 5% dextrose or 0.9 mg BPP in 30% PEG 300. Only three sheep received 0.6 mg (2 ml) intravenously, hence why the cross-over design was modified. All nasal preparations were administered with the sheep in a fixed standing position forcing its head slightly backward by holding the horns while administrating the nasal solution with a Pfeiffer device, Unit Dose, with a 3.2 cm tip giving one stroke corresponding to 150 μl. The sheep was kept in this position for ~ 1 min post-administration.

Blood samples of 4 ml were withdrawn from the jugular vein on the neck just before and 2, 5, 10, 15, 20, 30, 45, and 60 min after the administration of BPP. Serum was obtained by centrifug-

Table 1
Mean time (t_{max}) to maximal serum concentration (C_{max}) and bioavailability from 0 to 60 min of intranasal buprenorphine formulations (30% PEG 300 and 5% dextrose) after administration of 0.6 mg buprenorphine

Formulation	t_{max} (min)	C_{max} (ng/ml)	Bioavailability (%)
i.v	–	46 ± 21	100
PEG 300	10 ± 5	37 ± 17	70 ± 27
Dextrose	9 ± 6	48 ± 10	89 ± 23

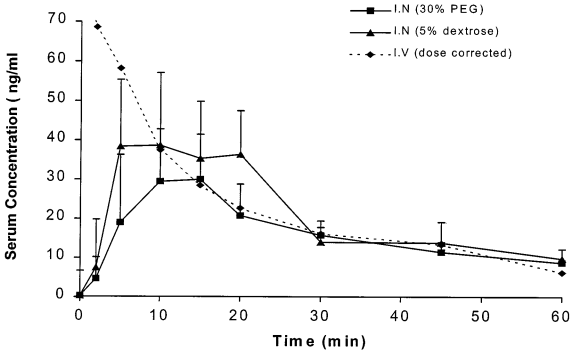

Fig. 1. Mean serum concentration–time profiles of buprenorphine after intravenous administration of 0.6 mg buprenorphine. The dotted lines represent elimination lines used for calculation of half-lives.

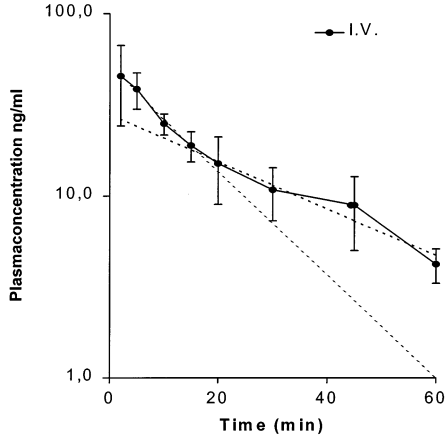

Fig. 2. Mean serum concentration–time profiles of buprenorphine after intranasal administration of two formulations containing 6 mg/ml buprenorphine in 30% polyethylene glycol 300 (PEG 300) (■) and in 5% dextrose (▲). The dose corrected data from the intravenous administration is represented by a dotted line (. . . .).

ing at $6163 \times g$ at room temperature for 25 min taking the supernatant. The serum samples were stored at -20°C until analysis.

2.4. Serum analysis of buprenorphine

A double antibody RIA method from Diagnostic Products Corporation (Los Angeles, CA) with prior liquid extraction (phosphate buffer pH 7 and cyclohexane) was used for the analysis of BPP in sheep serum. This specific method was a modification of a method described for human plasma (Lee and Dockham, 1991; Lee and Shaver, 1991). The serum samples were diluted with demineralized water to provide samples within the linear range of the serum standard curve. The serum concentrations were calculated from a standard curve, prepared fresh every day.

2.5. Calculations

The area under the curve (AUC) was calculated using the trapezoidal method. AUC from 0 to 2 min for intravenous administration was determined by extrapolation to a zero value by the mean of linear regression analysis. In average, $AUC_{0-2\ min}$ accounted for $< 5\%$ of the $AUC_{0-60\ min}$. The bioavailability ($F\%$) was calculated using:

$$F(\%) = \left(\frac{AUC_{i.n.(0-60\ min)} \times 0.6}{AUC_{i.v.(0-60\ min)} \times 0.9}\right) 100\%$$

Statistical significant differences between the nasal formulations were tested by a student's t-test.

3. Results and discussion

The bioavailability in sheep after nasal administration of two formulations containing BPP in 30% PEG 300 and 5% dextrose was found to be 70% (S.D. $\pm$ 27%) and 89% (S.D. $\pm$ 23%), respectively, as shown in Table 1 and Fig. 2. The absorption rate was very fast ($t_{max} = 10$ min) and C_{max} was found to be 37 (S.D. $\pm$ 17) and 48 (S.D. $\pm$ 10) ng/ml for PEG 300 and dextrose, respectively.

The pharmacokinetics after intravenous application (Fig. 1.) may be described as a two-com-

partment model with initial and terminal half-life of 10 and 23 min, respectively. In humans, the elimination is described as a three-compartment model, with half-lives of ~2, 20, and 180 min, respectively (Bullingham et al., 1980). The lack of the third elimination phase in the sheep study may be due to the relatively short sampling time.

As described, Eriksen et al., 1989 estimated the nasal bioavailability of buprenorphine in humans to 48%. The study was carried out over a period of 12 h, and the calculations are based on $AUC_{0-720\ min}$, although it may be questionable if the plasma profiles exceeding 1 h is relevant in acute treatment. If only the data from the first 0 to 60 min is used the bioavailability is ~20%. The bioavailability in sheep was found to be much higher and one possible explanation may be the relatively short tip on the device used in the human study. The tip is only 2.7 cm and the fingers for holding the device will only leave 1–1.5 cm for insertion in the nostrils. Further the tip is pressed backwards ~0.3 cm when activated. Newly developed devices have a longer tip, which make it possible to administer the formulation more directly into the nasal cavity, where the absorption takes place.

It may be possible to prepare a clinical relevant formulation for nasal delivery in pure water as the solubility is 16.3 mg/ml (Roy et al., 1994). However, such a formulation is relatively close to saturation, why it may be preferable to choose a vehicle with a higher solubility, e.g. 25 mg/ml for 30% PEG 300, which provided a solubility maximum of buprenorphine in various PEG/water mixtures. As 30% PEG 300 was expected to be clinically acceptable, it was applied in the formulation.

The RIA analysis is found to be sensitive and accurate and because of the liquid extraction it is expected to be relatively specific. Lee and Dockham have evaluated the specificity of the extraction and at pH 7 the recovery of BPP was almost 100% while the recovery of nor-buprenorphine was lower than 20%. As the cross reactivity is only ~10% at the relevant concentrations it is not expected to have significant influence on the analysis. The other major metabolite buprenorphine-3-glucoronide is very hydrophilic and is, therefore, discarded with the water phase.

No statistical difference in the bioavailability was observed between the two nasal formulations, but PEG 300 has an advantage in relation to freezing point depression and solubility, which may be considered if further studies are going to be initiated. The high nasal absorption rate in sheep with and without co-solvent indicates that the 5% dextrose formulation is not the reason for the low initial bioavailability in humans. However, it is likely that an improved nasal device for humans may be beneficial. The short t_{max} indicate that nasal administration of BPP is likely to give a more rapid effect than the sublingual formulation. As the time to effect is very important in pain treatment the fast absorption nasally is a major advantage. Variations in the bioavailability are moderate, indicating that intranasal delivery provides less dosing difficulties than observed after sublingual administration.

In conclusion the high nasal bioavailability and short time to maximal plasma concentration suggests that it is possible to make a clinically relevant nasal formulation of BPP for the treatment of pain.

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