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Bioavailability of the sedative propiomazine after nasal administration in rats

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Abstract

The bioavailability of the sedative propiomazine after nasal administration in rats was evaluated. Two salt forms, hydrochloride and maleate, in saline and a test vehicle were administered in two doses (0.2 and 0.4 mg/kg). The composition of the test vehicle was propylene glycol (5%), polysorbate 20 (2.5%), polyethylene glycol 400 (20%) and water. The plasma concentration was determined by blood sampling up to 4 h after administration. The results indicated that nasal administration of propiomazine resulted in fast absorption followed by rapid reduction of the plasma concentrations. Maximum plasma concentrations were reached within 5 min in all groups. A rapid rate of absorption and elimination is an advantage for sedatives since a speedy onset of action is desirable and unwanted hang-over symptoms may be minimised. The mean absolute bioavailability of approximately 40% (mean range 38–51%) was equivalent for both the low and high doses of the hydrochloride salt and for the low dose of the maleate salt, but not for the high dose of the maleate salt. There were no differences in the bioavailabilities of the different vehicles studied. Copyright © 1996 Elsevier Science B.V.

Keywords: Nasal administration; Propiomazine; Rat

1. Introduction

Nasal administration is no longer associated only with local treatment of rhinitis but is currently also regarded as an alternative administration route to achieve systemic effects. Known major advantages of this administration route are avoidance of first pass metabolism compared with p.o. administration and a facilitated administration routine. The human nasal cavity also has a relatively large surface area (150 cm^2) and a rich vascularised epithelial layer, which promote absorption. Another attractive feature is the rapid onset of action compared to oral administration (Chien et al., 1989; Lui et al., 1991).

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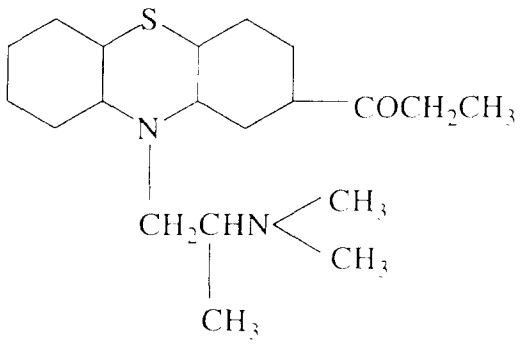

Fig. 1. Molecular structure of propiomazine (10-(2-dimethylaminopropyl)-2-propionylphenothiazine).

Propiomazine is a derivative of phenothiazine with the chemical formula (10-(2-dimethylaminopropyl)-2-propionylphenothiazine) (Fig. 1). The molecular weights of the hydrochloride (HCl) and the maleate ($C_4H_4O_4$) salts are 377 and 457 Da, respectively. Since oral propiomazine has been marketed for almost half a century, pharmacokinetic data from clinical studies on its oral administration in humans are freely available. However, as a consequence of the age of the substance, fewer preclinical data are available. A variety of indications have been proposed for propiomazine, including its use in anaesthesia (Lear et al., 1963; Elliot et al., 1969), psychosis and anxiolytic sedation (Hartvig et al., 1981).

The maleate salt of propiomazine is currently used as an oral sedative, particularly in geriatric patients. A low incidence of side effects and a decreased risk of tolerance and dependency have been reported (Hartvig et al., 1981). Propiomazine has a relatively short elimination half-life after oral administration, which minimises the incidence of hang-over symptoms (Hartvig et al., 1981). Since the substance also causes minimal damage in overdose, it is specifically suitable in patients with known or suspected suicidal tendencies. Moreover EEG recordings are not influenced by the administration of propiomazine and the substance is also reported to reduce spontaneous awakening during the night (Viukari and Miettinen, 1984; Almqvist et al., 1987; Roslund and Olsen, 1987).

Nasal administration of propiomazine has potential for several reasons. The rapid onset of action, as expected after nasal administration, should be emphasised regarding a sedative. Compared with oral intake, where the peak serum concentrations occur approximately 1–2 h after administration (Hartvig et al., 1981), nasal administration of propiomazine may offer an attractive alternative. The present study was undertaken to investigate the absorption and bioavailability of propiomazine in rats after nasal administration.

2. Materials and methods

2.1. Test materials

Propiomazine hydrochloride, propiomazine maleate and the excipients of the test vehicle were obtained from Pharmacia & Upjohn, Stockholm, Sweden. All other chemicals were of analytical grade and purchased from Kebo lab AB, Stockholm, Sweden.

2.2. Preparation of solutions and suspensions

The doses used in this study were calculated from oral doses in humans and were compensated for body weight and different administration route. Propiomazine hydrochloride, which has a solubility in water of 222 mg/ml, was dissolved in NaCl (9 mg/ml), pH 6, to concentrations of 2.5 and 5.0 mg/ml. Propiomazine maleate has a solubility in water of 3.8 mg/ml, and was dissolved in NaCl to a concentration of 2.5 mg/ml, while a suspension was made at the higher concentration (5.0 mg/ml). The solutions and suspensions were freshly prepared each day.

The test vehicle contained additives which are common in marketed nasal preparations and the composition was as follows:

propylene glycol, 5.0%;
polysorbate 20 (Tween 20), 2.5%;
polyethylene glycol 400, 20%; and
H_2O (aqueous injection).

This formulation was based on earlier in vitro studies, where propiomazine had a high solubility in this composition (Lindberg, unpublished data).

Propiomazine hydrochloride, dissolved in the vehicle to a concentration of 2.5 mg/ml, was used within 3 days of preparation for the six rats in the group. The solution (pH = 5.61) was stored in 8°C, but was brought to room temperature before administration.

The volume left in the polyethylene tubes after administration of saline solutions and suspensions was considered as negligible. For the test vehicle the volume left was estimated as 2 μl. Thus, 22 μl of the test vehicle was administered compared with 20 μl of the saline vehicles.

2.3. Animal experiments

Male Sprague Dawley rats (Møllegaard, Denmark and B&K Universal HB, Sollentuna, Sweden) weighing 200–300 g were used. The animals were kept under standardised conditions, i.e. free access to food and water. Clean cages and fresh water were provided twice a week. The animals were acclimatised to laboratory conditions over the week before the experiments.

Anaesthesia and surgery were performed as reported earlier (Björk and Edman, 1988). After an intraperitoneal injection of thiobutabarbital sodium (Inactin, BYK) 130 mg/kg, the rats were placed on heated plates in the supine position to maintain their body temperature (37–38°C). The trachea and the arteria carotis were cannulated with polyethylene tubes (PE 200 and PE 50, respectively). In order to calculate the bioavailability of propiomazine given nasally, propiomazine hydrochloride was administered intravenously. Accordingly the animals in the i.v. group were also cannulated in the vena femoralis. Administration of the drug started 30 min post-operation.

Propiomazine in the two salt forms, dissolved in 0.9% NaCl or the test vehicle, was administered in doses of 0.2 and 0.4 mg/kg in 20–22 μl through the nostril with a polyethylene tube (PE 90) attached to a syringe. The animals in the i.v. group were given propiomazine hydrochloride intravenously at a dose of 0.19 mg/kg. Blood samples (300 μl) were withdrawn 0, 2, 5, 10, 15, 30, 45, 60, 120 and 240 min after administration. After centrifugation the plasma was separated and frozen (− 70°C) until analysed.

The animals were divided into six groups with six animals in each group.

2.4. Analysis

Propiomazine was determined by direct injection of rat plasma into a coupled column liquid chromatography system. An extraction column was used to separate the plasma proteins from the analyte. The analytical system consisted of two pumps (Constametric Bio 3000 and LKB 2150), a CMA/200 autoinjector, a Shimadzu CR3-A integrator and an ESA Coulochem detector (detection limit 2.0 ng/ml). The extraction column used was a Biotrap column, 3 × 10 mm, (Chromtech, Sweden) and the mobile phase was 0.05 M phosphate buffer, pH 3.5, pumped at a flow rate of 0.6 ml/min. A Supelcosil LC-CN (4.6 × 75 mm, 3 μm particle size) was used as analytical column. The mobile phase consisted of phosphate buffer (0.05 M, pH 3.5): acetonitril (73:27) v/v. The flow rate was 1.0 ml/min. Fifty microlitres of rat plasma was injected after centrifugation.

2.5. Calculations

The areas under the concentration-time curves (AUC) were calculated using the linear trapezoidal rule. The calculations on bioavailability were based on data gathered from 0 to 120 min. The incompleted data for the blood samples at 240 min were excluded after estimating $AUC_{120-240min}$ to be less than 10% of the total AUC for all groups. The intraindividual variability in maximum plasma concentrations between different vehicles was estimated by calculating the coefficent of variation (C.V.) (C.V. = standard deviation/mean).

3. Results and discussion

Nasal administration of propiomazine resulted in fast absorption followed by a rapid reduction in the plasma propiomazine concentration. The

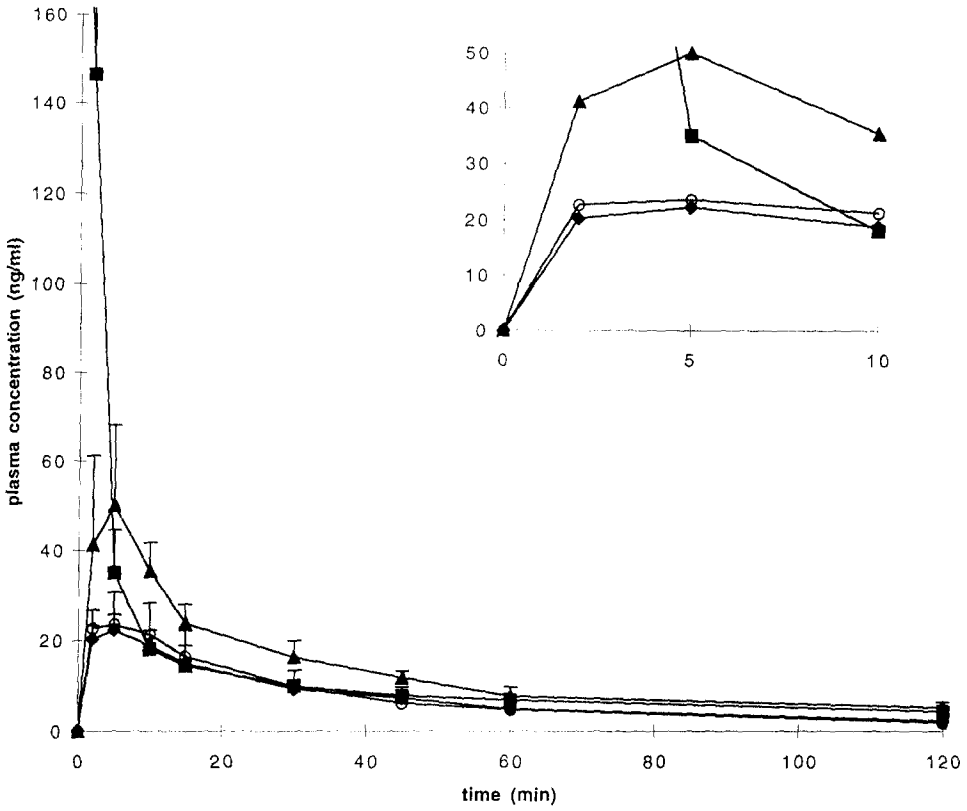

Fig. 2. Changes in plasma concentration with time after intravenous administration of propiomazine hydrochloride in saline (■) (low dose) compared with nasal administration of propiomazine hydrochloride in saline (low (○) and high (▲) dose) and a test formulation (◆) (low dose). The data are expressed as mean ± S.D. ($n = 6$). Inset shows an enlargement of the plasma concentration profile during the first 10 min after administration.

elimination phase was similar for low-dose propiomazine given intranasally in saline or the test vehicle, and intravenously (Fig. 2). Maximum plasma concentrations were reached within 5 min in all groups. The absorption phase after nasal administration is thus shorter than expected after oral administration. This is in agreement with a study on the nasal administration of the sedatives midazolam and triazolam in dogs, which showed higher and more rapidly achieved peak concentrations compared with oral administration (Lui et al., 1991).

3.1. Pharmacokinetics

Clinical studies have shown that maximum plasma concentrations (c_{max}) are reached in humans 1–2 h after oral administration of commercially available propiomazine maleate (Hartvig et al., 1981). Clinical effects are apparent about 30–60 min after oral administration. In contrast, the c_{max} for intranasal propiomazine was ≤ 5 min in this study.

The pharmacokinetics of propiomazine were estimated using drug concentrations after two doses. A linear relationship between high and low doses of propiomazine hydrochloride was noted, indicating dose independent kinetics in the dose interval studied (Table 1 and Fig. 2).

The hydrochloride salt was completely dissolved in both saline and the test vehicle at the two concentrations studied. The maximum plasma concentration achieved after administration of the higher dose was about twice that after

Table 1
Formulation, dose, maximum plasma concentration (c_{max}), time to c_{max} (t_{max}), area under the concentration-time curve (AUC) and absolute bioavailability (F_{abs}) after intranasal (i.n.) administration of propiomazine using intravenous (i.v.) administration as a reference

Salt form/adm. route	Dose (mg/kg)	c_{max} (ng/ml)[a]	t_{max} (min)[a]	AUC (ng min/ml)	F_{abs} (%)
HCl, i.n.	0.21 ± 0.03	23.6 ± 7.1	5	1090 ± 371	43.9 ± 11.8
Maleate, i.n.	0.22 ± 0.01	25.7 ± 9.9	5	1278 ± 325	51.0 ± 11.2
HCl,i.n., test form	0.18 ± 0.01	22.3 ± 3.5	5	873 ± 235	42.5 ± 11.2
HCl, i.n.	0.34 ± 0.01	50.0 ± 18.1	5	1471 ± 142	38.0 ± 2.8
Maleate, i.n.	0.36 ± 0.08	39.6 ± 34.9	2	1042 ± 454	26.3 ± 12.6
HCl, i.v.	0.19 ± 0.03	225.3 ± 130.8	—	2163 ± 640	100

[a]Results are based on measured maximum concentration. $n = 6$ in all groups. The data are expressed as mean ± S.D.

the lower dose (Fig. 2). The mean absolute bioavailability of 38 ± 3% to 44 ± 12% was equivalent for both low and high doses of the hydrochloride salt (Table 1). Keeping species differences in mind, these results may indicate a slightly higher bioavailability after intranasal than after oral administration in humans, where a bioavailability of 21–43% (mean 33 ± 8%) has been calculated (Hartvig et al., 1981).

The bioavailabilities of the hydrochloride and maleate salts after administration of low doses were comparable, which was expected as both salts were in solution (Table 1). However, the low solubility of the maleate salt resulted in a lower bioavailability at the higher dose than seen with the lower dose of the hydrochloride salt. Since propiomazine maleate is poorly soluble in water (3.8 mg/ml), the longer dissolution time may affect the rate of absorption of the drug. About 30% of the substance remains undissolved at the higher concentration and it may not have been possible for all of the substance to dissolve during the very short absorption phase, resulting in a lower bioavailability (Fig. 3). Thus the more water soluble salt form, i.e. propiomazine hydrochloride, appears the better choice for nasal administration.

Because of the steep absorption phase of the area under the concentration time curve and the rapid elimination of propiomazine from plasma, the duration of pharmacologically active plasma concentrations would be less and have less variability than that seen after oral administration. Accordingly, a lower risk of unwanted hangover symptoms would be expected. Furthermore, the relatively low molecular weight of propiomazine offers the advantage of achieving acceptable absorption after nasal administration without the addition of absorption enhancers. Also, propiomazine is currently used mainly in geriatric patients were nasal administration may be more convenient due to that these patients may have difficulties in swallowing tablets.

Last but not least, a direct drug route from the nasal cavity to the cerebrospinal fluid (CSF) has been reported (Sakane et al., 1991). Oestradiol (Kumar et al., 1974) and progesterone (Kumar et al., 1982) are examples of substances that have reached higher levels in the CSF after nasal than after intravenous administration. Although propiomazine has not been studied in this context, this direct pathway is an attractive feasibility for a sedative. In a recent study it was shown that substances with a molecular weight of less than 20 000 Da can be directly absorbed from the nasal cavity to the CSF (Sakane et al., 1995), but the degree of absorption is also influenced by factors such as the lipophilicity and ionisation of the drug (Sakane et al., 1991, 1994).

The duration of measurable concentrations of propiomazine after nasal administration was relatively short. The half-life ($t_{1/2}$) in the rat, estimated at 100 min, was considerably shorter than that in humans after oral administration (8–9 h) (Hartvig et al., 1981).

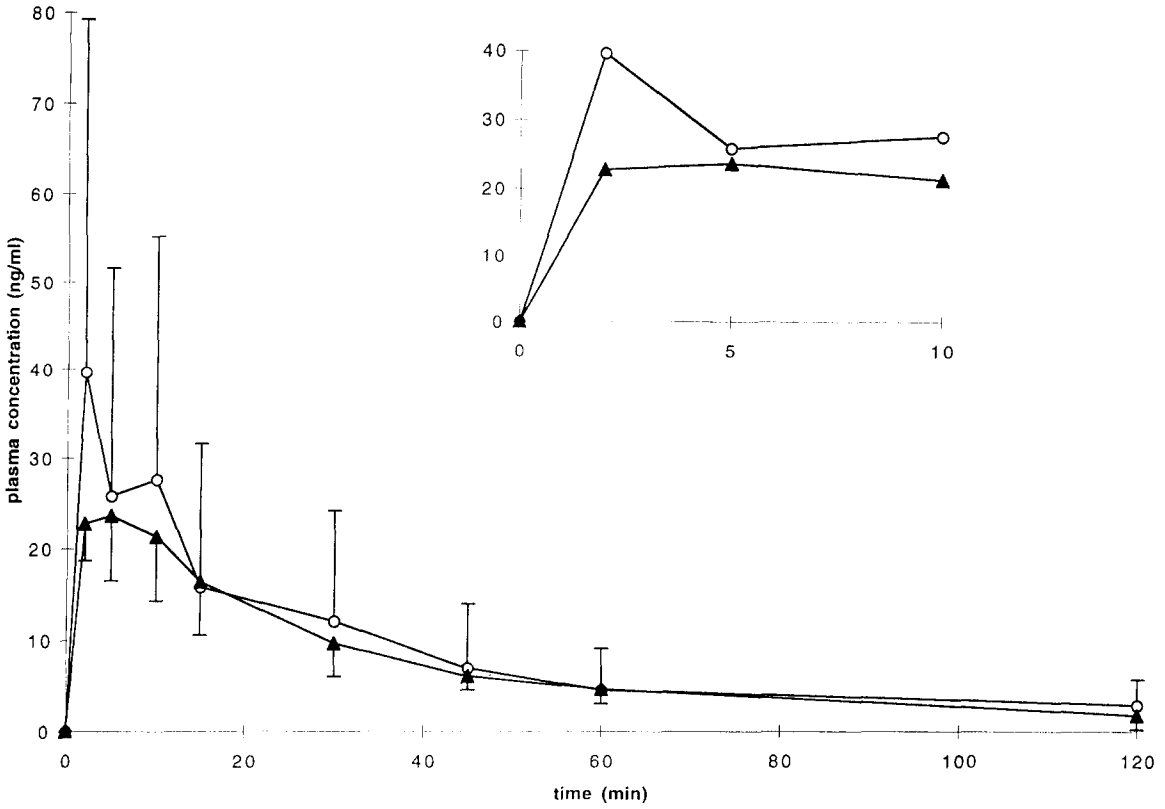

Fig. 3. Changes in plasma concentration with time after nasal administration of propiomazine maleate in saline (low (▲) and high (○) dose). The data are expressed as mean ± S.D. ($n = 6$). Inset shows an enlargement of the plasma concentration profile during the first 10 min after administration.

3.2. *Effects of test vehicle*

The absorption and clearance of a nasally administered drug depend heavily on the formulation of the vehicle and the device used for administration (Harris et al., 1988; Hardy et al., 1985). As this was the first in vivo study on nasal administration of propiomazine, the drug was applied directly onto the mucosa in solution.

Previous studies have shown that a more viscous vehicle increases the adhesion of the substance under investigation to the mucus layer (Harris et al., 1988; Pennington et al., 1988; Duchêne and Ponchel, 1993). This study indicated that the inferred prolonged contact time for the test vehicle did not increase the bioavailability of propiomazine (Table 1), since the results were comparable to those seen with propiomazine hydrochloride in saline. These results were supported by another study in which viscosity-induced enhancement of drug absorption was not recorded (Johansson et al., 1992).

Concerning the vehicle many other factors will influence the bioavailability of nasally administered drugs. These include the mucoadhesive effects (Dondeti et al., 1995) and osmolality of the vehicle (Pereswetoff-Morath and Edman, 1995), and the addition of enhancers (Marttin et al., 1995). Earlier in vitro studies on propiomazine investigated a suitable formulation for nasal administration of propiomazine regarding

solubility of the substance in the vehicle and mucoadhesive characteristics of the formulation (Lindberg, unpublished data). Addition of propylene glycol and polyethylene glycol 400 as cosolvents in the test vehicle improved the solubility of the substance compared with saline. Increased solubility of the substance in the vehicle promotes faster release of the substance (Lindberg, unpublished data). The aim of using the same vehicle as in the study reported above was to evaluate the correlation between in vitro solubility, release rate and spraying ability of the vehicle and in vivo bioavailability after nasal administration.

Although the composition of the test vehicle might be expected to influence the membranes due to its higher lipophilicity compared with saline, no such indication was found in this study. Accordingly, the test vehicle appeared not to affect absorption compared to 0.9% NaCl. However, the intraindividual variability in maximum plasma concentrations was lower when using the test vehicle compared with propiomazine hydrochloride in saline. The C.V.% for the test vehicle was 16% compared with 30% for the saline solution (Table 1).

4. Conclusion

In conclusion, nasal administration of propiomazine appears to offer an interesting alternative route of administration, with the added advantages of a rapid onset of action and good bioavailability. However, further studies are required to evaluate short and long term morphological effects on the nasal mucosa, to determine the optimal dosage and to evaluate the effects of differing vehicles. Comparison of oral and nasal administration in the same species also requires further study.

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