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Nasal absorption of ergotamine tartrate in rats

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Summary

The nasal administration of ergotamine tartrate was studied in rats following a single dose of 0.5 mg/rat and compared to intravenous, intraduodenal and oral administration of the drug. The effect of the addition of caffeine on the extent of nasal absorption was also studied. Relative to the 100% bioavailability from the intravenous route, the bioavailabilities were nasal: 62.0%; intraduodenal: 12.7%; and oral: 5.1%. The addition of 2.5 mg/rat of caffeine slightly improved the extent of nasal absorption; however, such an enhancement was found to be statistically insignificant.

Introduction

Ergotamine tartrate has been the drug of choice for the symptomatic treatment of migraine for many years. Currently 5 dosage forms for the administration of ergotamine are used. These include: parenteral injection, oral and sublingual tablets, rectal suppositories and oral inhalation. Numerous clinical trials comparing different routes of administration indicate that except for the parenteral injection, all methods of administration of ergotamine are either ineffective or unreliable in the treatment of severe migraine. Absorption of the drug from oral dosage forms is slow and erratic. Further, since vomiting often accompanies migraine, loss of part or all of the administered dose in the vomitus may occur. Rectal dosage forms are impractical when diarrhea accompanies the migraine attack and moreover suffer from lack of patient acceptance for esthetic reasons. Following the administration of 2 mg oral, 2

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mg rectal and 5 mg intramuscular ergotamine tartrate to 33 volunteers (Ala-Hurula et al., 1979), both the oral and rectal routes showed highly variale blood levels with peak levels of 0.36–0.42 ng/ml reached in 1–2 h. The intramuscular administration, however, resulted in peak drug blood level of 1.94 ng/ml in 30 min. Buccal and sublingual administration of ergotamine have not been very effective (Sutherland et al., 1974; Crooks et al., 1964). Furthermore, the extremely bitter taste of ergotamine is a significant drawback to this type of administration. Oral inhalation of ergotamine has also been used, but the inhaler is very expensive and the method of administration is quite complicated and can lead to the delivery of variable doses. Clinical studies showed that although oral inhalation of ergotamine produces slightly better results than sublingual tablets, it is inferior to the rectal administration of suppositories (Graham et al., 1960).

Since fast and reliable relief is of utmost importance in the treatment of severe migraine, the injectable dosage form is still the most efficient and reliable treatment. This route of administration obviously has its inherent drawbacks, including lack of patient acceptance and lack of convenience as a method of self-medication. Therefore, an alternative method for the effective and reliable administration of ergotamine is needed.

Previous studies have shown that in man and animals selected drugs such as the beta blocker, propranolol, and the female contraceptive hormone, progesterone, are rapidly and completely absorbed following nasal administration (Hussain et al., 1979, 1980a and 1981).

The purpose of this work was to study nasal absorption of ergotamine tartrate. Since caffeine has been shown to solubilize and enhance oral absorption of ergotamine in man (Schmidt et al., 1974), the effect of caffeine on the nasal absorption of the drug was also studied.

Since previous studies with propranolol indicated that nasal absorption studies in rats correlated well with the results in man, the current initial studies were also carried out in the rat.

Materials and Methods

Ergotamine tartrate used in this study was purchased from Sigma Chemicals, St. Louis, MO. Doses used were 0.5 mg for the intravenous, nasal, intraduodenal and oral routes of administration. The drug solutions were prepared as shown in Table 1.

Animal studies and surgical procedures

Male Sprague–Dawley rats, each weighing approximately 300 g, were used. The surgical procedures and methods of administration were described previously (Hussain et al., 1980). For all the routes of administration, the animals were anesthetized with intraperitoneal injection of pentobarbital (50 mg/kg). For nasal administration, an incision was made in the neck of the rat and the trachea was cannulated with a polyethylene tube. A closed tube was inserted through the esophagus to the posterior part of the nasal cavity. The nasopalatine was closed with an adhesive agent (Super

TABLE 1

COMPOSITION OF ERGOTAMINE SOLUTIONS

Solution	Intravenous and nasal		Oral
	Expt. 1	Expt. 2	
Ergotamine tartrate (mg)	0.5	0.5	0.5
0.1 N Tartaric acid (ml)	0.013	0.025	0.013
Caffeine, anhydrous (mg)	-	2.5	-
Distilled water (ml)	ad 0.1	-	ad 0.2
Saline (ml)	-	ad 0.1	-

Glue, Woodhill Permetex) to prevent drainage of the drug from the nasal cavity to the mouth. The drug was administered to the nasal cavity by means of a micropipet and the nostrils were then closed with an adhesive agent. For intravenous administration, the drug was injected through the femoral vein. For intraduodenal administration, the abdomen was opened by means of a midline incision and the drug was injected directly into the the duodenum. For oral administration, the rats were administered the ergotamine solution by using an intubation needle.

Sample collection and assay

Blood samples (0.4 ml) were periodically withdrawn from the femoral artery of the rats and ergotamine was assayed according to the procedure previously described (Hooper et al., 1973). Plasma (0.2 ml) was separated after centrifuging and was made alkaline with 0.5 ml of saturated sodium carbonate solution. The mixture was extracted into 3 ml of toluene. After shaking and centrifuging, 2 ml of the toluene layer was added to 1 ml of methanol. The fluorescence of the mixture was determined spectrofluorophotometrically using an Aminco-Bowman Ratio II Spectrometer. The excitation and emission wavelengths were 314 nm and 404 nm, respectively. The recovery of known amounts of ergotamine tartrate added to rat plasma was 96.9 ± 2.06 ($n = 3$). The assay method employed was shown to be specific for ergotamine with no interference from caffeine (Sutherland et al., 1974).

Results and Discussion

Fig. 1 shows the mean plasma ergotamine levels following nasal, intravenous and intraduodenal administration of 0.5 mg/rat. A considerable amount of the drug was absorbed within 3–10 min after nasal administration. After intraduodenal administration, however, plasma levels were not detectable after the first 10 min despite the fact that the drug was injected directly into the duodenum.

Fig. 2 shows the mean plasma ergotamine levels following nasal and intravenous administration of the mixture of 0.5 mg of ergotamine tartrate and 2.5 mg of caffeine/rat.

Table 2 summerizes the area under the plasma drug level curve data calculated for

0–240 min for the different routes of administration. Table 2 also shows the relative bioavailability for the different routes of administration of ergotamine tartrate with and without caffeine. Relative bioavailabilities were calculated by comparison of the mean area under the plasma level–time curve. The relative bioavailabilities after dosing of 0.5 mg/rat for oral and intraduodenal routes were only 5.1% and 12.7%, respectively, while that of the nasal route in the absence or presence of caffeine was 62.0% and 65.4%, respectively.

Statistical analysis using an unpaired *t*-test indicated that their was no significant difference at the 5% level between the mean area calculated for ergotamine in the presence or absence of caffeine following either intravenous or nasal administration.

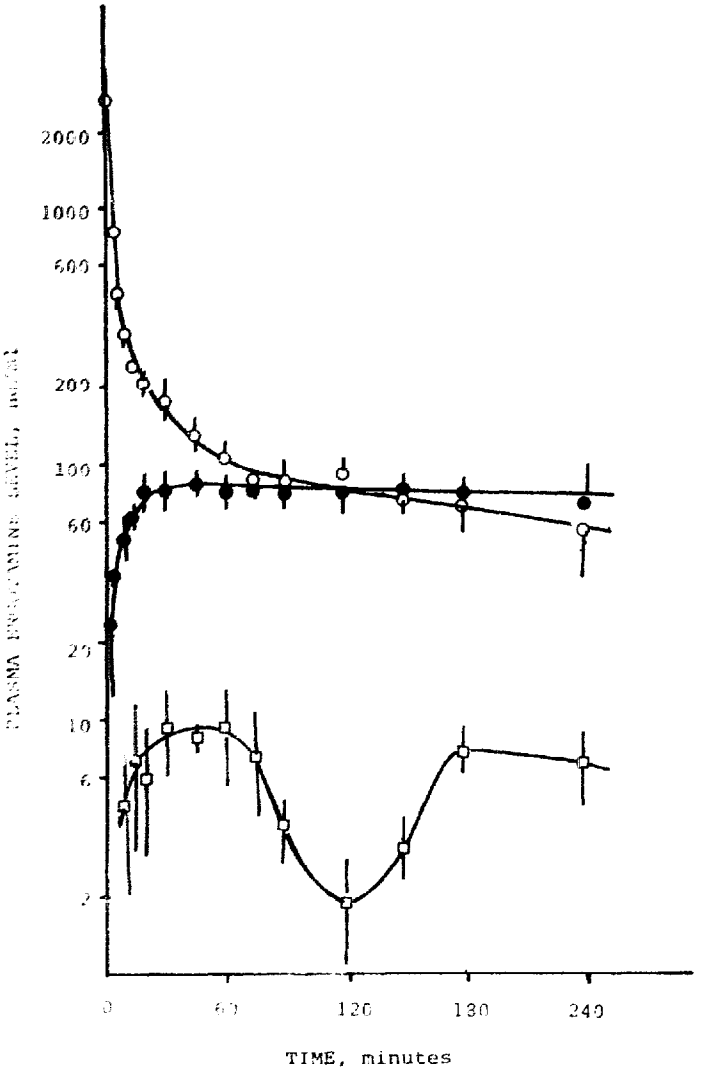

Fig. 1. Mean blood ergotamine levels following nasal (●), intravenous (○) and intraduodenal (□) administration of 0.5 mg of ergotamine tartrate/rat. Points represent mean values of 4 animals ± S.E.M.

TABLE 2

AUC AND RELATIVE BIOAVAILABILITY FROM 0 TO 240 MIN FOLLOWING INTRAVENOUS, NASAL, ORAL AND INTRADUODENAL ADMINISTRATION OF ERGOTAMINE TARTRATE WITH AND WITHOUT CAFFEINE IN RATS

Dose	Route	AUC 0–240 min ($ng \cdot ml^{-1} \cdot min$) mean ± S.E. for 4 rats	Relative bioavailability (0–240 min (%))
Ergotamine (0.5 mg/rat)	Intravenous	32,900 ± 3200	–
	Nasal	20,400 ± 4600	62.0
	Intraduodenal	4200 ± 1200	12.7
	Oral	1700 ± 1700	5.1
Ergotamine (0.5 mg) plus caffeine (2.5 mg/rag)	Intravenous	25,300 ± 6700	–
	Nasal	16,500 ± 3200 *	65.4

* 5 rats

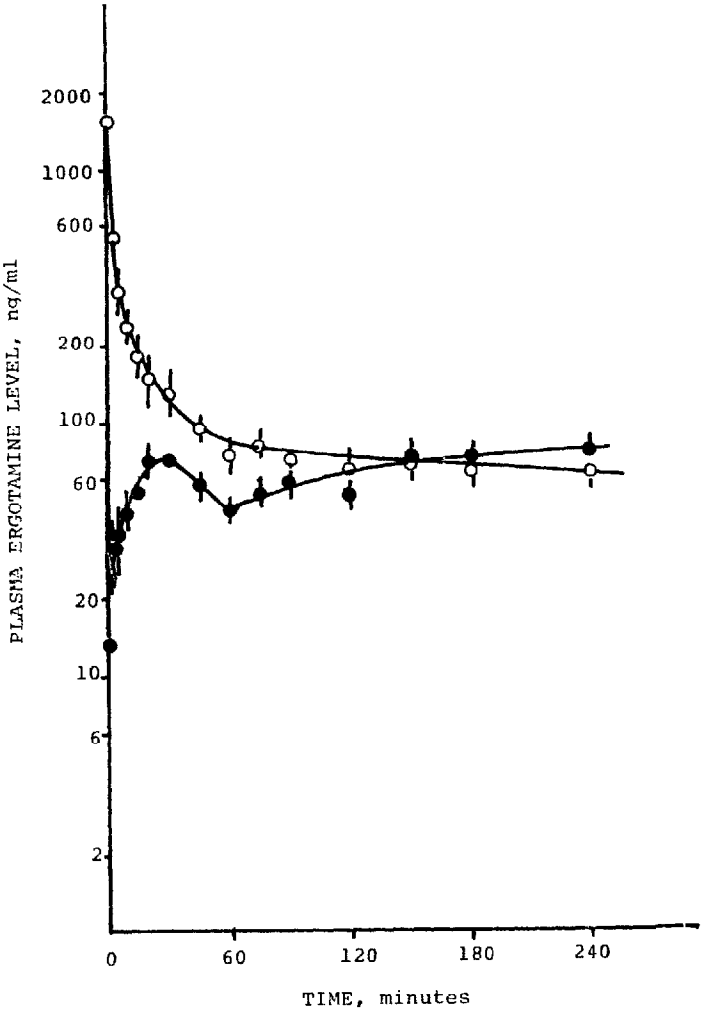

Fig. 2. Mean blood ergotamine levels following nasal (●) and intravenous (○) administration of the mixture of 0.5 mg of ergotamine tartrate and 2.5 mg of caffeine/rat. Points represent mean values of 4 animals ± S.E.M.

Because of the rapid rate and sufficient extent of absorption of ergotamine following nasal administration coupled with the convenience of this method, the nasal route offers an alternative to the parenteral route for the administration of this drug.

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