LOW BIOAVAILABILITY OF ERGOTAMINE TARTRATE AFTER ORAL AND RECTAL ADMINISTRATION IN MIGRAINE SUFFERERS

J.J IBRAHEEM, L. PAALZOW¹ & P. TFELT-HANSEN²

¹Department of Pharmacology, Central Research and Control Laboratory, National Corporation of Swedish Pharmacies, Solna, Department of Biopharmaceutics and pharmacokinetics, University of Uppsala, BMC, Uppsala, Sweden and ²Department of Neurology, Rigshospitalet, Copenhagen, Denmark

1 Fifteen migraine patients were administered 2 mg ergotamine tartrate in a partial cross-over design as a single, oral tablet, rectal suppository and rectal solution. Eight of these patients were in a previous investigation given 0.5 mg ergotamine tartrate intravenously. The blood samples were taken up to 54 h after oral and suppository while it was followed for only 3 h after rectal solution. The chemical analysis was performed by applying h.p.l.c. method with a limit of sensitivity of 0.1 ng/ml ergotamine base in plasma.

2 No ergotamine was detected in the blood samples after the oral route, whereas small and very variable quantities was found in blood after the rectal route. Regular calculation of bioavailability could therefore not be performed. An estimate of the maximal possible bioavailability was found to yield a mean value of 2% (tablets); 5% (suppositories) and 6% (rectal solution). Rectal solution elicited faster absorption and the extent of absorption was significantly higher ($P < 0.05$) than for the suppository.

Keywords ergotamine migraine bioavailability oral and rectal administration

Introduction

Ergotamine tartrate is still an important agent for symptomatic relief of migraine attacks (Rall & Schleifer, 1980), but its use is hampered by the poor knowledge of its clinical pharmacology. Tritium-labeled ergotamine has been used to investigate its pharmacokinetics (Aellig & Nuesch, 1977) but due to a lack of distinction between parent drug and metabolites the results do not allow a proper evaluation of the kinetics of the unchanged drug. With a radio-immunoassay the availability of ergotamine after i.m., oral and rectal administration has been studied (Ala-Hurula *et al.*, 1979a, b). Since no i.v. administration was used as a reference, the bioavailability could not be determined.

Recently, Edlund (1981) developed a high performance liquid chromatographic (h.p.l.c.) method using fluorescence detection for the determination of ergotamine in plasma. With this method we studied the pharmacokinetics of i.v. ergotamine tartrate in 10 migraine patients (Ibraheem *et al.*, 1982). At the same time eight of these patients were given ergotamine tartrate tablets and suppositories to allow exact calculations of bioavailability. As the result indicated a very low bioavailability and especially a slow appearance of ergotamine in blood, we subsequently

explored whether rectal solution of ergotamine tartrate could be an alternative.

This work was presented in part at the Meeting of the Scandinavian Section of I.A.S.P., March 1981, Geilo, Norway and at the eighth International Congress of Pharmacology, July 19–24, 1981, Tokyo, Japan.

Methods

Fifteen migraine patients were studied outside attacks. The physical and clinical parameters are shown in Table 1. Each study on a patient was performed at least 14 days apart. (Eight of the patients had previously been given ergotamine tartrate intravenously (Ibraheem *et al.*, 1982)). Ergotamine was not allowed for 1 week nor any medication for 3 days prior to the investigation. These restraints on the patients prompted the use of the partial cross over design. All investigations were started at 08.00 h. Seven patients were given 2 mg ergotamine tartrate as tablets (Gynergen -Sandoz) together with 200 ml water after fasting from midnight. After 2 h a light meal was served. Nine patients were given 2 mg ergo-

Table 1 Physical and clinical parameters of 15 migraine patients who received 2 mg ergotamine tartrate as tablets, suppositories and rectal solution.

Patient number	Age (years)	Sex	Weight (kg)	Height (cm)	Migraine type	Route of administration		
1*	53	M	67	173	Common	supp.	oral	
2*	37	M	57	167	Classical	supp.	oral	Rectal solution
3*	37	F	55	159	Classical	supp.	oral	Rectal solution
4*	39	F	57	165	Common	supp.	oral	Rectal solution
5*	43	F	51	160	Common		oral	
6*	54	F	59	176	Common	supp.	oral	
7*	37	M	73	174	Common	supp.		Rectal solution
8*	38	F	52	162	Common	supp.	oral	Rectal solution
9	42	M	106	180	Common	supp.		Rectal solution
10	28	F	50	164	Classical			Rectal solution
11	46	M	83	184	Common			Rectal solution
12	42	M	60	173	Common			Rectal solution
13	64	F	43	165	Common			Rectal solution
14	60	F	56	162	Common			Rectal solution
15	36	M	63	169	Common	supp.		Rectal solution

* These patients were given previously ergotamine tartrate intravenously (Ibraheem *et al.*, 1982).

tamine tartrate as suppositories (Ergotamin DAK). Twelve patients were given a solution of ergotamine tartrate (Gynergen -Sandoz) as a rectal solution (Table 1). This solution contains a mixture of ergotamine tartrate 60% and the isomer ergotamine 40% yielding a total alkaloids concentration of 0.5 mg/ml. Ergotamine tartrate was instilled in the rectum with a 8 cm plastic needle, the total dose was 2 mg ergotamine tartrate except in one obese patient where 3 mg was given. The patients then rested in the left recumbent position for 1 h.

Blood was drawn before administration and then after 10, 20, 30, 60, 90, 120, 180, 300, and 420 min from an indwelling venous catheter. Blood was taken again after 24, 30 and 54 h. Each time 10 ml blood was drawn and 5 ml plasma was transferred to test tube and kept deep-frozen at -20°C until analyzed.

The plasma samples were analyzed by h.p.l.c. using fluorescence detection as described by Edlund (1981). The practical detection limit (three times background noise) of the assay is 0.1 ng/ml in 3 ml plasma. The bioavailability was calculated from (e.g. for oral route):

$$\frac{\text{AUC}_{\text{oral}} \times \text{Dose}_{\text{i.v.}}}{\text{AUC}_{\text{i.v.}} \times \text{Dose}_{\text{oral}}}$$

The area under the curve of intravenous plasma concentration-time curve was calculated previously (Ibraheem *et al.*, 1982). For oral and rectal routes, the areas under the curves was obtained by the trapezoidal rule from time 0 and up to 10 h (five times the half-life). In order to estimate the maximal possible bioavailability, a concentration of 0.1 ng/ml (the detection limit of the analysis) was used when ergotamine was undetectable in plasma.

Results

Oral route

After administration of 2 mg ergotamine tartrate to seven patients, ergotamine could not be detected in plasma from 10 min up to 54 h. The estimated maximal possible bioavailability using a constant concentration of 0.1 ng/ml for 10 h was 2.1%, range 0.9–3.4%.

Rectal route

Suppositories of ergotamine tartrate (2 mg) resulted in low and very variable levels of the drug in plasma in nine patients (Table 2 and Figure 1). The maximal possible bioavailability is estimated to be 4.7%, range 0.9–10.8%, $n = 7$, in four of the nine patients maximum measurable levels were obtained 20–60 min following the administration.

Rectal solutions of ergotamine tartrate (2 mg) also resulted in low and very variable plasma levels ($n = 12$), as shown in Table 3 and Figure 2. For the five patients given intravenous ergotamine tartrate, the maximal possible availability was calculated to be 6.2%, range 1.6–11.1%, $n = 5$. Detectable levels were obtained in eight of 12 patients already at 10 min following the administration.

In seven patients the area under plasma concentration-time curves, for the suppositories and rectal solutions, could be compared for 3 h. Corrected for the dose, the AUC was approximately two times higher for the rectal solution than the suppositories. In all patients the corrected AUC was greater for rectal solution ($P < 0.05$, sign test).

Figure 1 Plasma concentrations of ergotamine base vs time after the administration of 2 mg ergotamine tartrate as a suppository. Each point represents the mean $\pm$ s.d. of nine migraine patients.

Discussion

In previous studies (Aellig & Nuesch, 1977; Meier & Schreier, 1976) with tritium-labelled ergotamine peak plasma concentrations of ergotamine from 1.5 to 3 ng/ml after administration of 1 and 4 mg ergotamine tartrate orally was found. Our results with ergotamine tablets strongly indicate that what was measured in these studies was mostly metabolites. In more recent studies (Ala-Hurula *et al.*, 1979a, b) a

Figure 2 Plasma concentrations of ergotamine base vs time after the administration of 2 mg ergotamine tartrate as a rectal solution. Each point represents the mean $\pm$ s.d. of 12 migraine patients.

Table 2 Concentrations of ergotamine in plasma (ng/ml ergotamine base) in nine migraine patients who received 2 mg of ergotamine tartrate as a suppository (Ergotamin-DAK)

Patient number	Dose ^a (μ g/kg)	Time	0	10 min	20 min	30 min	60 min	90 min	120 min	180 min	300 min	420 min	24 h	30 h	54 h
1	26.6		—	—	—	—	—	—	0.11	0.11	0.13	0.13	—	—	—
2	31.2		—	—	—	0.26	0.29	0.27	0.25	0.22	0.17	0.15	—	—	—
3	32.4		—	—	0.16	0.15	0.12	—	0.13	—	—	—	—	—	—
4	31.2		—	—	—	—	—	—	—	0.45	0.42	0.50	—	—	—
6	30.2		—	—	0.14	0.21	0.35	0.41	0.32	0.47	0.30	0.37	—	—	—
7	24.4		—	—	0.56	—	0.14	—	0.11	—	—	0.53	—	—	—
8	34.2		—	—	—	—	—	0.13	—	—	—	—	—	—	—
9	16.8		—	—	—	—	—	—	—	—	—	—	—	—	—
15	28.3		—	—	—	—	—	—	—	—	—	—	—	—	—
Mean	28.37		—	<0.1	0.16	0.14	0.16	0.16	0.15	0.19	0.17	0.23	<0.1	<0.1	<0.1
$\pm$ s.d.	± 5.27		—	—	± 0.15	± 0.06	± 0.10	± 0.11	± 0.08	± 0.16	± 0.12	± 0.18	—	—	—

^a Ergotamine base alone

^b Below detection limit of 0.1 ng/ml plasma, regarded as 0.10 for calculation of the mean (from 20–420 min)

Table 3 Concentrations of ergotamine in plasma (ng/ml ergotamine base) in 12 migraine patients who received 2 mg of ergotamine tartrate solution as a rectal solution (Gynergen®-Sandoz)

Patient number	Dose ^a (µg/kg)	Time (min)							
		0	10	20	30	60	90	120	180
2	18.7	—	0.42	0.33	0.55	0.15	0.15	0.35	0.33
3	19.4	—	— ^b	—	—	—	0.20	0.18	0.13
4	18.7	—	0.26	0.29	0.40	0.35	0.29	0.31	0.15
7	14.6	—	0.12	—	—	—	0.23	—	0.11
8	20.5	—	0.29	0.13	0.11	—	—	—	—
9	15.1 ^c	—	—	—	—	—	—	—	0.22
10	21.4	—	0.11	0.15	0.26	0.35	0.31	0.31	0.26
11	12.9	—	0.62	0.82	0.64	0.46	0.71	0.80	0.60
12	17.8	—	0.27	0.39	0.35	0.16	0.16	0.17	0.13
13	24.8	—	—	0.19	0.20	0.28	0.39	0.32	0.15
14	19.1	—	—	0.25	0.34	0.24	0.24	0.22	0.21
15	17.0	—	0.90	0.40	0.30	—	—	—	—
Mean	18.33	—	0.28	0.27	0.29	0.21	0.25	0.26	0.21
± s.d.	±3.22	—	±0.25	±0.21	±0.18	±0.13	±0.17	±0.20	±0.14

^a Ergotamine base alone^b Below detection limit of 0.1 ng/ml plasma regarded as 0.10 for calculation of the mean^c Patient number 9 was given 3 mg ergotamine tartrate solution

mean peak ergotamine concentration in plasma of 0.35 ng/ml after 1 h was determined with a radioimmunoassay after administration of 2 mg ergotamine tartrate plus caffeine as tablets or suppositories. In the present study, where ergotamine was determined with a h.p.l.c. procedure, pure ergotamine tartrate tablets (2 mg) did not result in plasma concentrations above the detection limit of 0.1 ng/ml. Caffeine improves the absorption of oral ergotamine tartrate (Schmidt & Fanchamps, 1974). This can, however, hardly explain the discrepancy in plasma concentrations as a total daily dose up to 5 mg ergotamine tartrate tablets containing caffeine did not result in any measurable amount in plasma with the HPLC procedure (Ekbohm *et al.*, 1981). Seemingly, with the development of more specific methods for determination of ergotamine one tends to measure continuously lower levels of the drug in plasma.

A second peak in plasma concentration of ergotamine was observed with the radioimmunoassay at 48 h and further on after administration (Ala-Hurula *et al.*, 1979a, b) indicating the possibility of accumulation and then redistribution of the drug to plasma. We therefore followed plasma concentrations of ergotamine up to 54 h. No second peak was found. Our results give no support to the risk of accumulation of ergotamine and the reason for the previously found second peak remains obscure.

The very low and most often unmeasurable concentrations of ergotamine in plasma did not allow exact determination of the bioavailability for oral and rectal ergotamine in the present study. Instead we calculated an estimate: the maximal possible bio-

availability. For dihydroergotamine, which can be given in much higher doses than ergotamine, the mean oral bioavailability is 0.5% (Little *et al.*, 1982), thus supporting our estimation of a few percent maximal oral bioavailability of ergotamine.

The very low bioavailability of oral ergotamine must be due to either poor absorption and/or high first-pass elimination of the drug. Aellig & Nuesch (1977) reported that the extent of oral absorption was 62% based upon measurement of total radioactivity. With the maximum bioavailability of about 2% found in our investigation, it means that at least about 97% of the absorbed drug is degraded by the first pass effect. Similar degree of first-pass metabolism was also reported for dihydroergotamine (Little *et al.*, 1982). Furthermore, the low oral bioavailability found in the present study is in accordance with our previous finding of the plasma clearance for ergotamine, which was similar to liver plasma flow after intravenous administration (Ibraheem *et al.*, 1982).

There has been no study of the absorption of ergotamine from suppositories but the marginal higher bioavailability of ergotamine suppositories indicates that part of the drug is absorbed directly to the systemic circulation; thus escaping the first-pass effect in the liver (Mayer *et al.*, 1980).

The very low bioavailability of ergotamine found in the present study raises the question of whether ergotamine is pharmacologically active in normal therapeutic doses by oral and rectal routes. Oral ergotamine has been found effective for migraine in double-blind trials (Hakkarainen *et al.*, 1979; Ostfeld, 1961) and even in a study where ergotamine

was not better than placebo, it caused significantly more side-effects than placebo (Waters, 1970). No controlled trial of the effect of ergotamine suppositories on migraine has been conducted, but a single ergotamine suppository causes a significant and long-lasting constriction of peripheral arteries in migraine patients (Tfelt-Hansen *et al.*, 1980). Thus ergotamine is pharmacologically active in normal therapeutic doses both as tablets and as suppositories despite almost undetectable plasma concentrations. The possible reason for the discrepancy between low plasma levels and pharmacodynamic effectiveness could be either active metabolites or an extremely high potency of this drug.

For any drug used in the treatment of acute pain the rate of absorption is important, confronted with the rather slow absorption of ergotamine from suppositories, we decided to investigate the absorption from rectal solution, since this route of administration has

improved the rate and extent of absorption of other drugs like diazepam (Knudsen, 1977) and theophylline (Bolme *et al.*, 1979). Since the purpose was the rate of absorption, plasma levels were only followed for 3 h. Rectal solution of ergotamine increased the bioavailability of the drug marginally, but more important ergotamine was detectable in plasma as early as 10 min in eight out of 12 patients which was never the case after administration of suppositories ($n = 9$). There are therefore strong indications that ergotamine absorption is faster and more complete from a rectal solution than from a suppository but there is still a great variation in the amount absorbed. Ergotamine tartrate was administered in the solution available for injection which might not be the most suitable solution for the rectal route. Pharmaceutical investigations of the ideal vehicle and volume for rectal solution of ergotamine tartrate might be worthwhile.

References

- AELLIG, W.A. & NUESCH, E. (1977). Comparative pharmacokinetic investigations with tritium-labeled ergot alkaloids after oral and intravenous administration in man. *Int. J. clin. Pharmac.*, **15**, 106–112.
- ALA-HURULA, V., MYLLYLÄ, V.V., ARVELA, P., HEIKKILÄ, J., KÄRKI, N.T. & HOKKANEN, E. (1979a). Systemic availability of ergotamine tartrate after oral, rectal and intramuscular administration. *Eur. J. clin. Pharmac.*, **15**, 51–55.
- ALA-HURULA, V., MYLLYLÄ, V.V., ARVELA, P., KÄRKI, N.T. & HOKKANEN, E. (1979b). Systemic availability of ergotamine tartrate after three successive doses and during continuous medication. *Eur. J. clin. Pharmac.*, **16**, 355–360.
- BOLME, P., EDLUND, P.O., ERIKSSON, M., PAALZOW, L. & WINBLADH, B. (1979). Pharmacokinetics of theophylline in young children with asthma: Comparison of rectal enema and suppositories. *Eur. J. clin. Pharmac.*, **16**, 133–139.
- EDLUND, P.O. (1981). Determination of ergot alkaloids in plasma by high performance liquid chromatography and fluorescence detection. *J. Chromatogr.*, **226**, 107–115.
- EKBOM, K., PAALZOW, L. & WALDENLIND, E. (1981). Low biological availability of ergotamine tartrate after oral dosing in cluster headache. *Cephalgia*, **1**, 203–207.
- HAKKARAINEN, H., VAPAATALO, H., GOTHONI, G. & PARATAINEN, J. (1979). Tolfenamic acid is as effective as ergotamine during migraine attacks. *Lancet*, **ii**, 326–328.
- IBRAHEEM, J.J., PAALZOW, L. & TFELT-HANSEN, P. (1982). Kinetics of ergotamine after intravenous and intramuscular administration to migraine sufferers. *Eur. J. clin. Pharmac.*, **23**, 235–240.
- KNUDSEN, F.U. (1977). Plasma-diazepam in infants after rectal administration in solution by suppository. *Acta Paediat. Scand.*, **5**, 563–567.
- LITTLE, P.J., JENNINGS, G.L., SKEWS, H. & BOBIK, A. (1982). Bioavailability of dihydroergotamine in man. *Br. J. clin. Pharmac.*, **13**, 785–790.
- MAYER, S.E., MELMON, K.L. & GILMAN, A.G. (1980). Introduction, the dynamics of drug absorption, distribution and elimination. In *The pharmacological basis of therapeutics*, eds. Gilman, A.G., Goodman, L.S. & Gilman, A., 6th edn, p. 7. New York: Macmillan.
- MEIER, J. & SCHREIER, E. (1976). Human plasma levels of some antimigraine drugs. *Headache*, **16**, 96–104.
- OSTFELD, A.M. (1961). A study of migraine pharmacotherapy. *Am. J. med. Sci.*, **241**, 192–198.
- RALL, T.W. & SCHLEIFER, L.S. (1980). Oxytocin, prostaglandins, ergot alkaloids and other agents. In *The pharmacological basis of therapeutics*, eds. Gilman, A.G., Goodman, L.S. & Gilman, A., 6th edn, p. 946. New York: Macmillan.
- SCHMIDT, R. & FANCHAMPS, A. (1974). Effect of caffeine on intestinal absorption of ergotamine in man. *Eur. J. clin. Pharmac.*, **7**, 213–216.
- TFELT-HANSEN, P., EICKHOFF, J.H. & OLESEN, J. (1980). The effect of single dose ergotamine tartrate on peripheral arteries in migraine patients: Methodological aspects and time effect curve. *Acta Pharmac. Tox.*, **47**, 151–156.
- WATERS, W.E. (1970). Controlled clinical trial of ergotamine tartrate. *Br. med. J.*, **2**, 325–327.

(Received May 16, 1983,
accepted August 10, 1983)