Ergotamine absorption and toxicity

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Summary

Adverse reactions to ergotamine were noted in 16 out of 41 studies in which therapeutic doses of the drug were given to normal, healthy volunteers. In 17 of the studies 0.25 mg ergotamine was given by injection, 6 i.v. and 11 i.m., in 20 studies 2 mg ergotamine was given by mouth, and 4 subjects received 2 mg ergotamine by suppository. Plasma and urinary ergotamine was measured by radio-immunoassay. Adverse reactions were significantly more frequent in subjects in whom plasma ergotamine exceeded 1.8 ng/ml.

Pharmacokinetic data derived from the study are presented and their relevance to the therapeutic use of ergotamine are discussed.

Introduction

Although ergotamine tartrate has been used in the treatment of migraine headache for more than 50 years (Dalessio, 1972) little is known about its rate of absorption, distribution, metabolism and excretion in man or about the relationship between plasma concentrations and toxic effects. Some information has come from recent pharmacokinetic studies using tritiated ergotamine (Aellig and Nuesch, 1977; Meier and Schreier, 1976; Schmidt and Fanchamps, 1974) but using this method it is not possible to distinguish between the parent drug and its metabolites. The authors have previously reported (Orton, 1978) the measurement of ergotamine in plasma by radio-immunoassay and they now report a pharmacokinetic study in subjects given ergotamine by the i.v., i.m., oral and rectal routes, with preliminary observations on the relationship between toxic effects and plasma concentrations.

Materials and method

Subjects

The subjects who took part in this were healthy young men and women aged between 18 and 37 years, with normal renal and hepatic function as measured by routine blood tests for urea, electrolytes, bilirubin, protein and hepatic enzymes. Six subjects

(3 male, 3 female) received ergotamine tartrate 0.25 mg by i.v. injection, 11 (3 male, 8 female) received ergotamine tartrate 0.25 mg by i.m. injection, and 11 subjects (4 male, 7 female) received 2 mg ergotamine by mouth. Two oral preparations were used: a solid tablet containing 100 mg caffeine and 50 mg cyclizine in addition to 2 mg ergotamine tartrate, and an effervescent tablet containing 2 mg ergotamine tartrate and 50 mg caffeine. Each preparation was studied in 10 subjects, 9 taking both preparations. Subjects fasted overnight before the oral studies, and each oral preparation was given with the same volume (100 ml) of water. Four subjects (2 male, 2 female) received 2 mg ergotamine tartrate by suppository, which also contained 100 mg caffeine, 100 mg allylbarbituric acid and 0.25 mg belladonna alkaloids. At least one week elapsed between successive administration of ergotamine to any one subject.

Blood samples were taken via an indwelling i.v. cannula into lithium heparin tubes at the following time intervals:

Intravenous studies: 0, 2.5, 5, 7.5, 10, 15, (20* 25*), 30, 45 and 60 min and then every 30 min until 240 min (* in 3 subjects only).

Intramuscular and rectal studies: 0, 15, 30, 45 and 60 min and then every 30 min until 240 min.

Oral studies: 0, 15, 30, 45 and 60 min and then every 30 min until 360 min.

The blood was centrifuged at 1000 *g* for 5 min and the plasma frozen within 30 min of collection.

Urine samples were collected from 4 subjects after i.v. ergotamine, from 10 subjects after i.m. ergotamine, and from all the oral and rectal studies. Subjects emptied their bladders before the start of the study, and at the end of each hour throughout the study. The volume of urine passed during each hour was recorded and an aliquot frozen. Plasma and urine were stored at -20°C until analysis.

Method

Samples were assayed for ergotamine using a

modification of the radio-immunoassay for dihydroergotamine (DHE) developed by Rosenthaler and Munzer (1976). Antiserum was prepared by immunizing rabbits with a conjugate of DHE and

bovine serum albumin. Tritiated DHE (9, 10, ^3H -DHE) with a specific activity of $30 \mu\text{Ci}/\mu\text{g}$ was used as label. Ergotamine quantitatively competes with the label for binding by the antibody, allowing measurement of ergotamine in plasma at concentrations down to 1 ng/ml with a coefficient of variation (CV) of 10%, the CV at 0.4 ng/ml being 30%.

Figure 1 shows the 95% confidence limits of the assay at concentrations of ergotamine below 1.4 ng/ml in plasma and below 14 ng/ml in urine. The precision of the assay declines greatly at concentrations lower than 0.8 ng/ml in plasma and 6 ng/ml in urine. Concentrations below 0.2 ng/ml in plasma and 1.5 ng/ml in urine cannot be distinguished from zero. Metabolites of the lysergic acid moiety of the ergotamine molecule, mainly lysergic acid amide, are not detected by the assay.

Results

Intravenous ergotamine

The mean plasma levels $\pm$ s.e. mean in the 6 subjects given i.v. ergotamine are shown in Fig. 2. As expected, drug concentrations declined rapidly over the first 15 min after injection. Thereafter, ergotamine concentrations fell more slowly and no drug was detected in the plasma at 240 min in 5 of the 6 subjects. The data for each subject were analysed by computer using a 2-compartment model with first-order kinetics, and the mean pharmacokinetic parameters derived are shown in Table 1.

The mean urinary excretion of ergotamine in 4 subjects after an i.v. dose are shown in Table 2. During the 4 hr of the study, 4.9% of the dose was

FIG. 1. Precision of ergotamine radio-immunoassay at low concentrations. 95% confidence limits = 2 s.d. from mean. (a) Plasma—205 measurements in duplicate. (b) Urine—129 measurements in duplicate.

FIG. 2. Mean ($\pm$ s.e. mean) plasma ergotamine concentrations (ng/ml) after administration of ergotamine 0.25 mg i.v. ($\bullet$ — $\bullet$ $n=6$), 0.25 mg i.m. ($\circ$ — $\circ$ $n=11$) and 2.0 mg by suppository ($\square$ — $\square$ $n=4$).

TABLE 1. Pharmacokinetic parameters derived from the i.v. ergotamine study

	Range	Mean	s.d.
Distribution half-life (min)	1.72-4.55	2.43	1.03
Elimination half-life (min)	63.8-154.1	96.53	24.49
Apparent volume of distribution (litre)	68-254	140.9	62.5

TABLE 2. Mean hourly ($\pm$ s.e. mean) urinary excretion (ng/hr) and cumulative excretion (ng) ergotamine over 4 hr after administration of ergotamine 0.25 mg i.v., 0.25 mg i.m. and 2.0 mg by rectal suppository

		0-60 min	60-120 min	0-120 min	120-180 min	0-180 min	180-240 min	0-240 min
0.25 mg i.v. <i>n</i> =4	Mean	7499 (1936)	2055 (626)	9554 (2498)	1469 $\pm$ 612	11023 $\pm$ 2999	1232 $\pm$ 631	12255 $\pm$ 3132
	% of dose	3.0 (0.8)	0.8 (0.25)	3.9 (1.0)	0.6 $\pm$ 0.25	4.5 $\pm$ 1.2	0.5 $\pm$ 0.25	5.0 $\pm$ 1.2
0.25 mg i.m. <i>n</i> =10	Mean	1247 (265)	1090 $\pm$ 253	2337 (454)	652 $\pm$ 152	2989 $\pm$ 486	469 $\pm$ 71	3458 $\pm$ 518
	% of dose	0.5 (0.1)	0.4 $\pm$ 0.1	0.9 0.2	0.3 $\pm$ 0.06	1.2 $\pm$ 0.2	0.2 $\pm$ 0.03	1.4 $\pm$ 0.2
2.0 mg suppository <i>n</i> =4	Mean	88 (80)	1158 $\pm$ 281	1246 235	1232 $\pm$ 100	2478 $\pm$ 331	1082 $\pm$ 158	3560 $\pm$ 482
	% of dose	-	0.06 $\pm$ 0.01	0.06 0.01	0.06 $\pm$ 0.01	0.12 $\pm$ 0.02	0.05 $\pm$ 0.01	0.17 $\pm$ 0.02

excreted, more than 50% of this during the first hour.

Intramuscular ergotamine

The mean plasma levels measured in 11 subjects given 0.25 mg ergotamine tartrate by i.m. injection

are shown in Fig. 2. Peak concentrations ranged from 0.5 to 2.6 ng/ml, and most subjects had maximum concentration within the first hour. The mean peak level was 1.5 ng/ml 15 min after injection.

Urinary excretion of ergotamine in 10 of these subjects is shown in Table 2; 1.4% of the dose was

FIG. 3. Mean ($\pm$ s.e. mean) plasma ergotamine concentrations (ng/ml) after administration of ergotamine 2.0 mg in an effervescent formulation ($\bullet$ - $\bullet$ *n*=10) and in solid tablet ($\circ$ - $\circ$ *n*=10). Note the different time-scale compared with Fig. 2.

TABLE 3. Mean hourly ($\pm$ s.e. mean) urinary excretion (ng/hr) and cumulative excretion (ng) of ergotamine over 6 hr after oral administration of ergotamine 2 mg in an effervescent tablet A and in a solid tablet B (both $n=10$)

	0-60 min	60-120 min	0-120 min	120-180 min	0-180 min
Mean A	311 (77)	497 (86)	808 (104)	299 (36)	1107 (133)
% of dose	0.01	0.03	0.04	0.01	0.05
Mean B	519 (80)	668 (78)	1187 (116)	446 (44)	1633 (110)
% of dose	0.03	0.03	0.06	0.02	0.08

	180-240 min	0-240 min	240-300 min	0-300 min	300-360 min	0-360 min
Mean A	194 (41)	1301 (134)	129* (28)	1430* (172)	119* (16)	1549* (181)
% of dose	0.01	0.06	0.01*	0.07*	0.01*	0.08*
Mean B	239 (23)	1872 (118)	154 (25)	2026 (120)	136* (28)	2162* (157)
% of dose	0.01	0.09	0.01	0.10	0.01*	0.11*

* = mean of 8 values.

excreted during 4 hr, 0.5% being excreted during the first hour. The fraction excreted during each subsequent hour decreased throughout the study.

Oral ergotamine

Mean plasma ergotamine concentration after taking 2 oral preparations containing 2 mg ergotamine tartrate are shown in Fig. 3. Peak plasma concentrations are achieved about 60 min after oral administration. It had been intended to compare the rates of absorption and the bioavailability of the 2 preparations but it was found that the drug concentrations were too low for small differences between the 2 preparations to be distinguished by the present assay. Nevertheless, useful information about time to peak and the time course of plasma and urinary ergotamine can be obtained within the limits of the assay.

The mean peak plasma concentrations following the effervescent and solid tablets were 0.5 and 0.6 ng/ml respectively. The difference is not significant. The mean time to peak concentrations after the effervescent tablet was 45 min, compared with 60 min for the solid tablet, and again the difference is not significant.

For this panel of subjects, 9 of whom were common to both studies, there was greater variation in plasma ergotamine after the solid tablet than after the effervescent tablet, and this variation is not accounted for by variation in the assay.

Mean urinary excretion of ergotamine after oral administration is shown in Table 3; 0.107% of the oral dose was excreted after the solid tablet, compared with 0.077% after the effervescent preparation. In both cases 50% of the total excreted at 6 hr was excreted in the first 2 hr of the study.

Rectal ergotamine

Mean plasma ergotamine concentrations following a suppository containing 2 mg ergotamine tartrate

are shown in Fig. 2. One subject had high drug concentrations at 15 min and thereafter reached a peak of 2.8 ng/ml at 2 hr, while the other 3 subjects had much lower concentrations which reached maximum recorded concentrations at 2, 3, or 4 hr. The mean plasma ergotamine concentrations after suppository were higher than after the same dose given by mouth, and the peak was later.

Urinary excretion of ergotamine after the rectal dose is shown in Table 2. The mean excretion was 0.18% of the dose after 4 hr, very little being excreted in the first hour and the remainder being distributed throughout the 2nd, 3rd and 4th hr of the study.

Adverse reactions

Adverse reactions to ergotamine were reported in

TABLE 4. Adverse reactions to ergotamine tartrate

Route	Dose (mg)	No. of adverse reactions	No. of studies
Intravenous	0.25	3	6
Intramuscular	0.25	5	11
Oral	2	6	20
Rectal	2	2	4
All		16	41 (40%)

TABLE 5. Types of adverse reaction to ergotamine

Nausea	8
Headache	5
Light-headedness (malaise)	4
Peripheral vasoconstriction	3
Vomiting	1
Tiredness	1
Tightness in throat and neck	1
Tingling in jaw	1
Total adverse reactions	24

16 of the 41 studies (Table 4), an incidence of 39%. The most frequent adverse reactions were nausea or vomiting (9 subjects), headache (5 subjects) and feeling light-headed and unwell (4 subjects) (Table 5). Adverse reactions were more likely at plasma ergotamine concentrations above 1.8 ng/ml, 8 of 11 subjects with concentrations above 1.8 ng/ml reporting adverse reactions, compared with 8 of 30 who had lower concentrations. This difference is significant at the 5% level (Table 6).

TABLE 6. Relationship between plasma ergotamine concentrations and adverse reactions

Plasma ergotamine	Adverse reactions	
	Present	Absent
> 1.8 ng/ml	8	3
< 1.8 ng/ml	8	22
	16	25

$$\chi^2 = 5.3 \quad P < 0.05$$

Discussion

Ergotamine directly stimulates the chemoreceptor trigger zone (CT zone) in the medulla oblongata (Nickerson and Collier, 1975). Nausea and vomiting are the most frequently observed side effects of ergotamine, although the incidence varies between different series, partly owing to variation in the doses and routes of administration employed. Lennox and Von Storch (1935) noted nausea in 77% and vomiting in 60% of patients treated for migraine with injections (subcutaneously, i.m., or i.v.) of ergotamine tartrate 0.25–1 mg. O'Sullivan (1936) observed vomiting in 42 of 97 patients (43.3%) treated with ergotamine 0.25–0.75 mg by subcutaneous injection. Sutherland and Eadie (1961) had an incidence of nausea or vomiting in 20 out of 77 patients (26%) treated with doses varying from 0.6 mg (inhalation) to 6 mg (sublingual). and pointed out that 'these doses were at times lower than those commonly employed'. Yuill, Swinburn and Liversedge (1972) found an incidence of nausea in 65% and vomiting in 25% of 61 headaches treated with ergotamine tartrate 2–6 mg by mouth.

As nausea and vomiting are often part of a migraine attack it may be difficult to assess the contribution made by the ergotamine to these symptoms. However, Lennox and Von Storch (1935) gave ergotamine to volunteers who did not have migraine and found an incidence of nausea or vomiting of about 40%. In the series of Yuill *et al.* (1972), ergotamine was compared in a double-blind trial with a non-ergotamine preparation without

anti-emetic properties. The incidence of nausea and vomiting in the non-ergotamine-treated headaches was 41% and 6.5% respectively, significantly less than for the ergotamine-treated group.

Nausea and vomiting after ergotamine are dose-related. M. I. P. Wilkinson (personal communication, 1979) found no nausea or vomiting in 12 migraine patients treated with 0.25 mg ergotamine tartrate by i.m. injection, whilst of 12 similar patients given 0.5 mg, 4 developed nausea or vomiting. Remission of headache and time to recovery was identical in both groups.

In this study adverse reactions were found to occur after ergotamine by all 4 routes of administration, and were much more frequent when plasma ergotamine exceeded 1.8 ng/ml. Nausea or vomiting occurred in more than 50% of the subjects with side effects, and in 22% of the studies.

The short distribution half-life after i.v. administration (2.43 ± 1.03 min) indicates that ergotamine passes rapidly into the tissues from the plasma, which would be expected of a small, lipid-soluble molecule. The volume of distribution was calculated as 140.9 ± 62.5 litres, i.e. greater than the total body water, indicating that the drug is concentrated in the tissues. Kalberer (1970) has shown that after administration of ^3H ergotamine to rats, radioactivity is concentrated in the liver, lungs, kidney and heart, but not in the brain of the rat. It is thus unlikely that ergotamine concentration at receptors in the CT zone reflects uptake of the drug into the brain, and is more likely to be related to plasma concentrations.

The authors' value of 96.5 ± 24.5 min for the elimination half-life of ergotamine corresponds closely with the figure of 1.9 hr derived by Aellig and Nuesch (1977) from the measurement of total radioactivity in plasma after giving ^3H -ergotamine, but is considerably shorter than the 6.6 hr found by Meier and Schreier (1976) using a similar technique. Both these studies identified a further, slow phase of elimination of radioactivity from plasma of 21 hr (Aellig and Nuesch, 1977) and 30–35 hr (Meier and Schreier, 1976) which may represent a later, slower phase of elimination of ergotamine, or the elimination of a metabolite with a longer half-life than the parent compound. An alternate explanation may be that the late, slow phase is due to the release of ergotamine or a metabolite from tissue stores. Some support for this hypothesis comes from the observation by Ala-Hurula *et al.* (1979) of an apparent rise in ergotamine concentration in some subjects 24–28 hr after administration of ergotamine. Further studies using a more sensitive radio-immunoassay and taking samples over a longer period of time are required to elucidate this point.

The authors' value for the urinary excretion of ergotamine after an i.v. dose was 4.9% which is of the same order as the 6.7% found by Aellig and Nuesch (1977). However, after oral administration the present authors found 0.1% of the dose or less in the urine, compared with a urinary excretion of 3-4% which was found in the radioisotope studies. This discrepancy would be accounted for if the majority of the urinary radioactivity were due to metabolites, and not to unchanged ergotamine.

Ergotamine is metabolized mainly in the liver (Nimmerfall and Rosenthaler, 1976) and after oral administration there would be a large first pass effect, leading to reduced systemic and urinary drug concentrations and an increased proportion of metabolites compared with parenteral administration. The first pass effect would explain the high drug plasma concentrations after suppositories compared with the same dose given orally. Ergotamine absorbed *per rectum* passes to a large extent into the systemic circulation while drug absorbed from the upper gastrointestinal tract passes to the liver, where it is extensively metabolized. This suggests that the clinical dose of ergotamine by suppository should be lower than the oral dose.

These observations following single doses in volunteers require confirmation in patients who are receiving ergotamine as treatment for migraine, and who may also be receiving other medication which could influence absorption, metabolism and excretion. As mentioned above, ergotamine is extensively metabolized, and the adverse reactions may be due to ergotamine itself or to a metabolite.

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