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REVIEW ARTICLE

Ergotamine in the acute treatment of migraine
A review and European consensus

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Summary
Ergotamine has been used in clinical practice for the acute treatment of migraine for over 50 years, but there has been little agreement on its place in clinical practice. An expert group from Europe reviewed the pre-clinical and clinical data on ergotamine as it relates to the treatment of migraine. From this review, specific suggestions for the patient groups and appropriate use of ergotamine have been agreed. In essence, ergotamine, from a medical perspective, is the drug of choice in a limited number of migraine sufferers who have infrequent or long duration headaches and are likely to comply with dosing restrictions. For most migraine sufferers requiring a specific anti-migraine treatment, a triptan is generally a better option from both an efficacy and side-effect perspective.

Keywords: migraine; headache; acute treatment; serotonin pharmacology; 5-$HT_{1B/1D}$ receptors

Introduction
Ergotamine burst onto the medical scene during the Middle Ages when mass poisoning by ergotamine occurred throughout Europe due to eating bread contaminated with the sclerotia of the mushroom *Claviceps purpurea*, which is a parasite on rye, wheat, barley and other cultivated grains, climaxing in St Anthony's Fire. Due to its remarkable uterotonic and vasoconstrictor effects, ergotamine was used to precipitate childbirth and to control post-partum haemorrhage, first mentioned clearly by John Stearns in 1808 in a letter published in the *Medical Repository of New York* (Thoms, 1931). The evolution of the use of ergot derivatives in obstetric practice is covered elsewhere (Moir, 1974). An extract of ergot was used in clinical practice by Eulenberg (1883), and ergotamine itself was first isolated by Stoll (1918) and has been used in the acute treatment of migraine since 1926 (Maier, 1926), with no alternative specific acute anti-migraine treatment for decades. Remarkably, despite widespread use, there is little consensus as to its place in practice. In this review, we attempt to set out information concerning ergotamine and then make conclusions concerning its use based on current evidence. The American Academy of Neurology has published recommendations on ergotamine use (Quality Standards Subcommittee of the American Academy of Neurology, 1995), but here we sought to provide detailed evidence for our position. Most clinicians feel ergotamine has some place in treating acute migraine, and we have attempted a consensus to present the core of its role.

Table 1 *Receptor profile of ergotamine compared with dihydroergotamine and sumatriptan*

Receptor type	pK_i value on human cloned receptors in radioligand-binding assay[a]		
	Ergotamine	Dihydroergotamine	Sumatriptan
5-HT_{1A}	7.89[b]	9.30[c]	6.43[c]
5-HT_{1B}	7.88[b]	9.22[c]	7.82[c]
5-HT_{1D}	8.36[b]	8.60[c]	8.46[c]
5-HT_{1E}	6.22[d]	6.22[c]	5.80[c]
5-HT_{1F}	6.77[d]	6.96[c]	7.86[c]
5-HT_{2A}	7.69[e]	8.54[c]	< 5.0 (pIC_{50})[c]
5-HT_{2B}	8.17 (pEC_{50}, pig, functional)[f]	7.70 (pEC_{50}, pig, ND functional)[f]	
5-HT_{2C}	7.25 (pig, native)[e]	7.43 (pig)[c]	< 5.0 (pIC_{50}, pig)[c]
5-HT_3	ND	< 5.0 (pIC_{50}, mouse)[c]	< 5.0 (pIC_{50}, mouse)[c]
5-HT_4	ND	6.52 (guinea pig)[c]	< 5.0 (pIC_{50}, guinea pig)[c]
5-HT_{5A}	7.26[b]	7.34[b]	5.50[b]
5-HT_{5B}	8.50 (pK_d, rat)[g]	ND	ND
5-HT_6	ND	6.78[b]	5.31[b]
5-HT_7	7.49 (pK_d, rat)[g]	7.17[b]	6.51[b]
α_1 adrenoceptor	8.00 (?)[h]	8.00 (rat)[c]	< 5.0 (pIC_{50}, rat)[c]
α_2 adrenoceptor	8.20 (?)[h]	8.00 (rat)[c]	< 5.0 (pIC_{50}, rat)[c]
β_1 adrenoceptor	ND	5.27[c]	< 5.0 (pIC_{50})[c]
β_2 adrenoceptor	ND	< 5.0 (pIC_{50})[c]	< 5.0 (pIC_{50})[c]
Dopamine D_1	ND	5.32 (rat)[c]	< 5.0 (pIC_{50}, rat)[c]
Dopamine D_2	8.50 (?)[h]	8.21[c]	< 5.0 (pIC_{50})[c]

[a]Unless otherwise stated; ? = species and test not specified; ND = not determined. [b]P. J. Pauwels, personal communication to P.R.S.; [c]Leysen *et al.*, 1996; [d]Adham *et al.*, 1993; [e]Hoyer, 1998; [f]Glusa and Roos, 1996; [g]Hoyer *et al.*, 1994; [h]Leysen and Gommeren, 1984.

Pharmacology of ergotamine

Receptor binding profile and mode of action

The ergot alkaloids have a complex mode of action that involves interaction with a variety of receptors. Indeed, as shown in Table 1 (Leysen and Gommeren, 1984; Hoyer, 1988; Adham *et al.*, 1993; Hoyer *et al.*, 1994; Glusa and Roos, 1996; Leysen *et al.*, 1996), both ergotamine and dihydroergotamine have affinities for 5-HT (5-hydroxytryptamine), dopamine and noradrenaline receptors. In contrast, sumatriptan and the newer triptans are much more selective, showing high affinity for 5-HT_{1B} and 5-HT_{1D} receptors and a moderate affinity for 5-HT_{1A} and 5-HT_{1F} receptors (Goadsby, 1998).

The α-adrenoceptor-blocking property of ergotamine, first described by Dale (Dale, 1906), is textbook knowledge (Hoffman and Lefkowitz, 1996). However, this property is often overemphasized, since it is observed only with high doses used in some animal experiments and bears no relevance to therapeutic use in humans. In lower therapeutically relevant concentrations, ergotamine acts as an agonist at α-adrenoceptors, 5-HT (particularly 5-$HT_{1B/1D}$) and dopamine D_2 receptors (Müller-Schweinitzer and Weidmann, 1978; Saxena and Cairo-Rawlins, 1979; Müller-Schweinitzer, 1992; De Vries *et al.*, 1998; Villalón *et al.*, 1999). In addition, there is evidence that both ergotamine and dihydroergotamine can activate novel, as yet uncharacterized receptors (De Vries

Effects on blood vessels

The most important and conspicuous pharmacological effect of ergot alkaloids is undeniably the vasoconstrictor action (Müller-Schweinitzer and Weidmann, 1978; Müller-Schweinitzer, 1992). Extensive studies in animals show that this vasoconstrictor effect is particularly marked within the carotid vascular bed and the selectivity extends to the arteriovenous anastomotic part; blood flow to a number of tissues, including that to the brain, is little affected (Johnston and Saxena, 1978; De Vries *et al.*, 1998). Similar vasoconstrictor effects on cephalic arteriovenous anastomoses are also observed with sumatriptan as well as with other triptans (Saxena and Ferrari, 1996).

In humans, ergotamine can constrict several isolated blood vessels, including the pulmonary (Cortijo *et al.*, 1997), cerebral (Müller-Schweinitzer, 1992), temporal (Østergaard *et al.*, 1981) and coronary (MaassenVanDenBrink *et al.*, 1998) arteries. The drug seems to be more active on large arteries (conducting vessels) than on arterioles (resistance vessels). Basal cerebral (Andersen *et al.*, 1987; Dixon *et al.*, 1997) or myocardial (Gnecchi-Ruscone *et al.*, 1998) blood flow may not change, although ergotamine does affect coronary vasodilator reserve (Gnecchi-Ruscone *et al.*, 1998). Arterial blood pressure is moderately increased in therapeutic doses (Bulow *et al.*, 1986; Dixon *et al.*, 1997). An important feature of ergotamine and dihydroergotamine, as illustrated

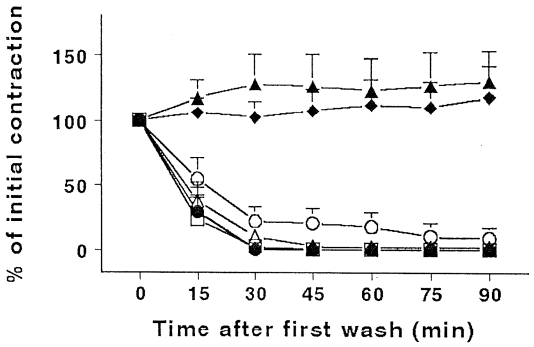

Fig. 1 Persistent contractile response by ergots, but not triptans, on human isolated coronary arteries. Filled triangles = ergotamine; filled diamonds = dihydroergotamine; filled circles = sumatriptan; open squares = zolmitriptan; stars = rizatriptan; open triangles = naratriptan; open circles = avitriptan. All drugs were administered once at a concentration twice their EC_{50}. Data are displayed as mean ± standard error of the mean (MaassenVanDenBrink *et al.*, 1998).

effects in isolated human coronary arteries are resistant to repeated wash. This appears to be due mainly to slow diffusion from the receptor biophase and, therefore, their effects last far longer than can be expected from plasma concentrations (Bulow *et al.*, 1986; Tfelt-Hansen and Johnson, 1993).

Other effects

Ergotamine and dihydroergotamine have been reported to inhibit dural plasma extravasation after stimulation of the trigeminal ganglion in rats (Buzzi and Moskowitz, 1991; Buzzi *et al.*, 1991). In addition, as has been demonstrated for dihydroergotamine (Goadsby and Edvinsson, 1993; Hoskin *et al.*, 1996), ergotamine derivatives may block the trigeminovascular pathway centrally. Ergotamine also has a prominent uterotonic action (Graves, 1996).

Pharmacokinetics of ergotamine

Oral absorption of ergotamine is 60–70%, and the concurrent administration of caffeine improves both the rate and extent of absorption. Due to high first-pass metabolism, ergotamine has a very low bioavailability from oral administration. There is considerable subject variability with respect to bioavailability and lack of consistency in the clinical response over multiple attacks. Compared with intravenous bioavailability (100%), oral bioavailability of ergotamine is <1% (Sanders *et al.*, 1983; Ibraheem *et al.*, 1983), rectal bioavailability is 1–3% and intramuscular bioavailability is 47% (Tfelt-Hansen and Johnson, 1993). Ergotamine is metabolized in the liver by largely undefined pathways; 90% of the metabolites are excreted in the bile and the elimination half-life is 2 h (Tfelt-Hansen and Johnson, 1993). An interaction with erythromycin may dramatically increase the oral bioavailability of ergotamine (Francis *et al.*, 1984), and

clarithromycin (Horowitz *et al.*, 1996) and ritonavir (Liaudet *et al.*, 1999). Since the same cytochrome P450 enzyme metabolizes a number of other drugs, including bromocriptine, dexamethasone, ethinyloestradiol, ketoconazole, nifedipine, omeprazole and verapamil (Christians *et al.*, 1996), this interaction may extend to these drugs as well.

Ergotamine formulations

Most formulations of ergotamine are not very useful due to an inappropriate amount of ergotamine or compounding with other drugs, such as caffeine, chlorcyclizine or meprobamate. Ergotamine is marketed as aerosol (which is slowly being withdrawn), oral and suppository formulations. In some countries, ergotamine can be used alone in an oral formulation, or particularly in the very useful inhalational form, but most often the suppository formulation is compounded and contains 1–2 mg of ergotamine with caffeine.

Clinical studies with ergotamine

Ergotamine is a relatively old drug and thus did not undergo a controlled clinical trial programme as would be expected of a modern drug. Nevertheless, oral ergotamine has been used over the past 30 years as the standard comparative drug in controlled trials of other medicines, although the number of good clinical trials incorporating this widely used drug is not large. A recent review (Dahlof, 1993) stated that 'there is little evidence that it is significantly more effective than placebo' and further 'the recommended doses of ergotamine cannot be justified'. Despite the limited number of studies with contemporary methodology that involve ergotamine (The International Headache Society Committee on Clinical Trials in Migraine, 1991), there is evidence for the efficacy of ergotamine in the literature, and this will be summarized briefly here.

Randomized controlled clinical trials with ergotamine

A summary of 18 controlled double-blind trials of oral ergotamine, or oral ergotamine plus caffeine, is given in Table 2. In 10 trials (Ostfeld, 1961; Ryan, 1970; Waters, 1970; Hakkarainen *et al.*, 1979; Kinnunen *et al.*, 1988; Sargent *et al.*, 1988; Friedman *et al.*, 1989; Cortelli *et al.*, 1996; McNeely and Goa, 1999; Reches and Eletriptan Steering Committee, 1999) ergotamine was compared with placebo, whereas in eight other trials ergotamine served as the standard comparative drug (Adams *et al.*, 1971; Yuill *et al.*, 1972; Hakkarainen *et al.*, 1978, 1980; Pradalier *et al.*, 1985; The Multinational Oral Sumatriptan and Cafergot Comparative Study Group, 1991; Treves *et al.*, 1992; Le Jeunne *et al.*, 1999) without placebo control. The initial dose of ergotamine varied from 1 to 5 mg, and in several trials

Table 2 *Double-blind randomized trials with pure oral ergotamine (Erg) or an ergotamine compound with caffeine (ErgC) in the treatment of migraine attacks*

Trial	Drug	Initial (maximum) dosage (mg)	Study design	No. of attacks treated[a]	No. of patients (no. evaluated)	Result of trial
Ostfeld, 1961	Erg Pl	5	CO	1	44	More than 50% headache relief: Erg (70%) > Pl (39%)
Waters, 1970	Erg Pl	2–3	CO	?[b]	88 (79)	Benefited based on clinical interview: Erg (51%)/Pl (58%)
	ErgC Ergs Pl	2 (6) 2 (6)	CO	1	48	Escape medication: ErgC (22/48) = Ergs (22/46) > Pl (33/46)
Ryan, 1970	ErgC IsomC	2 (6) 130 (130)	CO	2	54	Mean headache duration: ErgC > IsomC
Yuill *et al.*, 1972	ErgC IsomC[c]	2 (6) 130 (390)	CO	1	38	Headache intensity[d]: IsomC (2.8) > ErgC (3.3). Nausea[d]: IsomC (1.1) > ErgC (2.0)
Hakkarainen *et al.*, 1979	Erg Tfa ASA Pl	1 200 500	CO	2	20	Mean duration of attack in h: Erg (3.8) = Tfa (3.2) = ASA (4.2) > Pl (7.1) Preference: all drugs > Pl
Hakkarainen *et al.*, 1978	Erg DextC[e] ASA	1 (3) 100 (200) 500 (1500)	CO	7	25	Mean of attack prevented: Erg (3.6) = DextC (2.6) > Pl (1.1)
Hakkarainen *et al.*, 1980	Erg DextC[e] ASA	1 (2) 100 (200) 500 (1000)	CO	7	25	Attack not prevented: Erg (53%) = DextC (59%) > Pl (82%)
Pradalier *et al.*, 1985	ErgC[f] Napxs	2 (4) 825 (1375)	Pa	6	114 (95)	For test drug taken within 2 h: Napxs > ErgC for headache relief. Later intake of test drug, NS[g]
Sargent *et al.*, 1988	ErgC Napxs Pl	2 (3) 825 (1100)	Pa	6	169 (122)	Relief of headache at 1 h: Napxs > Pl, ErgC = Pl. Overall efficacy: ErgC > Pl, Napxs = Pl
Kinnunen *et al.*, 1988	ErgC[f] Pirp Pl	2 (5) 200 (500)	CO	1	67 (61)	Escape medication: ErgC (18/59) = Pirp (18/58) > Pl (32/60). Duration of attacks in h: ErgC (6.5) > Pl (10.5) but versus Pirp NS. For most parameters, ErgC vs Pirp NS
Friedman *et al.*, 1989	ErgC[f] Pl	2 (6)	Pa	2	? (104)	Mean improvement from baseline on a 5-point headache scale after 2 h: ErgC (1.0) > Pl (0)[h].
The Multinational Oral Sumatriptan and Cafergot Comparative Study Group, 1991	ErgC Sum	2 100	Pa	3	580 (577)	Headache relief[i]: Sum (66%) > ErgC (48%)
Treves *et al.*, 1992	Erg Napxs	2 (4) 750 (1750)	Pa	6	79 (71?)	Napxs > Erg for overall efficacy rating of treatments on a 6-point scale (none to excellent) .Improvement of headache: Napxs = Erg
Le Jeunne *et al.*, 1997	ErgC CASA+M	1 900 +10	Pa	3	268	Headache relief[i]: CASA + M (54%) > ErgC (36%)
Cortelli *et al.*, 1996	ErgC Diclo Pl	2 (6) 50 (150)	CO	1	63	Diclo > Pl (–15 mm mean difference for changes on a VAS scale after 1 h). Diclo > ErgC (–11.9 mm mean difference) ErgC = Pl (–2.8 mm mean difference)
McNeely and Goa, 1999	ErgC Diclo Pl	2 (5) 50 (200)	Pa	1	423	Diclo > Pl (–9 mm mean difference for changes on VAS scale after 2 h). Diclo = ErgC (–3.6 mm mean difference). ErgC = Pl (–5.4 mm mean difference).
Reches and Eletriptan Steering Committee, 1999	ErgC Ele Ele Pl	2 (4) 40 (80) 80 (160)	Pa	1		Headache relief[i]: Ele 80 (68%) > Ele 40 (58%) > ErgC (33%) > Pl (21%)

The table is modified from Tfelt-Hansen and Johnson (1993). ASA = aspirin; CASA + M = calcium carbasalate (equivalent to 900 mg of ASA) plus metoclopramide; DextC = dextropropoxyphene compound; Diclo = diclofenac; Erg = ergotamine; ErgC = ergotamine compound with caffeine (1 mg of ergotamine + 100 mg of caffeine); Ergs = ergostine (+ caffeine); Ele = eletriptan; IsomC = isometheptene compound; Napxs = naproxen sodium; Pirp = pirprofen; Sum = sumatriptan; Tfa = tolfenamic acid; Pl = placebo; CO = crossover; Pa = parallel group; NS or = = no statistical significant difference; > = more effective than. [a]Maximum number of attacks treated; [b]approximately one-quarter of patients did not have migraine (74); [c]only dose of isometheptene given (for other components, see reference); [d]verbal scale : 1 = very mild, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe; [e]only doses for dextropropoxyphene [65 mg of the chloride (9) or 100 mg of the napsylate (10)] are indicated (for other components, see references); [f]contains other components in addition to caffeine, see references; [g]study conclusions weakened by the lack of use of double dummy technique; [h]patients refractory to ergot therapy were excluded; [i]a decrease from severe or moderate headache to no or mild headache.

parameters for efficacy were not all validated and varied considerably, from benefit based on a clinical interview (Waters, 1970) to use of changes on a verbal headache scale (Yuill *et al*., 1972; Friedman *et al*., 1989; The Multinational Oral Sumatriptan and Cafergot Comparative Study Group, 1991). Methodological flaws in some of these trials include the lack of clearly stated inclusion criteria, no reporting of the baseline criteria and randomization procedures, unusual design of some of the crossover trials with a variable number of attacks per patient, and superiority claims without appropriate statistics.

Ergotamine (1–5 mg) was superior to placebo for some parameters in seven trials (Ostfeld, 1961; Ryan, 1970; Hakkarainen *et al*., 1979; Kinnunen *et al*., 1988; Sargent *et al*., 1988; Friedman *et al*., 1989; Reches and Eletriptan Steering Committee, 1999) and no better than placebo in three studies using a dose of 2–3 mg (Waters, 1970; Cortelli *et al*., 1999; McNeely and Goa, 1999). In two comparative trials, ergotamine was superior to aspirin (500 mg) (Hakkarainen *et al*., 1978, 1980), and was inferior to an isometheptene compound in one trial (Yuill *et al*., 1972) and superior to it in another trial (Adams *et al*., 1971). As shown in Table 2, the drugs, such as ergocristine, tolfenamic acid, dextropropoxyphene, naproxen sodium, pirprofen and diclofenac, were generally found to be comparable with ergotamine, although there is one recent study of diclofenac which showed superiority of this drug (Cortelli *et al*., 1999). Exceptions are sumatriptan (100 mg orally) which was superior to 2 mg of ergotamine plus 200 mg of caffeine (The Multinational Oral Sumatriptan and Cafergot Comparative Study Group, 1991), the combination of calcium carbasalate (equivalent to 900 mg of aspirin) and metoclopramide (10 mg), which was superior to a rather small dose of 1 mg of ergotamine plus 100 mg of caffeine (Le Jeunne *et al*., 1999), and eletriptan at 40 and 80 mg doses which were superior to 2 mg of ergotamine plus caffeine (Reches and Eletriptan Steering Committee, 1999).

These trials of ergotamine, some of them placebo-controlled, suggest that oral ergotamine is efficacious in the treatment of migraine but they do not quantify the benefit effectively. Thus no uniform picture of the utility of oral ergotamine emerges from these trials. Early use of ergotamine in migraine treatment was tried in two of the trials (Hakkarainen *et al*., 1978, 1980) in which the drugs were administered as soon as the patients felt the onset of an attack. The results from this strategy are not convincing. The use of escape medication is a clinically relevant efficacy parameter (The International Headache Society Committee on Clinical Trials in Migraine, 1991), and this was used by 31% (Kinnunen *et al*., 1988), 44% (The Multinational Oral Sumatriptan and Cafergot Comparative Study Group, 1991) and 46% (Ryan, 1970) of patients treated with ergotamine. No clinical trial data are available on within-subject consistency, which from results of pharmacokinetic studies and from clinical practice is probably poor compared with the use of triptans (Kramer *et al*., 1998; Pfaffenrath *et al*., 1998).

Non-oral routes of administration

Other routes of administration of ergotamine, which from a kinetic point of view should be more efficacious, have scarcely been investigated. In one trial, inhaled ergotamine (maximum dose of 1.8 mg) was found to be superior to sublingual ergotamine (maximum dose of 2 mg) which was no better than a sublingual placebo (Crooks *et al*., 1964). In a double-blind placebo-controlled study, a suppository of ergotamine (2 mg) was no better than placebo, whereas ketoprofen (100 mg as a suppository) was superior to placebo (Kangasniemi and Kaaja, 1992). In a recent randomized, crossover, double-blind trial including 251 patients, so far published only on the Internet (1998), ergotamine plus caffeine suppositories (2 and 100 mg, respectively) were superior to 25 mg sumatriptan suppositories, with response rates of 73 and 63% respectively, after 2 h. Headache recurrence (see below) occurred more frequently in sumatriptan- (22%) than in ergotamine- (11%) treated patients. However, significantly more patients preferred sumatriptan suppositories (44%) than preferred ergotamine suppositories (36%), due to more side-effects after the latter. Full publication of this study will be of great interest.

Headache recurrence with ergotamine

Headache recurrence can be defined as a return or worsening of the headache and associated migraine symptoms within 24–72 h after an initial medication-induced amelioration. It is a major issue for all acute migraine treatments, but has only been recognized during the clinical trial programme with subcutaneous sumatriptan (Visser *et al*., 1996*c*). Recognition was triggered by the often dramatic contrast of an excellent initial improvement, which was followed by a rapid and very disappointing return of the headache after 10–12 h. Subsequently, it has been observed that headache recurrence is common to all acute migraine treatments (Ferrari, 1998), including ergotamine (The Multinational Oral Sumatriptan and Cafergot Comparative Study Group, 1991), although some treatments are better than others in this regard.

The mechanism of headache recurrence is unknown, but breakthrough of a temporarily suppressed migraine generator seems more likely than a new attack (Weiller *et al*., 1995; Visser *et al*., 1996*a*, *b*, *c*). A longer drug plasma half-life does not reduce the incidence of headache recurrence, but may delay the time to recurrence (Visser *et al*., 1996*a*). Where the risk of headache recurrence has been studied in sumatriptan users, it seems to be a patient-dependent rather than an attack-dependent phenomenon. About one-third of migraine patients using sumatriptan, especially those with long attacks of 2–3 days, will consistently experience headache recurrence in each successfully treated attack, while patients with shorter attacks experience headache recurrence only rarely (Visser *et al*., 1996*b*, *c*).

A major point of discussion, even among the authors of the present review, is whether headache recurrence

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