The Effect of Ergotamine and Dihydroergotamine on Cerebral Blood Flow in Man

Allan R. Andersen, Peer Tfelt-Hansen, and Niels A. Lassen

The effects of ergotamine and dihydroergotamine on cerebral blood flow was investigated 4 hours after i.v. injection as these drugs might be of importance for migraine treatment. Eight normal male volunteers (not suffering from migraine) received 0.5 mg ergotamine and 1 mg dihydroergotamine i.v. Cerebral blood flow was measured by the xenon-133 inhalation method and single-photon-emission computerized tomography before and after intravenous acetazolamide administration (1 g). Cerebral blood flow was measured before and 4 hours after ergotamine and dihydroergotamine administration. Strain-gauge measurements of toe–arm systolic gradients were used to monitor the effect of the drug on leg arteries. Mean hemispheric and regional cerebral blood flow was unchanged after either drug (mean ± SEM, ml/100 g/min): for ergotamine, 57 ± 3 before and 57 ± 3 at 4 hours; for dihydroergotamine, 54 ± 2 before and 55 ± 2 at 4 hours. The acetazolamide response was unchanged as well. Only ergotamine decreased the toe–arm systolic gradient significantly (22 mm Hg at maximum after 240 minutes; p < 0.02). Thus, our study did not support the belief that ergot alkaloids should be withheld from patients during attacks of classic migraine, but this has to be investigated further. The discrepancy in the peripheral effects of ergotamine and dihydroergotamine might also be of clinical importance. (Stroke 1987;18:120-123)

The USE of ergotamine (E) in the treatment of classic migraine, where transient neurological symptoms form part of the attack, has been controversial for a long time since it was feared that E, a potent constrictor of peripheral arteries, might also increase the risk of ischemia by an effect on the cerebral vasculature and induce permanent neurological symptoms. E is in fact a potent vasoconstrictor of human basilar arteries in vitro,1 and a lowering of regional cerebellar blood flow in vivo has been reported.2 Serious cases of reversible cerebral arteriopathy with segmental stenosis and even completed strokes have been reported after E was administered inappropriately in high doses.3 On the other hand, many patients have been treated with E during classic migraine attacks without any serious cerebrovascular side effects.

The controversy of whether to treat classic migraine attacks by E or not was apparently solved when Ha-chinski et al4 demonstrated that intramuscular injection of 0.2–1.0 mg ergotamine tartrate did not change cerebral blood flow (CBF) in 16 subjects when measured before and 15–20 minutes after drug administration. At this time, soon after injection, E has a pressor effect — an effect on the arterioles — but only a minor vasoconstrictor effect on the arteries per se.5

Before concluding that E has no effect on CBF, the problem should be reinvestigated at a time when the effect on arteries should be maximal, i.e., 4–6 hours after administration of E.6 An alternative to E in classic migraine could be the analog dihydroergotamine (DHE), which is generally held to be a selective vasoconstrictor7 although its effect on arteries in man has never been directly studied. Therefore, we investigated the effects of E and DHE on CBF 4 hours after i.v. administration of the maximum doses in normal young volunteers. Furthermore, CBF was increased by the administration of acetazolamide (1 g i.v.) to reveal any flow limitation caused by arterial constriction.

Subjects and Methods

Eight healthy male medical students were studied. Exclusion criteria were smoking, migraine, or a heart rate less than 52/minute. The subjects were studied on 3 separate days at least 1 week apart with crossover design. On the control study day CBF was measured before and 20 minutes after i.v. injection of 1 g acetazolamide. On the E and DHE study days CBF was measured before and 210 minutes after i.v. injections of 0.5 mg ergotamine tartrate or 1 mg DHE. CBF was measured again 20 minutes after i.v. injection of 1 g acetazolamide (240 minutes after E or DHE injection). The time schedule is seen in Table 1. The schedule was randomized across days, and neither the volunteers nor the investigator responsible for the CBF measurements knew whether E or DHE was given.

CBF was measured by xenon-133 inhalation and single-photon-emission computerized tomography (Tomomatic 64; Medimatic, Hellerup, Denmark). This method has been described in detail elsewhere,8,9 and only a brief description will be given here. With the subject in the supine position, resting with the eyes closed, a rotating array of 64 sodium iodide crystals monitors the cerebral uptake and washout of xenon-133. Three brain slices are studied simultaneously, each 2 cm thick with an unseen interslice distance of 2 cm. These slices are positioned 1, 5, and 9 cm above the orbito–meatal plane. The study lasts 4.5 minutes,
during which xenon-133 is rebreathed from a closed system the first 1.5 minutes, yielding a lung concentration reaching a maximum of 10 mCi/l at equilibrium. A sequence of 4 tomographic pictures is recorded during the xenon-133 inhalation period and during each of the subsequent 3 minutes. A single stationary scintillation detector is placed over the upper part of the right lung to represent the arterial input curve. The sequence of the tomographic pictures, together with the recorded lung curve, allows one to calculate the mean CBF, displayed in a 32 × 32-pixel matrix. The resolution of the instrument is 1.7 cm in the horizontal plane and 2.0 cm in the axial plane (measured as full width at half maximum).

CBF is calculated by averaging the flow values for all meaningful pixels in the 3 slices. Studies on normal volunteers have revealed a stable, bilaterally symmetrical pattern of CBF distribution. Focal CBF changes can be identified by differences from the stable flow distribution of normal subjects at rest. Studies on regional CBF showing cortical activation after visual stimulation and skilled hand movements, indicating sensitivity of this method in physiological ranges, have been published.10,11 Mean flow in a region of interest can be calculated, yielding measures of CBF from this region and in the symmetrical area of the opposite hemisphere.

The mean value of the left-to-right-side difference as percent of the value in the higher side in these anatomically defined regions was calculated. Furthermore, calculations were performed on visually depicted high- and low-flow areas. The degree of side-to-side asymmetry (i.e., the difference in mean flow in these regions expressed as a percent of the higher value) never exceeded 10%. We have calculated from other data obtained in normal subjects that a side-to-side asymmetry in a given region of more than 10% is statistically significant. The mean hemispheric values were corrected for differences in Paco2 in expired air during the study in each subject. CBF was changed 4% per mm Hg of Paco2 to 37.5 mm Hg.

Systolic blood pressures were measured simultaneously in triplicate on the left upper arm and big toes with strain-gauge plethysmography.12 These measurements were performed before and 30, 120, and 240 minutes after drug administration. The toe–arm systolic gradient was calculated as the mean of 6 differences between toe and arm systolic blood pressures, in millimeters of mercury.

For statistical evaluation of the results Friedman’s 2-way analysis of variance by ranks was used.

### Results

Neither E nor DHE caused any change in resting CBF, and after acetazolamide, no significant differences were observed. The increases in CBF were 28% in the control experiment, 26% after E, and 35% after DHE (Table 2). No changes were found in the regional distribution of CBF in the cerebellum or the hemispheres. Both E and DHE caused a significant ($p < 0.05$) but transient increase in systolic arm blood pressure, and the increases were of similar magnitude (Table 3).

The constriction of extremity arteries, as measured by a decrease in the toe–arm systolic gradient, developed slowly after i.v. E; only 23% of the final response was observed after 30 minutes (Figure 1). DHE did not cause any significant effect on the toe–arm systolic gradient (Figure 1).

### Discussion

Although classified in many pharmacological textbooks as an $\alpha$-receptor blocker, the most prominent action of E in therapeutic doses is a general vasocostriction of arteries,13 arterioles,14 and veins13 in man. The mechanisms for vasocostriction are, however, probably different in different parts of the vascular system since these effects have different time-effect curves. Thus i.v. E causes an immediate increase of systemic blood pressure (due to an effect on the arterioles), which disappears 3 hours later.5 In contrast, the effects on arteries (decreases in finger and toe systolic

### Table 1. Time Schedule of the Study

<table>
<thead>
<tr>
<th>Treatment</th>
<th>0 minutes</th>
<th>40 minutes</th>
<th>70 minutes</th>
<th>160 minutes</th>
<th>250 minutes</th>
<th>260 minutes</th>
<th>280 minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ergot alkaloid</td>
<td>Toe–arm gradient, CBF</td>
<td>Toe–arm gradient, CBF</td>
<td>Toe–arm gradient, CBF</td>
<td>Toe–arm gradient, CBF</td>
<td>Toe–arm gradient, CBF</td>
<td>Toe–arm gradient, CBF</td>
<td>Toe–arm gradient, CBF</td>
</tr>
<tr>
<td>Control</td>
<td>CBF</td>
<td>Acetazolamide</td>
<td>CBF</td>
<td>Acetazolamide</td>
<td>CBF</td>
<td>Acetazolamide</td>
<td>CBF</td>
</tr>
</tbody>
</table>

DHE = dihydroergotamine; E = ergotamine.

### Table 2. Effect of i.v. Ergotamine (E) and Dihydroergotamine (DHE) on Resting and Acetazolamide-Stimulated Global CBF

<table>
<thead>
<tr>
<th>Treatment</th>
<th>210 min after ergot alkaloids</th>
<th>20 min after acetazolamide (240 min after E or DHE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>54 ± 2</td>
<td>69 ± 1 (28%)*</td>
</tr>
<tr>
<td>E</td>
<td>57 ± 3</td>
<td>72 ± 3 (26%)</td>
</tr>
<tr>
<td>DHE</td>
<td>54 ± 2</td>
<td>74 ± 3 (35%)</td>
</tr>
</tbody>
</table>

Values for CBF are ml/100 g/min, mean ± SEM. Studies were performed on 3 separate days.

*Percent changes are not statistically different (Friedman’s analysis of variance).
blood pressure) and veins (decrease in compliance) develop more slowly; after i.v. E the effect on arteries takes 4 hours to reach its maximum. In both animal and human studies the arterioles in different vascular beds react differently to E. Further, in in vitro studies the arteries show regional and species-dependent differences in sensitivity to E. When investigating the vasoconstriction effects of ergotamine, this complexity should be kept in mind.

E could theoretically decrease CBF by an effect on the cerebral resistance — the arterioles — or by a considerable constriction of cerebral arteries. Animal studies have shown increased vascular resistance in the internal carotid vascular bed in dogs whereas in monkeys only the external carotid vascular resistance increased after E. In the study of Hachinski et al a 6% increase in mean arterial blood pressure (p = 0.01, Wilcoxon test) was found 15-20 minutes after administration of E. Thus, CBF was measured while E exerted its pressor effects. Mean CBF was 49 and 50 ml/100 g/min before and after E, respectively, and it is therefore unlikely that E had any effect on cerebral arterioles when these measurements were performed. The study was performed in 13 control subjects and 3 migraine patients during attack. In a study by Lauritzen and Olesen 0.25 mg E had no lowering effect on regional CBF after i.m. injection. CBF was measured 4.5-7 hours after injection of E.

In the present study both E and DHE caused a transient pressor effect (Table 3), but this effect had disappeared after 3.5 hours when CBF was measured. At this time E caused a significant (and probably maximal) vasoconstriction of extremity arteries as measured by a decrease in toe-arterial systolic gradient (Figure 1). DHE had no effect on arteries per se. Resting CBF was unchanged after either E or DHE (Table 2). No effect on cerebellar blood flow was seen. This contradicts the results of Sakai and Meyer who found a decrease in regional cerebellar blood flow after administration of sublingual E during 3 migraine attacks. We do not find their study conclusive on this point.

Our study was performed in normal subjects without migraine, with a different method of measuring CBF and another route of E administration.

Arteries are normally not flow-limiting in the human cerebral circulation (unless a considerable constriction occurs) because of the large capacity for autoregulation. We therefore raised CBF approximately 30% with 1 g acetalozamide to reveal any flow limitation caused by arterial constriction. The increase in CBF was, however, quite similar in the control and after E and DHE administration. Despite these precautions with optimal timing and enhanced CBF, the present study failed to reveal any constrictory effect of the maximum doses of E and DHE on cerebral arteries. These results do not, however, exclude a minor effect, but if one were present, it would probably have no physiological relevance after a single therapeutic dose of these drugs. Another result might be found in migraine patients during attacks, as the reactivity of resistance vessels of the brain has been reported to be changed during attacks of classic migraine.

It is interesting that whereas E and DHE both had similar pressor effects (arteriolar effect), only E and not DHE decreased peripheral systolic blood pressure (arterial effect). The lack of an effect of DHE on peripheral arteries probably explains why it can be used continuously for migraine prophylaxis without side effects whereas E taken daily causes subclinical ergotism. If DHE, which can now be given nasally for treatment of migraine attacks, is shown to be as efficacious as E, this lack of peripheral arterial effects would favor the use of DHE.

In summary: We could not disclose any delayed effect of E and DHE on CBF, suggesting constriction of cerebral arteries. It was previously shown that E has no immediate effect on CBF in normal subjects (n = 13) or migraine patients during an attack (n = 4). A delayed response could not be shown after i.m. injection of a small dose of E. Therefore, there should be no reason for withholding E and DHE from patients with classic migraine. Yet, due to the possibility of increased vasoreactivity in patients suffering from migraine — in particular during an attack — firm conclusions on this point are not possible until similar studies are performed in patients with migraine, preferably both between and during attacks.
References


KEY WORDS • ergotamine • dihydroergotamine • cerebral blood flow • peripheral blood pressure • acetazolamide
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