Effects of ergotamine and methysergide on blood platelet aggregation responses of migrainous subjects

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SYNOPSIS Platelet aggregation responses to 5-hydroxytryptamine (5-HT) were measured in plasma from migrainous subjects taking either methysergide maleate or ergotamine tartrate and were found to be reduced. Blood 5-HT levels of subjects free of headache were not affected by these drugs. The results support the hypothesis that methysergide and ergotamine act by occupying 5-HT uptake sites in vessel walls, leaving 5-HT molecules available to occupy receptors concerned with vasoconstriction.

Ergotamine tartrate is of proved value in the relief of headache in an acute migraine attack (Graham, 1956), while methysergide maleate is a very effective prophylactic treatment for migraine (Sicuteri, 1963; Curran and Lance, 1964; Graham, 1964; Lance et al., 1970). In vitro tests have shown that ergotamine and methysergide suppress platelet aggregation responses to 5-hydroxytryptamine (5-HT) in plasma taken from control subjects (Cumings and Hilton, 1971).

This paper reports on aggregation responses and 5-HT levels in migrainous patients taking either ergotamine tartrate or methysergide maleate and the results obtained have been compared with those for patients not taking drugs. The effect of headache on aggregation responses and 5-HT levels has been noted.

METHODS
Blood was collected from patients with migraine during and between migraine attacks. Patients with migraine headache were asked to describe whether it was slight, moderate, or severe. Migrainous subjects were included in the between headache group if they had not suffered an acute migraine attack for three days. Patients were questioned carefully about any drugs or medication they were taking and were divided into groups: (1) patients who had not taken any drugs at all; (2) patients who had taken methysergide maleate (Deseril) 4–8 mg per day; and (3) patients who had taken ergotamine tartrate.

Ergotamine was taken in several different forms: (1) patients without headache took 1–2 mg daily, as Migrol, Cafergot suppositories, or Bellergal Retard; (2) patients with migraine headache had taken 2.4 mg ergotamine within the previous six hours, as Cafergot tablets, Cafergot Q, Cafergot suppositories, or Migrol.

Whole blood for 5-HT estimation was collected into heparin and deep frozen (−20°C) immediately. The estimation was carried out using the method of Ashcroft et al. (1964) and the 5-HT content was expressed per ml. blood, corrected to a theoretical platelet count of 250,000 per cubic mm.

Platelet aggregation responses to 5-HT were measured as previously described (Hilton and Cumings, 1971) using an EEL platelet aggregation meter linked to a Honeywell chart recorder, where aggregation was expressed as the rate of aggregation (R cm/min) shown on the chart paper. Values of R were corrected to a platelet count of 250,000 per cubic mm.

Aggregation was induced using 5-HT (serotonin creatinine sulphate, B.D.H.) 50 nmol in 0.1 ml.

RESULTS
Blood 5-HT levels and platelet aggregation responses of migrainous subjects who were free of headache but taking either ergotamine or methysergide regularly, are shown in Fig. 1. Results for migrainous subjects before the institution of drug therapy and also for control subjects have been included for comparison.
FIG. 1. Effects of ergotamine and methysergide on biochemical parameters of migrainous patients in the absence of headache. The number of subjects in each group is shown in parentheses. * See Hilton and Cumings (1971).

FIG. 2. Blood 5-HT levels in migrainous patients taking drugs. ○ Headache-free subjects; ● subjects with migraine headache. The number of subjects in each group is shown in parentheses. * See Hilton and Cumings (1972).
Blood platelet aggregation responses of migrainous subjects

Whereas there is no significant difference between the blood 5-HT levels before and during drug treatments, there is a highly significant drop in the platelet aggregation response, R, in patients treated with either ergotamine or methysergide. Values of R for each group of patients on drugs are significantly less than R for either the no drug group or control subjects, at the level P < 0.001. Results obtained from a few patients taking both ergotamine and methysergide (not included in this Figure) are similar to those for patients taking methysergide alone.

The influence of headache on the blood 5-HT levels of migrainous patients taking either ergotamine or methysergide, can be seen in Fig. 2. The expected fall in 5-HT during headache (which is seen in subjects who had not taken drugs) was not found in subjects taking ergotamine or methysergide, but only in patients taking both ergotamine and methysergide. The rather high mean value for patients with headache who were taking methysergide is due mostly to a high 5-HT content found for one patient.

The effect of headache on the platelet aggregation responses of migrainous patients taking drugs, can be seen in Fig. 3. The responses during headache, like those for headache-free patients, were reduced to values below those found for patients not on drugs. Headache patients taking ergotamine did not have such reduced responses.

It may be significant that, overall, patients on ergotamine suffered worse headaches than those
DISCUSSION

The results clearly show that the aggregation responses of migrainous subjects are markedly reduced by taking ergotamine or methysergide. Platelet aggregation in response to 5-HT is dependent on the availability of 5-HT uptake sites on the platelet membrane (Baumgartner and Born, 1968). When the uptake site is empty, aggregation can occur, but if the uptake site is already occupied by a molecule of 5-HT or an analogue, aggregation cannot take place. Thus, it is likely that the reduced responses after drug treatment are due to ergotamine or methysergide occupying the 5-HT receptor sites.

The similarity between results after ergotamine or methysergide ingestion is in agreement with earlier results found after in vitro pre-incubation of control plasma with those drugs, when both were found to inhibit the aggregation response, and methysergide had a stronger effect than ergotamine (Cumings and Hilton, 1971). In this earlier paper, good agreement was reported between the anti-5-HT activities of ergotamine and methysergide on blood platelets and published results using isolated organ or neuronal preparations. It was suggested that the vascular effects of ergotamine are due to interactions with 5-HT binding sites located on vessel walls. Thus 5-HT uptake sites on blood platelets may resemble those found on other body surfaces and drug action on platelets may indicate action on, for example, vessel walls and neuronal surfaces. Recently, Salzmann and Kalberer (1973) have suggested that the efficacy of ergotamine in relieving migraine is due to its occupying 5-HT uptake sites in the vessel walls, leaving 5-HT molecules available to occupy receptors concerned with vasoconstriction.

The similar results obtained for aggregation responses during and between headaches support the hypothesis that a permanent difference exists in the platelet membrane of migrainous subjects (Hilton and Cumings, 1972). Platelets from migraine sufferers more readily aggregate with 5-HT after one minute's pre-incubation with 5-HT than do platelets from controls, which implies that platelet uptake sites of migrainous subjects less readily accept 5-HT or retain it, than do those of control subjects.

The effects of drugs on blood 5-HT levels during headache are difficult to evaluate since, as shown in Fig. 4, groups of patients on ergotamine or methysergide suffered headaches of differing severity. The reason may be twofold, firstly, that methysergide, as a good prophylactic treatment, reduced the incidence of headache, and, secondly, that patients were likely to resort to ergotamine when they realized a bad migraine was starting. However, it does not appear that any part of these drugs' actions is due to raising blood 5-HT levels. The one high blood 5-HT level for a patient on methysergide may have arisen by chance. This female patient, aged 30 years, had a blood 5-HT level of 260 ng/ml and was suffering from a slight headache which had earlier been severe and had persisted about eight hours in all. On one other occasion she had a blood 5-HT level of 116 ng/ml in a headache-free interval. The high level could be due to recovery of 5-HT levels in the late stage of the migraine headache, since fairly high 5-HT levels were noted in a few other subjects between six and 14 hours after onset of headache. It should also be borne in mind that high blood 5-HT levels during headache have been reported by other workers (Giacovazzo et al., 1965; Tretyakova and Fets, 1969). Raised levels of urinary 5-hydroxyindoleacetic acid (the main metabolite of 5-HT) have been reported after ergotamine (Farris et al., 1967) and methysergide (Pokora, 1966; Curran et al., 1967); but no change was found in blood 5-HT levels after methysergide (Curran et al., 1965). The rise in urinary metabolite, with no change in blood levels of 5-HT, is consistent with the drug acting as competitive antagonist.

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