Methysergide in Prophylaxis of Migraine: A Clinical Trial in General Practice

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Migraine is one of the oldest recorded medical conditions, yet until recently treatment was empirical and little was known of its causative mechanism. Graham and Wolff (1937) showed that cerebral vascular dilatation was involved, and Ostfeld *et al.* (1957) that this and the adjacent liberation of a noxious substance, which reduced the pain threshold locally, were the probable mechanisms leading to the headache. Ostfelt *et al.* suggested that this substance might be serotonin.

In an attempt to prevent the headaches of migraine serotonin antagonists have been used. Methysergide (1-(hydroxymethyl)-propylamide of 1-methyl-(+)-lysergic acid; Deseril) is the most potent of these. Several trials have shown the value of this drug in hospital practice. As migraine is often encountered in general practice, many patients never being seen in hospital, the North-east England Faculty of the College of General Practitioners considered general practice a suitable situation in which to test the drug and organized the trial described.

Method

In any form of group research the condition to be studied must be accurately defined to ensure that all members are dealing with the same condition. With this in mind migraine was defined as a periodic throbbing headache, unilateral initially, with at least three of the following features: (*a*) sensory prodromata, (*b*) photophobia, (*c*) nausea or vomiting, (*d*) family history of migraine, and (*e*) fluid retention before or diuresis during the attack. Patients under 15 and over 65 years were excluded, as were those with known arterial disease, peptic ulceration, or pregnancy, or whose attacks were less frequent than once a month.

The trial was designed on the double-blind, cross-over principle. All patients were given a placebo for a settling-down of one month. Then by random selection half were given methysergide, 1 mg. q.d.s. orally, for three months, and placebo, again for three months. The others were given the drugs in the reverse order. Neither patient nor doctor knew which drug was being used. Patients were asked to record daily the duration of all migraine attacks and to classify these as mild, moderate, or severe, according to a prearranged classification. Dosage was uniform throughout the trial.

Results

Forty-four members of the North-east England Faculty of the College of General Practitioners took part and 74 patients were included in the trial. Of the 50 who completed the trial 40 were female and 10 were male. The average age was 42 years and the mean duration of symptoms was 20 years.

Headaches

Table I shows the number of headaches suffered, classified according to severity, when the patients were taking methysergide and placebo for three months each. Table II shows the duration of these headaches in all patients.

TABLE I.—*Total Number of Headaches in 50 Patients During Two Periods of Three Months*

	Placebo	Methysergide	% Improvement on Methysergide
Mild	194	208	− 7·2%
Moderate	433	400	+ 7·6%
Severe	167	135	+19%
Total	794	743	+ 6·6%

TABLE II.—*Total Duration of Headaches in 50 Patients During Two Periods of Three Months*

	Placebo	Methysergide	% Improvement on Methysergide
Mild	990	1,020	− 6·8%
Moderate	2,451	2,507	− 1·0%
Severe	2,020	1,508	+25·5%
Total	5,461	5,035	+ 8%

With methysergide there was a small reduction in the frequency of attacks, a slightly larger reduction in the total duration, and consequently an improvement in the mean duration of attacks. This improvement was essentially limited to severe attacks. The duration of the severe attacks shows a mean reduction of 10.6 hours over the three-month period, which is more than twice the standard error and therefore significant at the 5% level. None of the other criteria showed a significant result. It seems that the slight increase in the number and duration of mild attacks in patients taking methysergide was due to the conversion of some severe attacks to mild ones.

The sequence in which the tablets were given apparently modified the result. When methysergide was given before placebo there were slightly more attacks on methysergide than on placebo (4.7%), but a 16% reduction in number of attacks when this drug was given last.

An attempt was made to compare the effects of methysergide in cases which showed different features. The symptoms considered were the various criteria necessary for inclusion in the trial, and, in addition, response to ergotamine, previous history of cyclical vomiting or travel-sickness, menstrual association, and allergic factors. Success and failure were distributed equally in all types except those cases which at the beginning of the trial showed fluid-retention before or diuresis during attacks. Of the 22 patients who showed this feature 9 (41%) improved by at least 50%, compared with only 4 (14%) of the 28 not complaining of fluid-retention.

Side-effects

Eleven patients complained of side-effects when taking methysergide and seven on placebo. One patient complained of two symptoms—giddiness and nasal congestion. No cases

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of vasospasm were noted, and there has been no evidence of retroperitoneal fibrosis.

TABLE III.—*Side-effects in Patients Taking Methysergide and Placebo*

Side-effects	Placebo	Methysergide
Tiredness	2	—
Nausea or vomiting	4	5
Nervous tension	—	2
Depression	1	—
Giddiness	—	2
Conjunctival congestion	—	1
Nasal congestion	—	1
Difficulty in focusing	—	1

Twenty-four patients did not complete the investigation—18 for lack of cooperation, three because of side-effects, and three because the tablets they took in the second three-month period were not so effective as those which they had taken in the previous three months. In all cases it was methysergide from which they had obtained benefit. Of the three who withdrew because of side-effects only one was taking methysergide. She complained of excessive nausea.

Discussion

There was a reduction in the number and duration of attacks of migraine in patients taking methysergide. This was more apparent with respect to severe attacks, whose total duration was lessened significantly. Although not statistically significant in themselves the number of attacks, mean duration, and severity were all diminished.

Other reports (Sicuteri, 1959 ; Graham, 1960, 1964 ; Friedman and Losin, 1961 ; Harris, 1961 ; Friedman and Elkind, 1963 ; Southwell *et al.*, 1964) have shown a greater improvement, but not all these studies were adequately controlled. In this trial the dosage was on the low side compared with some of the others. Perhaps freedom to adjust doses in suitable cases may have improved some individual results (Graham, 1960), but, with 40 doctors participating, the trial design would have been too complicated. It was thought better to use a fixed dose. Side-effects were fewer than in most trials, supporting the contention that frequency and severity of side-effects are related to the dosage used.

Methysergide seemed to give better results when taken after the placebo rather than before it. Southwell *et al.* (1964) reported similar findings, which they attributed to the drug continuing to act beneficially in the placebo phase that followed. If, however, there was a tendency for spontaneous improvement to take place during the trial a similar result might be expected. The continuing improvement would have masked the relative improvement when methysergide was given first and increased it when it was given last. Migraine is a variable condition, and great care is necessary in the evaluation of any prophylactic therapy. Patients present themselves when they are in a bad phase, and the factors which have precipitated this may regress during the course of a clinical trial. Because of this, and the extra attention and the aura associated with a therapeutic trial, some spontaneous improvement early in the trial was expected. It was to anticipate this that all patients were given the placebo for one month before the trial actually started, but this may not have been sufficient. The patients who received the placebo for three months immediately after the initial one-month period showed a relative improvement of 16% during this phase. The other group taking methysergide after the initial one-month placebo period showed a comparable improvement of 27%. It would therefore appear that some spontaneous improvement took place after the initial one-month period. The trial was not designed to decide between the relative effects of spontaneous regression or continuing effect of methysergide, so an accurate assessment cannot be given.

Dalessio *et al.* (1961) showed that when migraine patients were overhydrated and oliguria was induced the conjunctival vessels dilated and the vascular response of these vessels to noradrenaline was diminished. Migraine was precipitated in some cases. Methysergide, administered before this, reduced the dilatation and the magnitude of the vascular reaction during the oliguria, which was also reduced ; migraine attacks did not ensue. Migraine attacks can probably be provoked by more than one mechanism ; one of these may be stimulation of the neurohypophysis with production of antidiuretic hormone and overhydration (Wolff, 1963). The better results obtained in this trial in patients who had previously admitted to fluid retention suggested that it was those patients whose attacks were initiated in this manner who were likely to benefit most from methysergide.

Summary

Fifty patients completed a double-blind trial of methysergide for prophylaxis of migraine, receiving 4 mg. a day in divided doses. The duration of severe headaches when taking methysergide was reduced significantly ($P<0.05$). The number of headaches was also reduced but not to a significant extent. Severe headaches were reduced to a greater degree than moderate or mild ones.

Methysergide appeared to have most effect when given after the placebo, but this may have been due to a spontaneous improvement taking place during the course of the trial.

Patients in whom oedema and subsequent diuresis were a feature appeared to benefit most.

Side-effects were not unduly troublesome in the dosage used.

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