states, as judged by the various reports already quoted. We are now investigating possible reasons for this.

From the practical aspect, as there is no means of forecasting immediate anaphylactoid or delayed reactions, intravenous infusion of iron dextran must be regarded as a potentially dangerous treatment in rheumatoid arthritis. The precaution should be taken of giving an intravenous test dose of 2 ml. of the solution so as to detect anaphylactoid reactors; this can then be followed by the total dose infusion, which should be begun very slowly under close clinical observation, including frequent blood pressure checks, in order to discover early signs of anaphylactoid shock.

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Controlled Clinical Trial of Ergotamine Tartrate

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Summary: A double-blind controlled clinical trial of cross-over design for the treatment of headache was conducted in 88 women identified during a community survey as having headaches with the features of migraine. Of 79 subjects who completed the trial, 40 benefited from oral ergotamine tartrate and 46 benefited from the placebo. There was no evidence that ergotamine in doses of 2 or 3 mg. was more effective than the placebo. Ergotamine aggravated the attack significantly more often than the placebo. Neither the colour of the tablets nor the order of therapy significantly affected the results of the treatment.

Introduction

Since ergotamine tartrate was first used in the treatment of migraine over 40 years ago it has steadily gained favour and is now regarded as the most useful single drug in the treatment of attack (Wolff, 1963; Dunlop, 1969). Indeed relief by ergotamine is often considered a useful criteria in the diagnosis of migraine (Friedman and Merrit, 1959; Ostfeld, 1963) as it is said to give little relief in other headaches (Brazeau, 1965) and may aggravate muscle-contraction headache (Wolff, 1963). The differentiation of migraine from muscle-contraction headache is not always easy and in fact was found to be especially difficult during studies of headache in random samples of the general population (Waters, 1970). It was therefore hoped to use the response to ergotamine as a method of validating a questionary designed for use during epidemiological studies of headache. A clinical trial of oral ergotamine tartrate against a placebo for the treatment of attacks was conducted in 88 women. These women were identified from questionaries during a community study as having headaches with the features of migraine.

Methods

Selection of Subjects.—During a community survey, in which over 86% of women aged 20 to 64 years living in a defined area of the Rhondda Fach (Glamorgan) were seen, 129 women were identified by questionaries for consideration for the trial. These women had headaches with at least two of the following features: unilateral distribution, warning of attack, and accompanying nausea. Forty-one were found unsuitable for the trial (Table I). In a separate investigation, 43 of the women who completed the trial were examined by a neurologist (Waters and O'Connor, 1970)—31 were diagnosed clinically as migraine (group A) and in 12 the diagnosis was uncertain or of non-migrainous headaches (group B). The other subjects (group C) had all three migraine features listed above, and this correlates with a diagnosis of migraine, based on a conventional clinical interview, in nearly 90% of cases (Waters and O'Connor, 1970).

TABLE I.—*Exclusions Before and During Clinical Trial*

Excluded Before Trial		Excluded During Trial	
Left area	2	Died	1
Infrequent headaches (<1 per month)	17	Infrequent headaches	4
Ergotamine tartrate contra-indicated:		Pregnant	2
Cardiovascular and renal disease	8	Unco-operative	2
Pregnant	4		—
Already on effective tablets	5		9
Other	5		
	41		

Conduct of Trial

The trial was double-blind and of cross-over design. The subjects received tablets of ergotamine (1 mg.) and placebo (lactose) in random order for periods of eight weeks each. The tablets were green or white and the order in which the colours were given was randomized. Tablet colour was independent of contents to prevent colour preferences being confused with pharmacological effect (Asher, 1948). Tablets were all of the same size. With a balanced experimental design each treatment combination (Table II) occurred randomly three times within blocks of 12.

The subjects were told to swallow two tablets as early as possible in each attack. Another tablet might be taken if relief was not obtained after half an hour. After a further

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TABLE II.—*Treatment Combinations Used in Trial*

First Period (8 Weeks)	Second Period (8 Weeks)
Green — Placebo	White — Ergotamine
White — Placebo	Green — Ergotamine
Green — Ergotamine	White — Placebo
White — Ergotamine	Green — Placebo

half-hour, if this treatment was not effective, they could take the additional tablets of soluble aspirin *B.P.* (300 mg.) that were provided. The exact dose of this additional treatment was not specified except that it was suggested that up to two tablets could be taken three-hourly if required. Each subject was given a printed card, to be kept with the tablets, on which the directions and dosage were clearly set out. Forms were given for recording details of each headache and the treatment taken.

The subjects were revisited by a nurse after about a month to answer any queries and to supply further tablets if required. After eight weeks the efficacy of the tablets was assessed by a clinical interview, the remaining tablets were counted, and new tablets were provided. During the second period the nurse again called and after eight weeks the benefit was assessed clinically. The subjects were also asked which tablet they preferred. All clinical assessments of treatment were made "blindly" by the same observer in the subjects' homes.

TABLE III.—*Response in 79 Women Treated with Ergotamine and Placebo*

	Worse	No Change	Slight Benefit	Considerable Benefit	Total
Ergotamine:					
Group A ..	9	5	10	7	31
Group B ..	0	3	5	4	12
Group C ..	8	14	10	4	36
Total No. (%) ..	17 (22)	22 (28)	25 (32)	15 (19)	79 (100)
Placebo:					
Group A ..	3	11	13	4	31
Group B ..	1	4	4	3	12
Group C ..	1	13	15	7	36
Total No. (%) ..	5 (6)	28 (35)	32 (41)	14 (18)	79 (100)

Group A = Clinically diagnosed as migraine. Group B = Clinically not migraine or doubtful. Group C = Selected by questionary (see text).

TABLE IV.—*Response in 79 Women Treated with Ergotamine and Placebo*

Placebo	Ergotamine				Total
	Worse	No Change	Slight Benefit	Considerable Benefit	
Worse	1	1	2	1	5
No change ..	4	9	11	4	28
Slight benefit ..	9	8	8	7	32
Considerable benefit	3	4	4	3	14
Total	17	22	25	15	79

Tablets beneficial χ^2 (McNemar's test) = 0·86; D.F. = 1; 0·3 < P < 0·5. Not significant.
Tablets detrimental χ^2 (McNemar's test) = 7·20; D.F. = 1; 0·001 < P < 0·01. Significant.

Results

Of 88 subjects who entered the trial, nine were excluded (Table I); one felt so giddy on ergotamine that she refused to continue in the trial. The analyses are based on 79 women in whom clinical assessments were made at the end of both treatments, and a comparison between treatments in the same individual is available. All 79 had taken the tablets for at least one headache, with the features of migraine, in each eight-week period.

The response (Table III) was similar in all groups. Overall, 51% showed some benefit with ergotamine and 58% with placebo. As the same subjects received both ergotamine and placebo, the effect of treatment was examined with McNemar's (1947) Test. There was no significant difference (0·3< P<0·5) between the number who improved with ergotamine and with the placebo (Table IV). Significantly more subjects, however, were made worse by ergotamine (0·001< P<0·01). Similar analyses showed no significant preferences for the order of treatments (0·7< P<0·8) or for the colour of the tablets (0·7< P<0·8). The subjects were also asked which treatment they preferred. Data for drug, colour, and order (Table V) show there was a tendency for subjects to prefer placebo to ergotamine and white rather than green tablets. The better response to placebo in Table V, compared with that in Tables III and IV, is probably due to the adverse side-effects with ergotamine (Table VI).

Further unbiased comparisons of the effectiveness of ergotamine and placebo were attempted in two ways. The number of soluble aspirins taken, after the initial treatment by ergotamine and placebo, was obtained from the subjects' diaries, which were checked by counting the tablets remaining at the end of the eight-week period. Satisfactory records were available for 59 women; 27 took more aspirin after the placebo, 26 took more after ergotamine, and six took the same number during each period. Thus there is no evidence that ergotamine significantly reduced the number of additional tablets required. Finally each subject was thanked for her help in the trial and was offered a small supply of the more effective tablets, if she wanted them for her own use. Forty-three women accepted this offer: 21 chose ergotamine and 22 chose placebo.

TABLE VI.—*Principal Side-Effects in Subjects Made Worse by Treatment*

Symptom	No. of Subjects Taking:	
	Ergotamine	Placebo
Nausea or vomiting	12	3
Pins and needles: numbness	3	—
Giddy	1	—
Headache worse	1	2
Total	17	5

Discussion

This trial gives no indication that the response to oral ergotamine is of help in diagnosing migraine. The fact that 58% improved on placebo obviously makes any beneficial response to an active drug difficult to evaluate. Also those

TABLE V.—*Table Preference for 79 Women in Relation to Order of Treatment, Colour of Tablets. and Content of Tablets*

Group	Treatment Order		Colour of Tablets		Content of Tablets		No Preference
	First Better	Second Better	Green Better	White Better	Ergotamine Better	Placebo Better	
A	15	12	10	17	14	13	4
B	4	5	5	4	7	2	3
C	14	18	16	16	10	22	4
Total	33	35	31	37	31	37	11

who were not diagnosed as definite migraine (group B) in fact showed the best response to ergotamine (Tables III and V). This was probably due to chance but it emphasizes the inadvisability of using the response to ergotamine as a criteria for diagnosis.

Ergotamine is widely accepted as the drug of choice in the treatment of migraine. Nevertheless, the danger of circular definitions, whereby migraine is a headache due to vasodilatation and ergotamine is highly specific because of its vasoconstrictor action, is obvious and has been stressed by Barrie *et al.* (1968). The possible fallacies in such definitions are already well documented in the case of ergotamine, which was introduced when migrainous headache was believed to be due to a spasm of the cranial arteries and when ergotamine was thought to act by producing arterial relaxation (Dunlop, 1969). It is now given for directly opposite reasons.

The absence of a beneficial effect of ergotamine over that of a placebo in this trial was surprising, and four possible reasons for this finding should be considered. Firstly, patients vary in their response to drugs, and this applies particularly in the treatment of migraine. It is difficult in a double-blind trial to adjust the dosage to each individual. In this trial a fairly standard regimen was followed so that attacks were treated with 2 or 3 mg. of ergotamine. In a double-blind sequential trial, Ostfeld (1961) found 5 mg. of oral ergotamine significantly more effective than a placebo. Some subjects in the present trial may have responded to higher doses but, as 22% had side-effects, a high dose would not seem appropriate for routine therapy.

Secondly, the women in this trial were identified in a community survey and are not highly selected individuals. It may be that only some migrainous patients respond to ergotamine. It should be stressed, however, that the subjects in this trial are representative of most women with migraine.

Thirdly, the swallowing of ergotamine tablets is considered to give less reliable results than if the drug is given by other routes. Oral administration, however, has the practical advantage that it can more conveniently be taken at what is thought to be the most effective time, early in the attack. Sublingual administration is often recommended, but in a small controlled trial comparing ergotamine and a placebo no evidence of a beneficial effect was found (Crooks *et al.*, 1964).

Finally, it may be relevant that over 80% of all ergotamine tablets prescribed in England and Wales in 1968 contained caffeine. Caffeine is thought to have a synergistic action with ergotamine but there seems little hard evidence for this general impression (Dunlop, 1969) and it may act by direct vasoconstriction of the cerebral blood vessels (Ritchie, 1965). Whatever the reasons for the results of this trial, it does focus attention on the difficulty of treating migraine. As nearly one in every five women aged 20 to 64 years in the original survey area had migraine (Waters and O'Connor, 1970) the need for further evaluation of therapy is obvious.

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Comparative Trial of Serotonin Antagonists in the Management of Migraine

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Summary: The effectiveness of five different serotonin antagonists in the prevention of migraine was compared in 290 patients followed for periods of up to three years. Methysergide 3-6 mg. daily was most effective, with 20% of treated patients becoming headache-free and a further 44% remaining more than "half improved." The corresponding figures for BC105 were 10% and 40%, respectively.

The results with BC105 were significantly better than those with placebo ($P<0.02$). The total improvement rates with methdilazine (45%) and cyproheptadine (43%) were better than those with placebo (32%) but did not achieve statistical significance. A new preparation, methylergol carbamide maleate, which is chemically related to methysergide, did not give better results than placebo.

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Introduction

When methysergide was first reported to be useful in the prevention of migraine (Sicuteri, 1959) the fact that it was a serotonin antagonist led to speculation that plasma serotonin may be increased during the migraine attack and be responsible for some of the symptoms of migraine. Subsequently Sicuteri, Testi, and Anselmi (1961) found that the major metabolite of serotonin, 5-hydroxyindoleacetic acid (5-HIAA), was often increased during migraine headache. Thus it was surprising to find that the plasma serotonin level dropped sharply at the onset of migraine headache and remained low as long as the headache persisted (Curran, Hinterberger, and Lance, 1965). Anthony, Hinterberger, and Lance (1967) showed that the reduction of plasma serotonin to about 40% of its former level was specific for migraine headache and did not occur with the headache following pneumoencephalography, even when this was accompanied by vomiting. It has since been found that plasma serotonin is unaltered in cluster headache, and the change in migraine is produced by a serotonin-releasing factor in the plasma, which is present only at the time of headache (Anthony, Hinterberger, and Lance, 1969).