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THERAPEUTIC TRIAL

MIGRAINE

Mefenamic acid (ponstan) in the treatment of attacks

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IT HAS BEEN ESTIMATED[1] that between five and ten per cent of the population suffer at some time from a form of migraine. For those whose attacks are frequent or severe and who have to work regardless of the intensity of the attack, migraine can become a major personal problem.

Prophylaxis. Physicians often advise their migrainous patients to change their jobs, to insulate themselves from the major stresses of modern living, or to find time for more relaxation, but it is seldom possible to do this. Therapeutically, small doses of barbiturates are often prescribed but in intractable cases nightly doses of ergotamine tartrate may be needed. More recently, considerable success has been claimed for the serotonin-antagonist methysergide, though this drug has numerous side effects if given in large doses or for long periods[2 3], and it is still very expensive.

Treatment. Ergotamine tartrate is still the drug of choice be it taken orally, sublingually, by aerosol or given by the parenteral route. Taken orally many people experience nausea which only adds to that already experienced in the attack, and some people are unduly sensitive to any

form of ergot[4]. It is contraindicated in the presence of cardiovascular disease, hypertension, pregnancy, hepatic or renal disease.

Trial

Purpose. There is a considerable need for an analgesic which will relieve the majority of attacks, have few side effects, and enable the sufferer to remain at work. It was considered that mefenamic acid might be such a drug, for drugs of this type have been shown to antagonize some of the effects of kinins[5] which have been claimed to be implicated in the pathogenesis of vascular headaches[6].

Mefenamic acid (ponstan) was first marketed in 1963, and is a non-narcotic analgesic, being N-(2, 3-xylyl) anthranilic acid. It is absorbed from the small bowel, and peak plasma levels are reached in two hours, effective analgesic levels being reached in one. It is mainly excreted by the kidneys. With short-term administration, constipation has been the commonest finding reported. Drowsiness is less marked than with aspirin. With long-term administration, gastric irritation is uncommon, but diarrhoea may occur.

Preliminary questionnaire

Of the 36 patients who entered the trial, all answered a set questionnaire, and the results are as follows:

1. Sex—29 females; 7 males.
2. Family history of migraine—66 per cent.
3. Precipitating factors:
   (*a*) Stress—84.8 per cent
   (*b*) Relaxation, including weekend migraine—42.8 per cent
   (*c*) Menstruation—48.5 per cent
   (*d*) Diet or alcohol—30 per cent
   (*e*) Sunlight—12 per cent
4. Age of onset: The youngest patients were five, seven and nine, the oldest 50, while the average age was 21 years 9 months, which compares with Sweetman and Childs figure of 23 years.
5. Frequency of attack: The variation was enormous from three per week to one per annum, with an average of just under two per month.
6. Duration of attack: The shortest was one hour, the longest a continuous unilateral headache for seven days. The average duration from initial aura to complete remission of all symptoms was 34.5 hours.
7. Other symptoms: For the purpose of the trial migraine was defined as a recurrent incapacitating headache with not less than one of the following confirmatory features:

Preceeding period of euphoria	(4)	*11.4* per cent
Preceeding visual aura	(21)	*60.0* per cent
Unilateral distribution	(26)	*74.2* per cent
Nausea and/or vomiting	(31)	*88.6* per cent
Vertigo	(18)	*51.4* per cent
Known responsiveness to parenteral ergotamine	(20)	*57.1* per cent

Method

The trial was designed as a double-blind, two-way cross-over on 36 patients, comparing mefenamic acid with a standard ergotamine compound tablet, migril. It began in July 1964 and so far 25 patients have received

treatment, 11 with mefenamic acid and migril, nine patients with only mefenamic acid, and five with only migril, the total number of attacks recorded being 104. It is estimated that it would take at least another two years to complete the trial, so it has been decided to publish the results to date.

Each patient was given a supply of 12 capsules of either ponstan or capsules containing the same constituents as a tablet of migril (BW), and were asked to report after three attacks and to record the following items during or immediately after each attack:

1. The number of capsules taken to afford relief according to the schedule—two immediately, one in one hour if no relief, and one more an hour later if needed.
2. To classify the attack as mild, moderate or severe.
3. To assess the relief obtained as complete, good, fair or none.
4. To note the duration of the attack.
5. Occurrence of vomiting.
6. Effect on work capacity:
   (*a*) Able to carry on at work
   (*b*) Activities restricted
   (*c*) Completely incapacitated.

Results

The average number of capsules taken per attack were 2.76 for ponstan and 2.83 for migril. The difference in dosage corresponds with the greater frequency of mild attacks in the ponstan-treated group. Other findings were as follows:

TABLE I

CHARACTERISTICS OF ATTACKS

Relief	*Ponstan*			*Migril*		
	Nature			*Nature*		
	Severe	*Mod.*	*Mild*	*Severe*	*Mod.*	*Mild*
Complete ..	2	2	6	2½	3	2½
Good	7	10	6	6	12	3
Fair	3	8	3	5	8	0
None	5	4	2	3½	½	0
Totals ..	17	24	17	17	23½	5½

TABLE II

DURATION OF ATTACK IN HOURS

Treatment	*0–2*	*2–4*	*4–6*	*6–12*	*12–24*	*24*
Ponstan ..	12	12	10	11	8	4
Migril	6	9	7	13	5	4

TABLE III
INCIDENCE OF VOMITING (PERCENTAGE)

	Felt sick		*Vomited*	
	Yes	*No*	*Yes*	*No*
Ponstan.. ..	*60·3*	*39·7*	*15·5*	*84·5*
Migril	*73·3*	*26·7*	*22·2*	*77·8*

TABLE IV
WORK CAPACITY

Treatment	*1*	*2*	*3*
Ponstan	19	24	15
Migril	8	21½	16½

1. Was able to continue with normal duties.
2. Was restricted in normal duties.
3. Was totally unable to carry out normal duties.

Discussion

The numbers taking part in the trial were small and the two groups are not well matched in that more had mild attacks on ponstan than on migril. Nevertheless, complete or good relief was obtained in moderate and severe attacks 21 times out of 41 attacks on ponstan and 23½ times out of 40½ attacks on migril, each drug therefore giving approximately 50 per cent relief in migraine attacks. The halfs mentioned above and in the tables result from intermediate gradings by the patients, e.g. 'mild-moderate', 'fair-good', etc. Ponstan appears to have shortened the attacks and to have caused less nausea, but the attacks were of a milder nature.

There was little difference between the efficiency of ponstan and migril and ponstan may prove to be a safe alternative to ergotamine preparations and is certainly worthy of further trial.

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