Voltaren in the Treatment of Rheumatoid Arthritis

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SUMMARY

A double-blind, crossover trial of a new non-steroidal, anti-inflammatory drug has been carried out in 79 patients with rheumatoid arthritis. The preparation, GP 45′840 (Voltaren), was tested against placebo, paracetamol, and high dosage acetylsalicylic acid. It was superior to placebo and paracetamol at a statistically significant level ($P<0,05$).

On both objective and subjective criteria its actions were similar to those of high dosage salicylate. Side-effects, however, were markedly less than with either paracetamol or salicylate, which contributed to the fact that most of the patients who completed the trial preferred the new preparation.

It was concluded that GP 45′840 has significant anti-inflammatory and analgesic actions in patients with rheumatoid arthritis. The drug is well tolerated and causes a minimum of side-effects.

S. Afr. Med. J., **48**, 949 (1974).

The oral preparation of GP 45′840 (Voltaren) is completely absorbed from the gastro-intestinal tract and causes little irritation of the gastro-intestinal mucosa. Maximum plasma concentration is reached after 1 - 4 hours. After absorption it is rapidly and completely excreted. During the first 12 hours after oral and intravenous administration 40% of the administered dose is found in the urine; after 72 hours the excretion is almost complete.

A short pilot study by one of us (L.S.) showed that the drug was effective in patients with rheumatoid arthritis (RA), and suggested that a full clinical trial was warranted.

MATERIAL AND METHODS

Trial Design

GP 45′840 was compared with three different preparations: (*i*) placebo; (*ii*) paracetamol, and (*iii*) acetylsalicylic acid. It was intended that this should assess the over-all efficacy and also distinguish the simple analgesic from the combined analgesic and anti-inflammatory properties of the test drug.

Each section of the trial was carried out by a double-blind crossover method using the two drugs consecutively in the same patient. Global results were plotted on a sequential analysis chart; only positive preferences for one drug or the other were recorded, and comparisons showing 'no appreciable difference' were discarded.

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Patients

Seventy-nine patients with classical or definite rheumatoid arthritis[1] entered the trial. None of the patients had taken systemic steroids during the previous 2 years, and only 4 had been on steroids at any time during the course of their disease. The age and sex distribution are shown in Fig. 1. The distribution of patients in the 3 trial groups is shown in Table I.

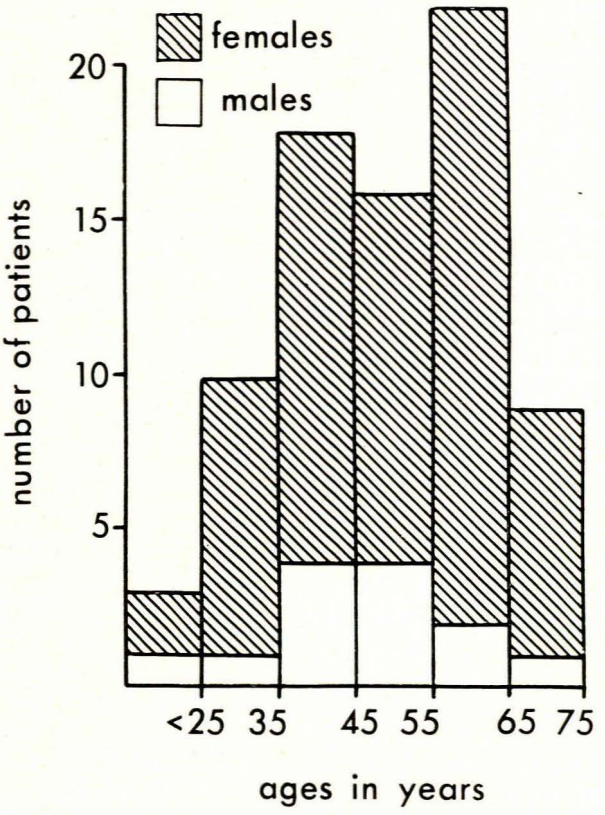

Fig. 1. Age and sex distribution of patients entering the trial.

Drug Administration

The two trial medications in each group were presented in identical form and administered 4 times a day after meals and after an evening snack. The daily dosages are

TABLE I. DISTRIBUTION OF PATIENTS IN THE 3 TRIAL GROUPS

Trial group	GP 45'840 during first period	GP 45'840 during second period	Total
GP 45'840 vs placebo	10	10	20
GP 45'840 vs paracetamol	17	18	35
GP 45'840 vs salicylate	12	12	24

shown in Table II. The sequence of drug administration was suitably randomised. After a wash-out period during which the patient received no medication whatever, each drug was given for 7 consecutive days, the crossover occurring without a further wash-out period. No other analgesic or anti-inflammatory preparations were permitted during the trial period.

TABLE II. DAILY DOSAGES (IN mg) OF DRUGS ADMINISTERED

Time	GP 45'840	Paracetamol	Salicylate
Breakfast	50	1 500	1 250
Lunch	25	1 500	1 250
Dinner	25	1 500	1 250
Evening	50	1 500	1 250
Total	150	6 000	5 000

Assessment

Assessments were carried out after the wash-out period and subsequently after each 7-day treatment period. Assessment was based on three principal criteria: the articular index of pain, grip strength and measurement of joint circumference.

Articular index: Joint tenderness was scored on a 4-point scale (0-1-2-3) after the method of Ritchie *et al.*[2] All joints were tested whether the patient complained of symptoms or not.

Grip strength was measured for each hand on an ordinary sphygmomanometer cuff inflated to 30 mmHg; the result of a single firm squeeze was recorded and the values for the two hands added for the final figure.[3]

Joint circumference was measured at the proximal interphalangeal joint of each finger and the values for the 10 digits added together for the final figure.

Subjective evaluation: In addition to these objective methods, the patient was asked to record his own evaluation of the following parameters on simple linear scales: degree of pain; degree of early morning stiffness; ability to walk and global feeling of well-being.

Finally the investigator's preference for either week 1 or week 2 medications (established by a simple majority of the principal criteria in favour of one or other), was subjected to a sequential analysis.

Over-all superiority of one drug over the other was indicated by an appropriate breakthrough on the sequential analysis chart.

RESULTS

GP 45'840 versus Placebo

Of the 20 patients in this section of the trial, 10 received GP 45'840 as the first and placebo as the second drug, and 10 *vice versa*. Three patients dropped out of the trial, 2 for reasons unrelated to the treatment, and one because of intense headaches and insomnia which he developed while on placebo.

The global preference based on the combination of objective criteria is represented in the sequential analysis chart (Fig. 2); GP 45'840 showed a statistically significant superiority over placebo ($P<0,05$).

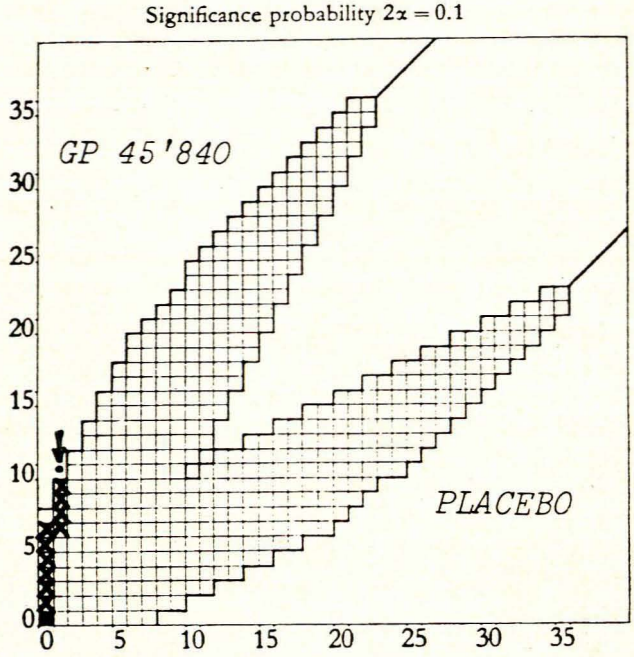

Fig. 2. Sequential analysis; GP 45'840 versus placebo. Note rapid breakthrough in favour of GP 45'840.

The individual criteria were also assessed separately. No difference in joint circumferences was detected in the two treatment sequences. GP 45'840 was significantly superior to placebo in improving the 'ability to walk' ($P<0,05$). In all the other parameters GP 45'840 was superior to placebo, but this did not reach the level of statistical significance.

Ten patients complained of side-effects while being treated with placebo, and 6 of side-effects during the GP 45'840 treatment period. Gastro-intestinal symptoms occurred in 8 patients on placebo and in 2 on GP 45'840.

GP 45'840 versus Paracetamol

Thirty-five patients entered this section of the trial; 17 received GP 45'840 as the first drug, and 18 received paracetamol as the first drug. Nine patients dropped out, 3 for reasons unrelated to the trial, and 6 because of side-effects associated with paracetamol.

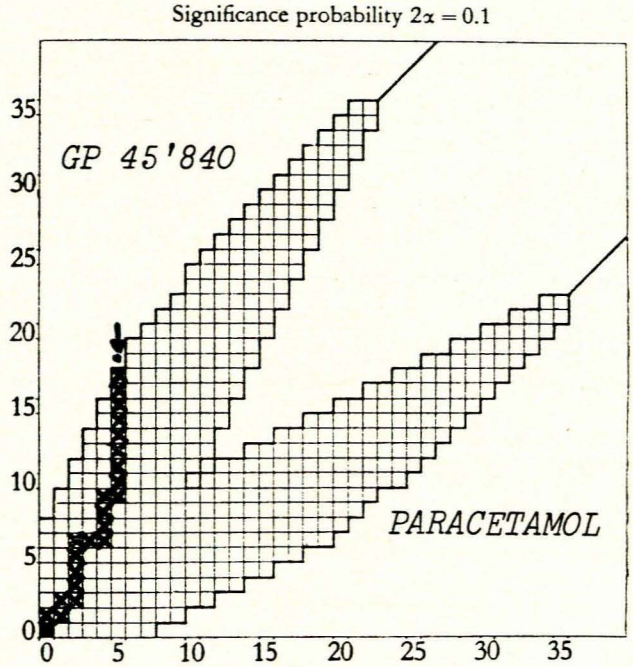

Fig. 3. Sequential analysis: GP 45'840 versus paracetamol.

A breakthrough on the sequential analysis chart indicated that GP 45'840 was significantly ($P<0,05$) superior to paracetamol in the over-all objective assessment (Fig. 3). Of the individual criteria, joint circumference showed no difference in the two treatment sequences; grip strength indicated superiority for GP 45'840, though this did not reach statistical significance; the remaining parameters all showed statistically significant superiority for GP 45'840 ($P<0,001$ - $0,025$).

Of the 26 patients who completed the trial, 11 complained of side-effects while receiving paracetamol, and 6 had side-effects on GP 45'840. Gastro-intestinal symptoms occurred in 6 patients on paracetamol and in 1 patient on GP 45'840.

GP 45'840 versus Acetylsalicylic Acid

There were 24 patients in this section, 12 of whom received GP 45'840 as the first drug in the sequence. Three patients dropped out of the trial, 2 for reasons unrelated to the drugs administered and 1 because of severe nausea and tinnitus attributed to salicylate.

In this group there was no breakthrough on the sequential analysis chart though the investigator's preference slightly favoured GP 45'840 (Fig. 4). Response to treatment as assessed by changes in the degree of pain, early-morning stiffness, ability to walk and over-all feeling of well-being. The common and adjusted means, obtained by analysis of covariance, after 1 week and 2 weeks of medication, thus provided a treatment profile. Further analysis gave variance ratios in the order of 1 in all parameters, indicating negligible differences between the treatments. Analysis of both the investigators' and patients' global preferences supported this observation.

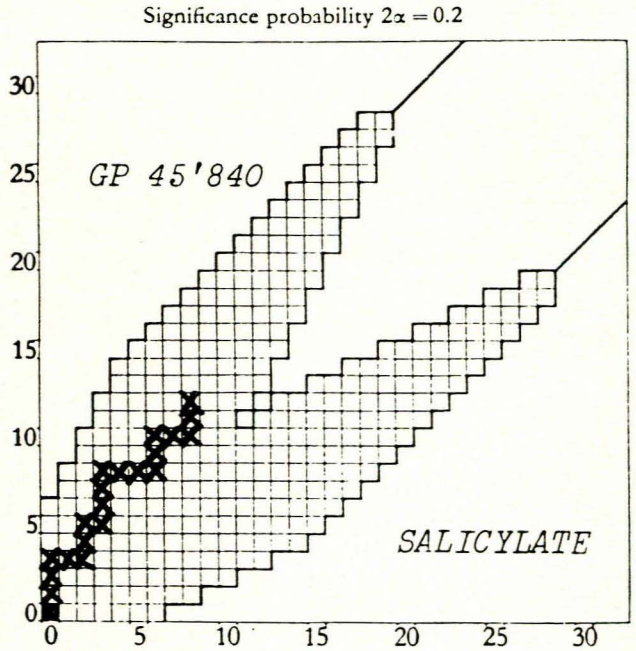

Fig. 4. Sequential analysis: GP 45'840 versus salicylate.

Eighteen of the 24 patients who started the trial developed side-effects while on salicylate; 15 had tinnitus or deafness and 9 had gastro-intestinal symptoms. Seven patients complained of side-effects while on GP 45'840; 3 of these had nausea, and 2 had mild indigestion.

DISCUSSION

The two prime requirements in the choice of drugs for the long-term treatment of RA are that they should have a demonstrable anti-inflammatory effect, and that they should produce the minimum of unpleasant side-effects. The results of the present trial suggest that GP 45'840 has analgesic and anti-inflammatory actions superior to those of paracetamol and equal to those of salicylate in high dosage.

Conducting the trial as an inpatient, crossover assessment during a relatively short period reduces the likelihood that the results were influenced by natural fluctuations in disease activity and variations between different patients. Since it is recognised that the order in which the drugs are given might also influence the results during each trial period, the order of administration was appropriately randomised.

It is well known that the clinical features of inflammatory polyarthritis may be lessened by effective analgesia, which increases the range of motion of individual joints and the over-all activity of the patient. For this reason the trial drug was tested separately against an analgesic and a known anti-inflammatory drug in the form of high-dosage salicylate. In both cases GP 45′840 produced a response at least as good as that with the comparative drug; as might be expected it was markedly superior to a placebo preparation.

On the second criterion, the incidence of side-effects, GP 45′840 was preferred over the comparative drug in each of the trial combinations. Of the 64 patients treated with GP 45′840, 19 complained of side-effects (Table III). In all but 3 cases, however, these were mild and transient, and in no instance did the patient stop taking the drug on this account. The commonest symptom noted was nausea, which occurred in 6 cases and was described as severe in 2 instances. It is noteworthy that 6 patients also complained of nausea while on placebo! Gastro-intestinal symptoms (apart from nausea) were seldom troublesome during treatment with GP 45′840 (2 cases out of 64), but occurred in 12 patients while receiving one of the other preparations.

TABLE III. SIDE-EFFECTS OF GP 45′840 (64 PATIENTS)

Side-effects	No. of patients
No side-effects	**45**
Nausea	**6**
Headache	**2**
Lethargy and tiredness	**3**
Gastro-intestinal symptoms	**2**
Minor rash	**2**
Hot flushes or sweating	**2**
Nocturnal pain	**1**
Giddiness	**1**

In addition to the clinical assessment described, the subjective opinion of the patient was solicited in each trial. There was a reasonably close correlation between these results and the results of the objective evaluation. In some cases, however, it was clear that the patient's preference was determined as much by an aversion to the side-effects of one drug as by a positive response to the other.

Supplies of GP 45′840 and matched drugs used in the trial were provided by Ciba-Geigy (Pty) Ltd.

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