

Clotrimazole in rheumatoid arthritis

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SUMMARY Forty-seven patients with active rheumatoid arthritis took part in an 8-week controlled study in which clotrimazole was compared with a standard nonsteroidal anti-inflammatory agent, ketoprofen. Although clotrimazole was shown to be effective in the treatment of the disease and superior to ketoprofen in certain measurements, it was also responsible for a high incidence of adverse effects. Improvement with clotrimazole took place more slowly but was more sustained than with ketoprofen. A significant rise in plasma cortisol and a fall in white cell count was observed in the clotrimazole treated patients.

Clotrimazole is a tritylimidazole derivative which has been used chiefly as a broad spectrum antimycotic agent.¹ On the assumption that a protozoan might play a major role in the pathogenesis of rheumatoid disease the drug was used to treat a number of patients suffering from this condition. The results of an uncontrolled study were extremely encouraging: with active disease reported to disappear within 1 month of starting treatment and spectacular improvement observed in practically every case.² It was because of these findings³ and the fact that other imidazole derivatives had been shown to improve rheumatoid arthritis³⁻⁵ that the present controlled study was embarked upon.

Patients and methods

Forty-seven patients suffering from definite or classical rheumatoid arthritis as defined by the American Rheumatism Association⁶ were admitted into the study. Patients with peptic ulceration, renal or hepatic insufficiency, diabetes, or any other serious medical disorder were excluded. Patients on corticosteroids or on antirheumatic drugs such as gold and pencillamine and on immunosuppressive therapy were not considered for entry into the study. The trial was double-blind. Two parallel groups of patients were randomly allocated to treatment with either clotrimazole or ketoprofen, a propionic acid derivative of proved efficacy in the treatment of rheumatoid arthritis.^{7,8} The double dummy technique was used. The daily dose of clotrimazole was 40 mg per kg weight during the first week,

increasing to 80 mg per kg given in divided doses. The dose of ketoprofen was 50 mg twice daily for 1 week, increasing to 50 mg 3 times a day. The total treatment period was 8 weeks. Because oral clotrimazole was known to be poorly tolerated^{9,10} all patients were observed in hospital for the first fortnight of treatment but not confined to bed. All antirheumatic therapy was discontinued on admission, and only paracetamol was allowed as the 'rescue' analgesic. Paracetamol consumption was recorded throughout the trial period.

Clinical and laboratory measurements were made at the beginning of the trial and these were repeated at weekly intervals throughout the study. These included proximal interphalangeal joint circumference,¹¹ duration of morning stiffness, grip strength, articular index,¹² visual analogue pain assessment, and the patient's total assessment of treatment, as well as a full blood count, platelet count, ESR, Rose-Waaler test, C-reactive protein, blood urea, standard liver function tests, immunoglobulins, and plasma cortisol. The assessment took place each week at approximately the same time in the morning. The 2 groups were well matched for age, sex, and duration of their disease. Student's *t* test was used to compare differences between changes in the treatment groups.

Results

Seventeen of the 24 patients in the clotrimazole group and 20 of the 23 patients in the ketoprofen group completed the study. All 7 withdrawals from the clotrimazole group were caused by gastrointestinal intolerance, a feature which accounted for only 1

withdrawal from the ketoprofen group. The remaining 2 withdrawals from the latter group were due to flare-up of the disease.

Significant improvement of most clinical measurements was noted in both groups of patients (Table 1), but the rate at which this improvement took place differed between the groups. It was faster in the ketoprofen group, with maximum progress being made during the first 4 weeks, thereafter followed by a steady decline. Improvement in the clotrimazole

group was delayed, with many cases making no progress in the first week. However, by the end of the first month this group was beginning to fare better, and superiority became more marked during the second month.

The majority of measurements showed no statistical difference between the groups, although the trend in favour of the clotrimazole treated patients was a feature during the second month of the study. The exception was the consumption of 'rescue'

Table 1 Changes in clinical measurement

		Grip strength (mm)	Pain (VAS)	Articular index (Riecke)	Joint swelling (mm)	Duration of morning stiffness (hours)	Patients total assessment (5 point scale - = Improved)
Week 1	Clotrimazole	+2.3	-0.9	-1.1	-7.9†	-0.2	-0.1
	Ketoprofen	+7.25	-1.0†	-3.45†	-3.2	-0.1	-0.2
Week 4	Clotrimazole	+58.8†	-2.6†	-9.1†	-18.9††	-0.65†	-1.0†
	Ketoprofen	+50.0†	-2.0†	-7.0†	-7.05†	-0.2	-0.55†
Week 8	Clotrimazole	+74.4†	-2.6†	-9.2†	-23.1†	-0.5	-0.8†
	Ketoprofen	+23.3	-1.3†	-5.25†	-14.6†	-0.2	-0.3

† Significant improvement from pre-entry, P < 0.05. * Significant difference between groups, P < 0.05.

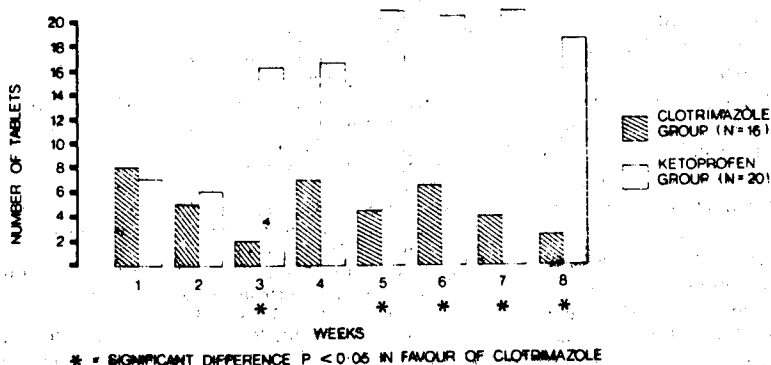


Fig. 1 'Rescue' drug count.

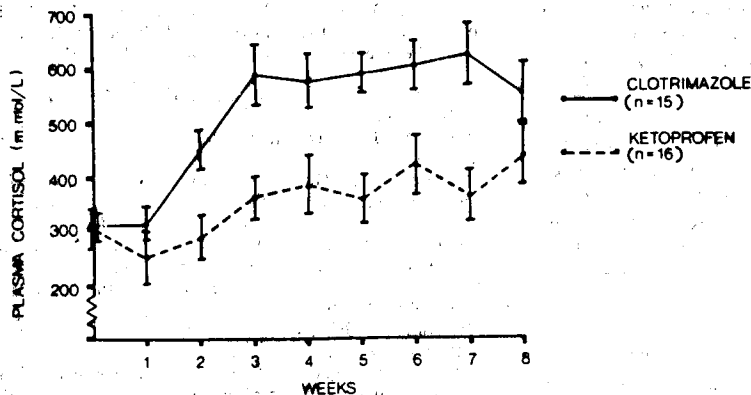


Fig. 2 Plasma cortisol (mean ± SEM).

SIGNIFICANT CHANGE IN CLOTRIMAZOLE GROUP P < 0.001 FROM WEEK 2 ONWARDS
SIGNIFICANT DIFFERENCE BETWEEN GROUPS P < 0.01 FROM WEEK 2 TO WEEK 7

drug, which became significantly lower in the clotrimazole treated patients during the second month of the study and, in contrast to the ketoprofen group, was still decreasing at the conclusion of the study (Fig. 1). Adverse effects were substantially commoner in the clotrimazole treated patients, with gastrointestinal symptoms predominating (Table 2). Lethargy, drowsiness, and pain on micturition were also noted by some patients in this group.

Little change was observed in most of the laboratory values (Table 3). In the clotrimazole treated group, however, a marked rise in plasma cortisol (Fig. 2) and a significant fall in white cell count

(Fig. 3) involving predominantly the polymorphs was seen. In no case, however, was leucopenia observed.

Discussion

The results of this controlled study fail to demonstrate the dramatic improvement which has previously been described in patients with rheumatoid arthritis taking clotrimazole.² In the present study the improvement in the clotrimazole treated group was slower but more sustained than that in patients who received treatment with ketoprofen. The extent of improvement leaves us in no doubt as to the efficacy of clotrimazole in the treatment of rheumatoid arthritis. Previously reported work suggested that a 2-month treatment period was sufficient to observe optimum therapeutic effect, and the design of the current study was drawn up with this in mind. However, the fact that after 2 months' treatment improvement was still continuing suggests that longer periods of treatment may be necessary before maximum benefit is observed. Our observations of cases treated for up to 8 months in an uncontrolled study tend to substantiate this, and

Table 2 Main adverse effects

Complaint	Number of patients		
	Clotrimazole	Ketoprofen	
Nausea/vomiting	16	6	P<0.02
Diarrhoea	14	5	P<0.025
Anorexia	10	0	P<0.002
Anorexia	10	0	P<0.0002

Table 3 Changes in laboratory values

		C-reactive protein (Dilution)	ESR (mm/h)	Urea (mmol/h)	Alkphos (U/L)	SGOT (U/L)	LDH (U/L)	IgG (IU/ml)	IgM (IU/ml)	IgA (IU/ml)
Week 1	Clotrimazole	—*	-6.3	-0.5*	-4.4	+3.2	-1.4	—	—	—
	Ketoprofen	—	-1.7	+0.8*	-1.4	+0.9	-0.3	—	—	—
Week 4	Clotrimazole	-0.07	-9.8	-0.7*	-7.9†	-3.4	+21.5	—	—	—
	Ketoprofen	-0.18	-0.1	-0.7*	+7.9†	-0.2	+5.5	—	—	—
Week 8	Clotrimazole	-0.64*	+11.5	-1.5**	-7.3	+1.8	+14.0	-24.4†	+8.8	-31.4
	Ketoprofen	+0.28*	-9.9	-0.4*	-5.2	+0.5	+15.9	-5.8	+45.3†	-163.6

† Significant change from pre-entry, P<0.05. * Significant difference between groups, P<0.05.

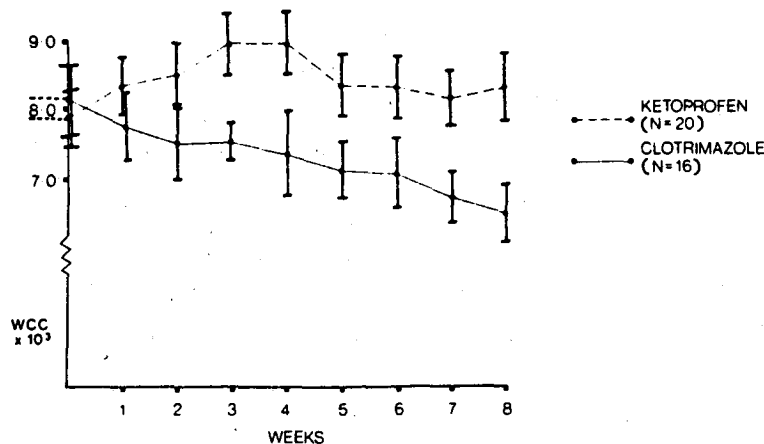


Fig. 3 White cell count (mean ± SEM).

SIGNIFICANT CHANGE IN CLOTRIMAZOLE GROUP P<0.01 FROM WEEK 5 ONWARD

SIGNIFICANT DIFFERENCE BETWEEN GROUPS P<0.05 FROM WEEK 3 ONWARD

suggest that maximum clinical improvement occurs between 3 and 6 months and is accompanied by a fall in the ESR. Certainly experience with imidazole derivatives, such as levamisole, indicates that full benefit may not take place until 6 months after treatment is begun.

The mode of action of clotrimazole in rheumatoid arthritis is open to debate. It has been suggested on the basis of animal studies that this drug might exert an anti-inflammatory effect by stimulating the adrenal glands.¹³ The raised levels of plasma cortisol that were so consistently observed in the patients on clotrimazole would certainly support this suggestion.

An in-vitro study¹⁴ has shown that the addition of clotrimazole to normal lymphocytes causes both an inhibitory and an enhancing effect on mitogenic stimulation. This was dependent on the concentration used, but a predominantly immunosuppressive effect was observed at concentrations equivalent to therapeutic serum levels. A subgroup of rheumatoid patients in the present study also showed a significant reduction in mitogenic lymphocyte responsiveness while on clotrimazole, whereas no change occurred in patients taking ketoprofen.¹⁴ Although it is possible that this finding related to the increased cortisol production in the clotrimazole group, the of correlation with cortisol concentration and the existence of suppression despite the absence of autologous serum suggest an inherent immunosuppressive action of clotrimazole. This contrasts with the immunopotentiating effect of levamisole.

On the basis of our results we would suggest that clotrimazole affects rheumatoid arthritis in 2 ways. The initial effect, though not immediate, appears to take place sooner than is normally seen in patients who respond to immunosuppressive drug therapy for rheumatoid arthritis and may be the result of increased cortisol release by adrenal stimulation. The fact that plasma cortisol increased gradually during the first 3 weeks before reaching a steady level would lend support to this suggestion. The continued improvement during the latter part of the study and associated with the gradual fall in white cell count could be attributed to the immunosuppressive action of the drug.

What role, if any, is clotrimazole likely to play in the management of rheumatoid arthritis? The positive features of the present study are more than counterbalanced by the unacceptably large

number of side effects. If, as has been suggested,² treatment with a substantially lower dose of clotrimazole were to prove equally effective without the disadvantage of a high degree of intolerance, then clotrimazole could yet play a role as an alternative to some of the more specific drugs currently used in the treatment of the more severe and resistant cases of rheumatoid arthritis. On the other hand we suggest that investigation of other similar but potentially less toxic oral antimycotic agents for the antirheumatic properties which clotrimazole has been shown to possess might prove a more useful area of research.

We thank Dr R. J. Holt, principal microbiologist, Department of Clinical Microbiology, Queen Mary's Hospital for Children, Carshalton, Surrey, for serum C-reactive protein studies, and Mr John E. Bailey for the statistical analysis.

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CLOTRIMAZOLE AND RHEUMATOID ARTHRITIS

SIR,—The nitroimidazole drug BT 985 (Merck) is a derivative of naxogin (Erba) and metronidazole and is protozoocidal. It has been used successfully in the treatment of amœbiasis, giardiasis, and trichomonas infections.¹ Dramatic disappearance of evidence of active disease in nine of ten cases of rheumatoid arthritis treated by this drug has been reported.² Levamisole also contains an imidazole group and has antiprotozoal properties. It was at first thought to affect immune mechanisms,³ but this has been denied.⁴ Schuermans⁵ has reported on six patients with active classical or definite long-standing rheumatoid arthritis who had responded poorly to anti-inflammatory or analgesic drugs; on levamisole the patients improved strikingly within a month, and rheumatoid factor became negative in three patients. Similar results have been recorded by others.⁵ Clotrimazole is another imidazole-containing antiprotozoal drug.⁶ The manufacturers say it has no anti-inflammatory effects.

Twelve successive patients whose active rheumatoid arthritis had not been controlled by antirheumatoid drugs, including steroids or tetracosactrin (Synacthen), were studied. They were admitted to hospital but were not confined to bed. Drugs were withdrawn, sometimes resulting in severe exacerbation of the symptoms, and oral clotrimazole was started orally. No other drugs were given. The daily dose was adjusted to between 25 and 100 mg/kg body-weight depending on tolerance. Gastrointestinal disturbance proved a problem in four patients, and a further two patients were withdrawn from the study due to intolerance. Treatment was continued for 6–12 weeks and the patients were followed up for 12–15 months.⁸

All ten patients tolerating treatment showed a rapid improvement, often beginning within 24 h, with reduction in joint pain, swelling, and stiffness, improvement in joint mobility, and cessation of pyrexia. Active disease disappeared in 3–28 days. After 6 weeks the blood-count and erythrocyte-sedimentation rate became normal. In 4–6 months the albumin/globulin ratio and the electrophoretic pattern returned to normal. At the end of the follow-up the rheumatoid factor and autoantibodies had disappeared from the blood. There was no return of disease activity during the period of observing during which no other treatment was necessary.

Subsequent experience with clotrimazole revealed that similar results could be obtained with daily doses of only 10–12 mg/kg. Occasionally treatment with clotrimazole, even though previous drugs were continued, resulted in a transient violent increase in joint pain, swelling, and hotness with pyrexia and blood eosinophilia, constituting a Herxheimer reaction and typical of many parasitic diseases treated by drugs which kill the causative organism.

The similar effects on the activity of rheumatoid arthritis of a number of antiprotozoal drugs containing imidazole groups, the rapid action of clotrimazole, the efficacy of clotrimazole when other drugs had failed, the non-recurrence of disease activity long after clotrimazole treatment was stopped, the disappearance of the rheumatoid factor and auto-antibodies from the serum, and the occasional Herxheimer reaction all point to a parasitic, probably protozoal, cause of the disease.

Dr Otterness and Dr Niblack (Jan. 17, p. 148) suggest that clotrimazole acts in rheumatoid arthritis through an anti-inflammatory effect and by stimulating adrenal secretion. Their findings, however, cannot explain the action of clotrimazole because some of my patients were already taking steroids or tetracosactrin before clotrimazole was successfully substituted. An anti-inflammatory and adrenal stimulating action cannot

explain the Herxheimer reactions. Daily doses of clotrimazole of 10–12 mg/kg produce much lower tissue concentrations than do the doses used by Otterness and Niblack. At 33 mg/kg they found only a 2% inhibition of inflammatory response; 10–12 mg/kg would have even less effect. Similar arguments apply to any adrenal-stimulating effect of the drug. Disease activity did not recur when the drug was stopped as it would if its action had been anti-inflammatory and adrenal stimulating.

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CLOTRIMAZOLE IN RHEUMATOID ARTHRITIS.

Legend:

Table 1

Effect of Clotrimazole on plasma cortisol which returns to normal after discontinuation of the drug.

Table 2 and table 3

Cross-over study to compare the effect of Ketoprofen and Clotrimazole on plasma cortisol with one week "wash-out" period.

Table 4

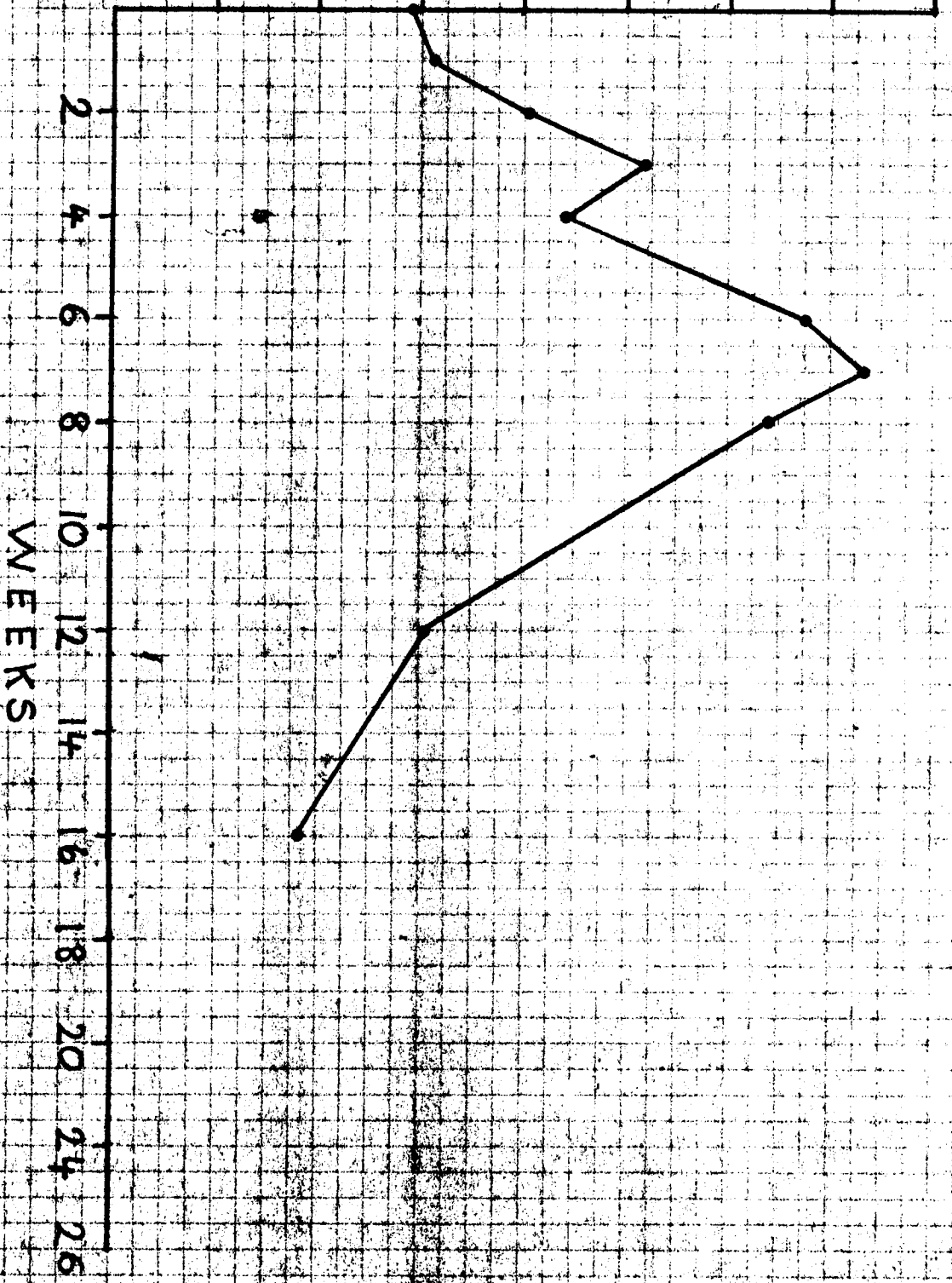
Cross-over study to compare the effect of Ketoprofen and Clotrimazole in P.I.P.joint swelling(both hands) with one week "wash-out" period.

Table 5

Effect of Clotrimazole in various dosages on ESR,JOINT SWELLING,PAIN and ARTICULAR INDEX.

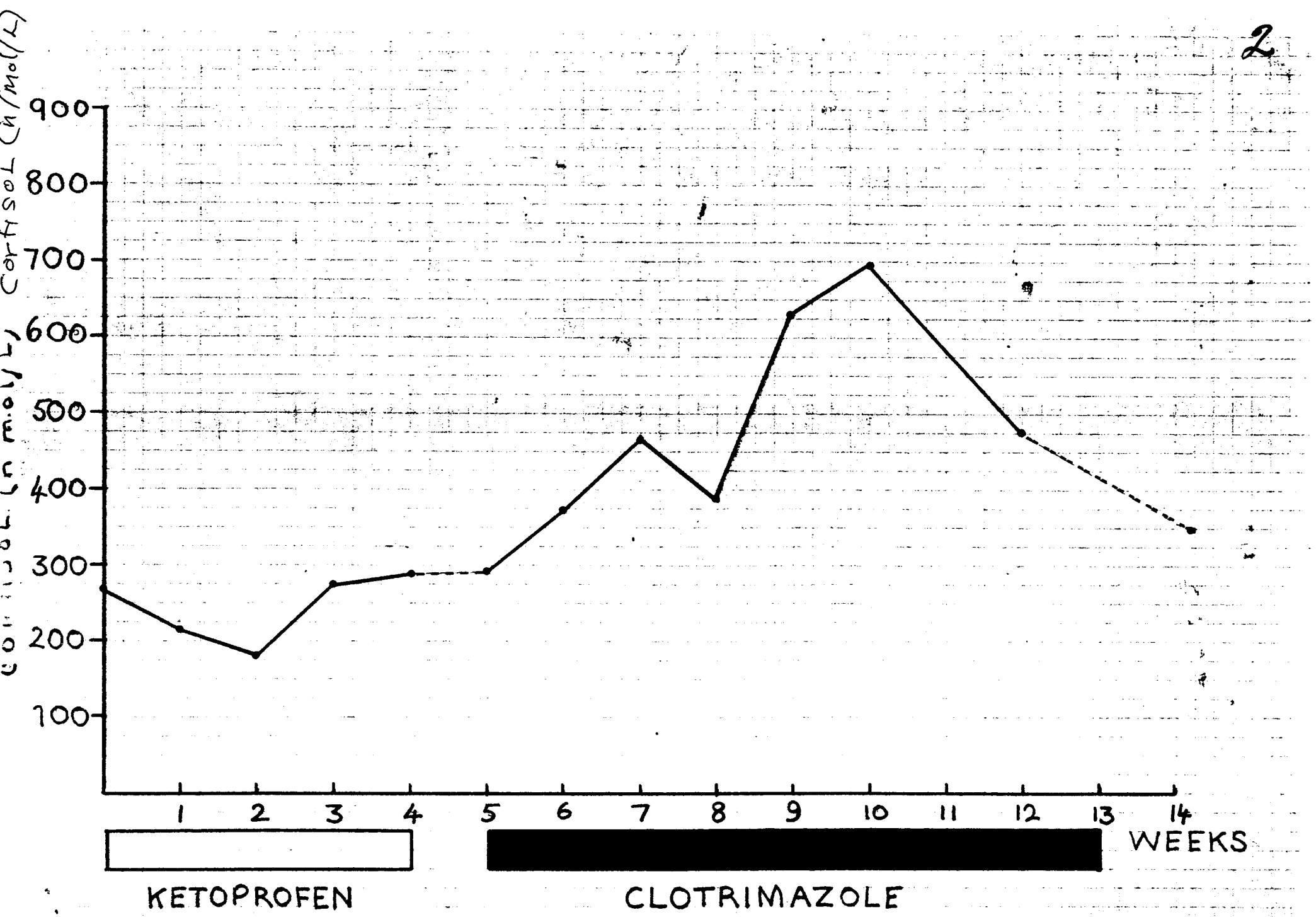
CORTISOL (n mol/L)

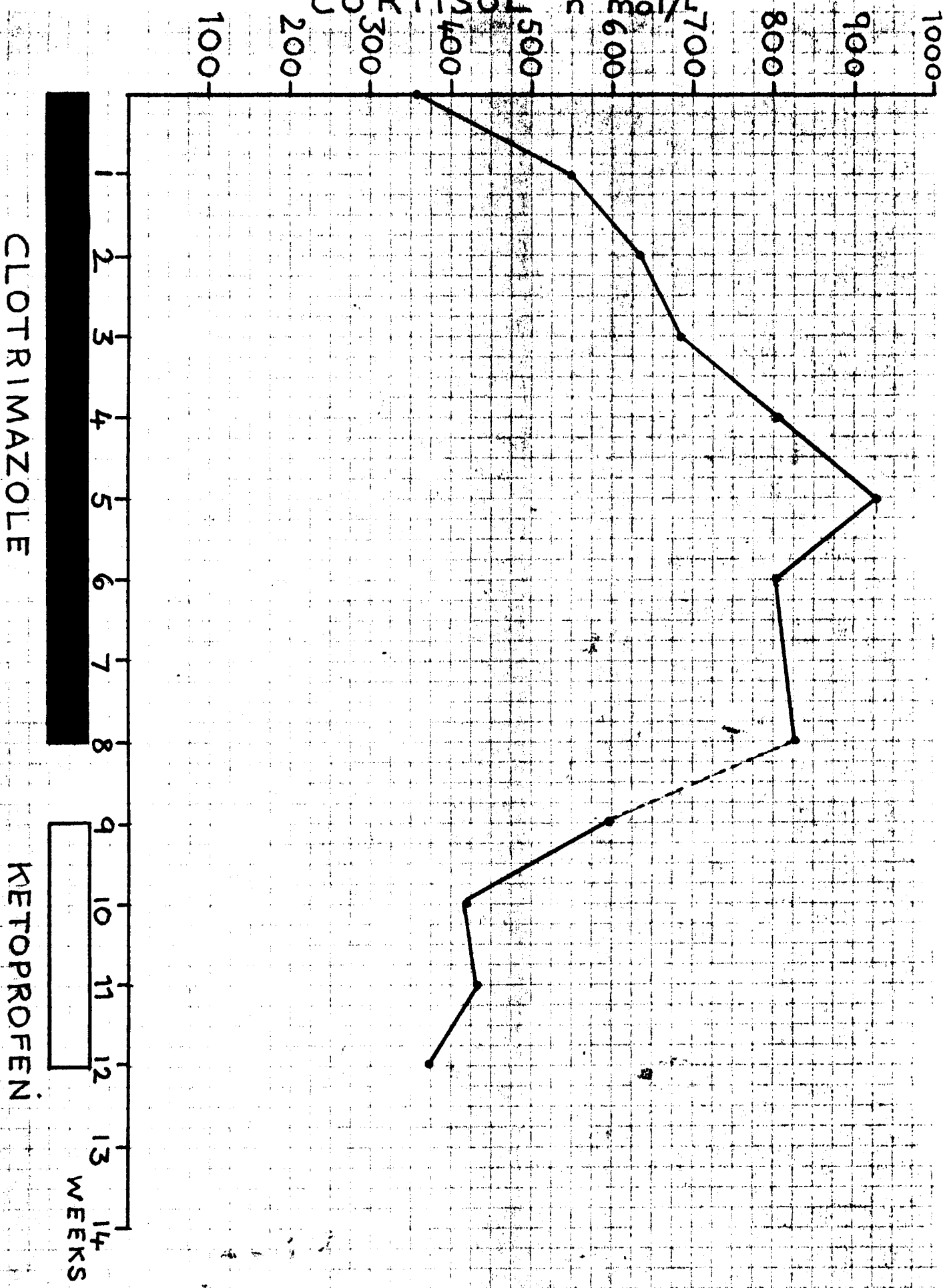
800
700
600
500
400
300
200
100



CLOTRIMAZOLE

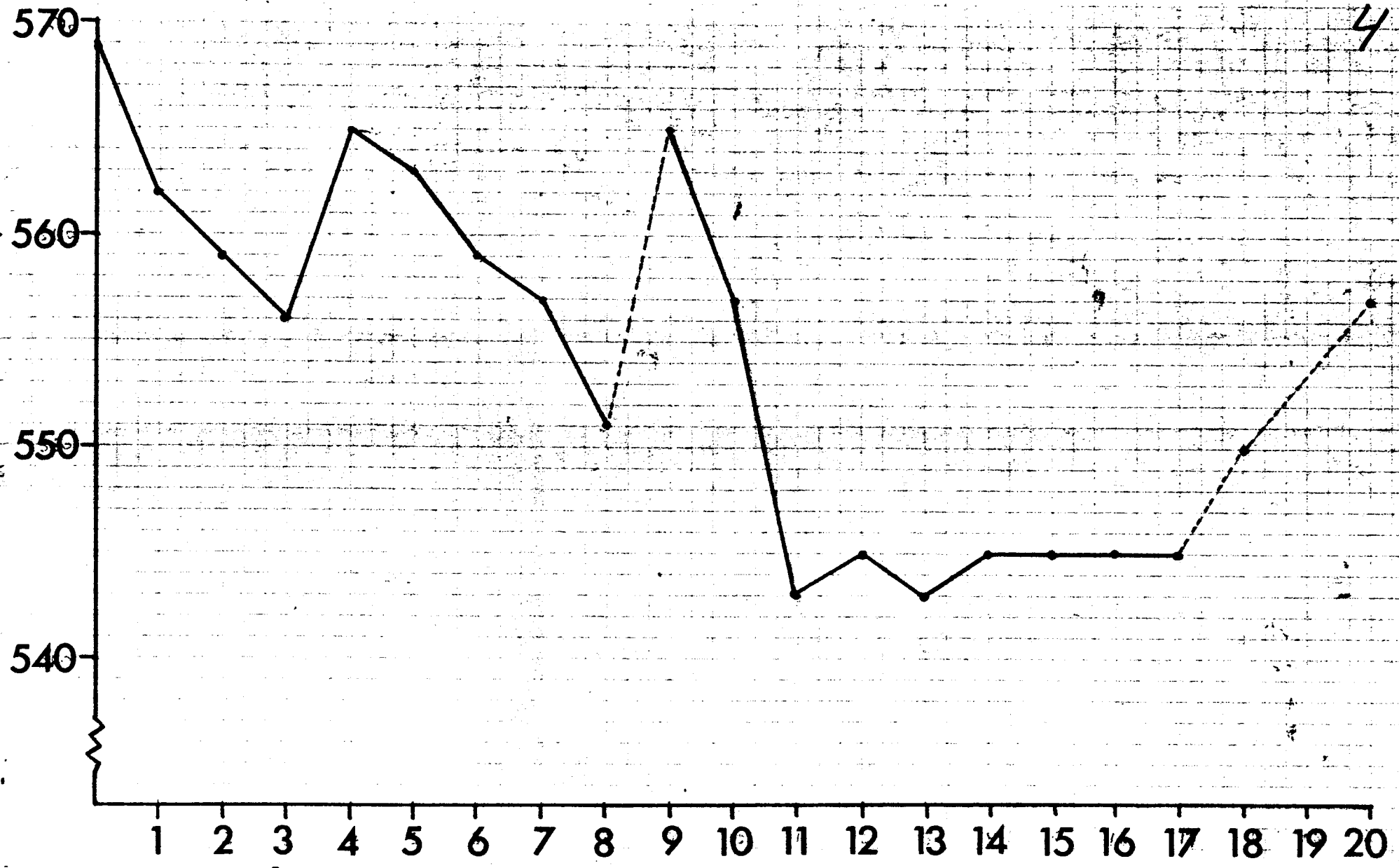
WEEKS





Joint swelling (joint diameters)

4



KETOPROFEN

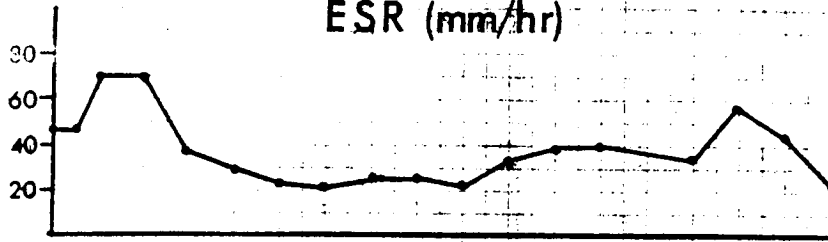
CLOTRIMAZOLE

KETOPROFEN

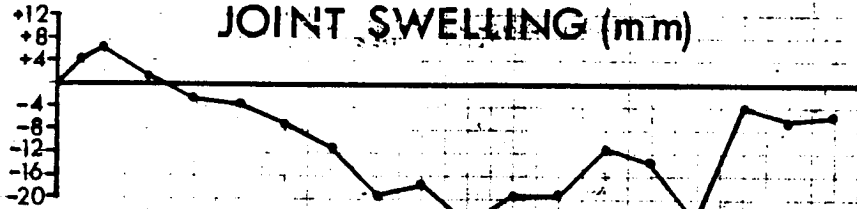
CLOTRIMAZOLE

ESR (mm/hr)

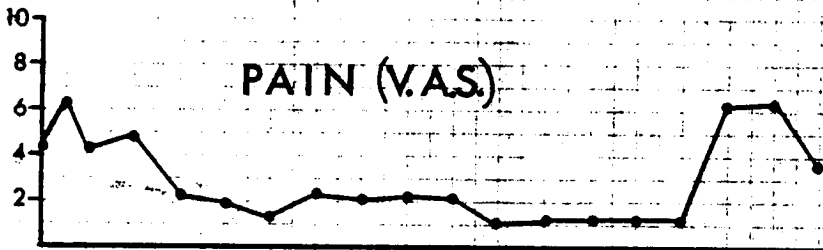
5



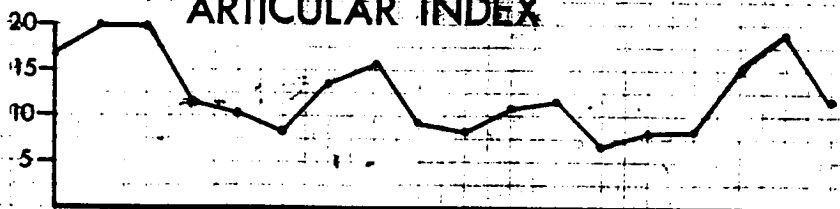
JOINT SWELLING (mm)



PAIN (V.A.S)



ARTICULAR INDEX



CLOTRIMAZOLE DOSE 1G



2 4 6 8 12 14 16 18 20 22 24 26 28 30 32 36