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EFFECT OF GLYVENOL (CIBA) ON PAIN AND ON CAPILLARY RESISTANCE IN RHEUMATOID ARTHRITIS

BY

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Glyvenol† (CIBA), a glucofuranoside derivative (Fig. 1) has been shown to have potent anti-allergic and anti-inflammatory properties in experimental animals (Jaques and Schär, 1967).

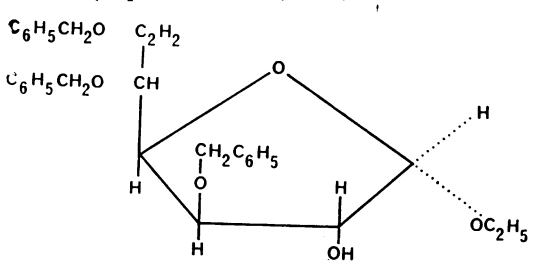

Fig. 1.—Chemical formula of Glyvenol (CIBA 21,401-Ba).

It antagonizes a number of pharmacologically active substances, including histamine, serotonin, acetylcholine, angiotensin, bradykinin, and oxytocin. It decreases the speed of leucocyte migration, inhibits the Arthus reaction and passive cutaneous anaphylaxis, and can prevent the fatal outcome of anaphylactic shock in experimental animals. Unlike corticosteroids, however, it does not inhibit antibody production nor does it affect complement levels.

As these students showed Glyvenol to possess a quite unusual combination of anti-inflammatory and other pharmacological properties with very low toxicity in animal experiments, we thought it of interest to study the effect of the drug in patients with rheumatoid arthritis and in particular its effect in them on capillary resistance.

Material and Methods

Forty patients (34 female and 6 male) with "classical" rheumatoid arthritis as defined by the diagnostic criteria of the American Rheumatism Association (Ropes, Bennett, Cobb, Jacox, and Jessar, 1959) were studied. Their mean age was 48·6 years (range 30 to 75). All had positive tests for rheumatoid factor, all had radiographical erosions of the joints, and thirteen had subcutaneous nodules. Five were receiving long-term low-dosage corticosteroid therapy and the remainder were being treated with salicylates or with indomethacin.

A double-blind cross-over trial using Glyvenol and identical placebo capsules, each given for a period of one week, was undertaken. Glyvenol was administered orally, one 400 mg. capsule being taken three times a day. The patients were started randomly on either the placebo or the active drug. During the 2-week period of therapy an attempt was made to discontinue all other therapy with the exception of corticosteroid drugs, but eighteen patients required their previous analgesic therapy to be restarted. All eighteen were then given 1·2 g. aspirin three times a day and five required small doses of indomethacin in addition (25 mg. twice or three times a day).

Clinical assessment of the patients' progress was carried out by the same observer at the same time of day at the end of each week's treatment. At this time the erythrocyte sedimentation rate (Westergren), the capillary resistance, the fresh platelet count, and platelet adhesiveness were estimated.

Joint pain was assessed by the articular index of Ritchie, Boyle, McInnes, Jasani, Dalakos, Grieveson, and Buchanan (1968). This index is based on the pain felt by the patient during firm pressure on the joints. Four grades of response are recorded:

Grade 0—the patient feels no pain;
Grade +1—the patient complains of pain;
Grade +2—the patient complains of pain and winces;
Grade +3—the patient complains of pain, winces, and withdraws.

The maximal score is +78. This index has been shown to correlate with the joint scoring system of the Co-operating Clinics Committee of the American Rheumatism Association (1965) and to have an acceptable intra-observer error (±1·07).

Capillary resistance was measured by the "*angiosterromètre*" of Parrot (1954). This instrument consists of a suction pump attached to a suction head which is applied

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†Glyvenol = 3,5,6-Tribenzyl-ethyl-glucofuranoside = CIBA 21,401-Ba, an experimental drug not marketed in Great Britain.

to the skin. A graduated manometer is attached showing the pressure in cm. Hg, and the suction head is fitted with a lens to facilitate observation of the skin. The suction head was applied to the skin and a negative pressure of 10 cm. Hg maintained for one minute. If no petechiae were produced the pressure was increased by 5 cm. increments until at least three petechiae were produced in the centre of the field. The mean of this pressure and of the previous one was taken as the capillary resistance to suction. Marginal petechiae were excluded, as they may be produced by abrasion of the skin by the rim of the suction head. All measurements were made in the infraclavicular area by the same observer; 24 duplicate measurements in twelve rheumatoid subjects gave a standard error of $\pm 1 \cdot 34$ cm. Hg.

Platelet adhesiveness was estimated by the Chandler tube technique (Cunningham, McNicol, and Douglas, 1965). Platelet rich plasma was obtained by centrifugation of whole blood at 600 G for 5 minutes at a temperature of 4°C. in a refrigerated centrifuge. This was then transferred with a siliconized pipette to a Chandler tube and, after the addition of 0·9 per cent. sodium chloride solution to give a final volume of 15 ml. in the tube, the plasma was re-calcified by the addition of one tenth the volume of 0·25 M. calcium chloride. The tube was then made into a circular loop by means of a nylon adaptor and placed on the turntable of a red blood cell suspension mixer revolving at 28·5 r.p.m. at 37°C. The time taken for the "snowstorm" effect to appear after re-calcification is considered to represent a measure of platelet adhesiveness.

To determine the reproducibility of the effect of Glyvenol, four patients were given 1·2 g./day for one week and the clinical and laboratory assessments were performed before and after this course of therapy. A period of one month was then allowed to elapse and the same patients were again given Glyvenol 1·2 g./day for a further 7 days. The same parameters were again recorded before and after the second course.

Results (Tables I and II and Fig. 2)

No significant differences were noted in the articular index or the ESR during the periods of treatment with Glyvenol and placebo. The patients were unable to distinguish between the different courses of therapy. There were no significant differences between the results obtained for the platelet count and for the platelet adhesiveness during these different courses of therapy (Table I).

However, the mean capillary resistance was $22 \cdot 5 \pm 4 \cdot 4$ cm. Hg while on placebo and $35 \cdot 0 \pm 3 \cdot 6$ cm. Hg while on Glyvenol; this difference is highly significant ($P = 0 \cdot 001$) (Table I). Fig. 2 shows the results of 27 of these results in graph form.

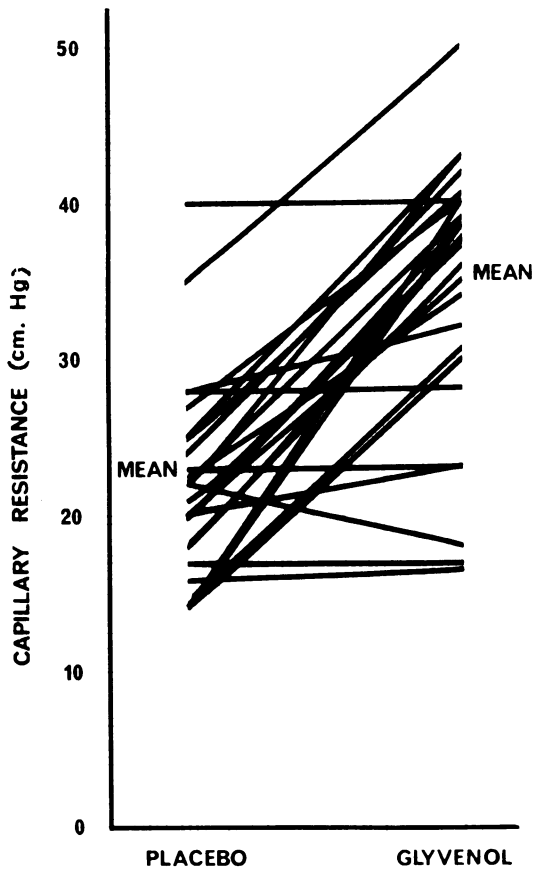

Fig. 2.—The mean and standard error of the values for capillary resistance while on placebo and while on Glyvenol.

TABLE I
MEAN AND STANDARD DEVIATION OF PARAMETERS INDICATED AT CONCLUSION OF TREATMENT FIRST WITH PLACEBO AND THEN WITH GLYVENOL

Drug	Articular Index (score wrists)	Erythrocyte Sedimentation Rate (mm./1st hr)	Capillary Resistance (cm. Hg)	Platelet Count (cells/cu. mm.)	Time for Platelet Aggregation (sec.)
Placebo	43 ± 10·0	56 ± 14·4	22·5 ± 4·4	190·6 ± 13·3	281·5 ± 154·4
Glyvenol	43 ± 9·7	55 ± 13·2	35·0 ± 3·6	188·0 ± 10·5	245·0 ± 136·0
Significance	Nil	Nil	P = 0·001	Nil	Nil

Reproducibility

The results of repeating the course of Glyvenol in four selected patients are shown in Table II. The values before the administration of Glyvenol on the first occasion were 35:40:20 and 25 cm. Hg, and after the first week's course 50:40:33 and 40 cm. Hg. On the second occasion the results before and after the administration of Glyvenol to the same four patients were 35:40:20 and 25 cm. Hg and 50:40:35 and 40 cm. Hg respectively (Table II).

TABLE II
REPRODUCIBILITY OF THE EFFECT OF GLYVENOL, 1,200 MG./DAY FOR ONE WEEK IN FOUR PATIENTS,
This course of therapy was repeated after an interval of one month. The capillary resistance was determined before and after each course

Patient No.	Capillary Resistance (cm./Hg)			
	Course I		Course II	
	Before	After	Before	After
1	35	50	35	50
2	40	40	40	40
3	20	33	20	35
4	25	40	25	40

Side Effects

In a pilot study before the commencement of the present double-blind cross-over trial, Glyvenol 1·2 g. three times a day was given to six patients, all of whom developed mild diarrhoea after 3 or 4 days of treatment. This consisted of five or six soft but formed bowel motions of normal colour per day and it ceased within 24 hours of withdrawing the drug. During the trial itself, in which Glyvenol was given in a dose of 400 mg. three times a day, seven patients developed diarrhoea of the same severity as in the pilot study and again this ceased within 24 hours of stopping the drug. No patients developed diarrhoea while on placebo therapy.

Four patients developed transient pruritic maculopapular erythematous eruptions while receiving Glyvenol. In one this rash appeared over the upper limbs, face, and trunk, and there were several purpuric area on the legs. In the other three the rash was wholly maculopapular. In three patients the rash developed on the fifth day and in one on the last day of therapy with Glyvenol. In all patients the eruption faded and disappeared without desquamation within 24 hours of stopping the drug. No patient developed a rash while receiving the placebo.

Discussion

In this study we have shown that Glyvenol, a new glucofuranoside derivative, in a daily dose of 1·2 g. a day for one week increases the capillary resistance of patients with rheumatoid arthritis. It did not affect the fresh platelet count or the platelet adhesiveness.

Various factors have been shown to influence capillary resistance, including age (Gough, 1962), menstruation (Brown and Wasson, 1947), environmental temperature (von Borbély, 1930), and corticosteroid therapy (Robson and Duthie, 1950). The patients in this study, however, were used as their own controls and all were in hospital during the period of study where the environmental temperatures were reasonably constant. Moreover, all the patients were either males or postmenopausal females, and the five who were receiving corticosteroid therapy did not have the dose altered during the trial period. It seems reasonable, therefore, to conclude that the changes recorded in capillary resistance were due to the Glyvenol therapy. The similar effect of Glyvenol on capillary resistance when administered to the same patients throughout two periods of one week each with an interval of one month suggests that this effect is fairly reproducible and also that it is not sustained for a month after the cessation of therapy.

The mode of action of the drug is obscure. Changes in capillary resistance could be due to intravascular platelet mechanisms, but we have found no change in either the fresh platelet count or the platelet adhesiveness measured by the Chandler tube technique. Jaques and Schär (1967) have shown that Glyvenol has powerful anti-inflammatory properties in experimental animals, and this may be an operative mechanism in this change in capillary resistance. It is, of course, also possible that Glyvenol may affect dermal collagen or the mucopolysaccharides of the supporting connective tissue of the capillaries, but no information is available on this possibility. Ascorbic acid levels are known to be rather low in the serum of patients with rheumatoid arthritis compared with normal subjects (Rinehart, Greenberg, and Baker, 1936; Abrams and Sandson, 1964). The effect of Glyvenol on ascorbic acid metabolism has, however, not been studied.

Glyvenol 1·2 g./day for one week did not affect the pain of rheumatoid arthritis in the patients in this trial. They showed no preference for the drug compared to the placebo and there was no depression of the articular index. It has been shown elsewhere that aspirin 5 g./day for one week significantly depresses this index (Ritchie and others, 1968). Glyvenol also failed to lower the ESR rate in the patients in this study.

It is concluded therefore that Glyvenol increases capillary resistance in rheumatoid arthritis but has no effect on pain. It is possible that Glyvenol may be a useful adjuvant in the prevention of the occurrence of ecchymosis due to corticosteroid therapy.

The mode of action of Glyvenol in increasing capillary resistance in rheumatoid arthritis is worthy of further study.

Summary

The effects of Glyvenol, a new glucofuranoside derivative, on the pain and capillary resistance of patients with rheumatoid arthritis were assessed in a double-blind cross-over trial. Glyvenol was given orally for a period of one week in a dose of 400 mg. three times a day. The drug was shown to increase capillary resistance, but had no effect on pain.

It is suggested that Glyvenol may be of possible therapeutic value in preventing ecchymoses due to long-term corticosteroid therapy.

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L'effet du Glyvénol (CIBA) sur la douleur et sur la résistance capillaire dans la polyarthrite rhumatoïde

RÉSUMÉ

Les effets du Glyvénol, un nouveau dérivé de glucofuranoside, sur la douleur et la résistance capillaire des malades atteints de polyarthrite rheumatoïde ont été évalués dans un essai "double blind cross-over". Le Glyvénol avait été donné par voie buccale pendant une période d'une semaine à la dose de 400 mg. trois fois par jour. Il a été démontré que le médicament augmente la résistance capillaire, mais n'avait pas d'effet sur la douleur.

Il est suggéré que le Glyvénol peut être d'une valeur thérapeutique possible en empêchant les ecchymoses dues à la thérapie cortico-stéroïde à long terme.

Efecto del Glivenol (CIBA) en el dolor y sobre la resistencia capilar en la poliartritis reumatoide

SUMARIO

Los efectos del Glivenol, un nuevo derivado glucofuranosido, sobre el dolor y la resistencia capilar de pacientes con poliartritis reumatoide se determinaron mediante un método cruzado dobleciego. El Glivenol fue administrado por vía oral durante un período de una semana, en una dosis de 400 mg. tres veces al día. Se notó que la droga aumentó la resistencia capilar, pero no tuvo efecto alguno en el dolor. Se sugirió que el Glivenol quizá sea de posible valor terapéutico para evitar la equimosis debida a la terapia corticosteroide de largo plazo.