PHENFORMIN (DIBOTIN) IN POLYARTHRITIS

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Since 1956 biguanides have received attention as oral hypoglycaemic agents (Krall and Bradley, 1959). Ungar, Madison, and Carter (1960), using phenformin (Dibotin, phenethyl biguanide), showed their effect on peripheral utilization of glucose, Butterfield, Fry, and Holling (1958) having previously demonstrated increased uptake of insulin in hepatic and peripheral tissues. Since then the drug has been used with sulphonylureas for oral control of diabetes and with insulin in brittle diabetics and when they are partly insulin resistant.

Fearnley and Chakrabarti (1964) showed that phenformin increased fibrinolytic activity in occlusive heart disease and Fearnley, Chakrabarti, and Hocking (1965) used this drug in rheumatoid arthritis in hopes of removing fibrin from the inflammatory lesions. In a follow-up of twenty cases treated with phenformin 100 mg. and ethyloestrenol 8-16 mg. for 5 to 14 months, (Fearnley, Chakrabarti, and Evans, 1966), they found some clinical improvement in twelve. In seventeen patients there was a 20 to 63 per cent reduction of plasma fibrinogen and in twelve the erythrocyte sedimentation rate (ESR) decreased by over 30 per cent.

Material and Methods

In view of these results it was decided to carry out a double-blind cross-over trial; 26 patients with rheumatoid arthritis were selected and allocated randomly to start treatment either with 100 mg. phenformin tablets or with placebo tablets of identical appearance. All were patients with typical, active, sero-positive, rheumatoid arthritis and throughout the trial no change was made in treatment except in the number of analgesic tablets. The number taken in each period was recorded but there was little variation and this did not influence the trial.

The patients' conditions were assessed before treatment and after 6 weeks on each medication, the assessment including the patients' estimate of pain and stiffness (graded 0-3), strength of grip, ring-size measurement of the worst affected finger, ESR, haemoglobin, and weight.

In four patients, who also had diabetes, blood sugar estimations were made three hours after the same light breakfast.

Results

Twenty patients completed the trial with little or no toxic symptoms, while six discontinued treatment. Two of the six were withdrawn because pre-existing mental instability made records unreliable and one with Felty's syndrome for splenectomy; the remaining three refused further phenformin treatment because of dyspepsia (1), diarrhoea (1), and general malaise (1). In two patients who completed the course, the dose of phenformin was reduced from 100 to 50 mg. per day, because of indigestion and diarrhoea, and were symptomless on the lower dose. Two other patients who had dyspepsia and diarrhoea with the tablets, were subsequently able to take the same dose of phenformin in slow-release capsules without digestive upset.

On comparing the results of treatment of the twenty patients who completed the course, three showed less pain and stiffness with the phenformin and one with the placebo. Weight showed no trend of variation. A comparison was made by sequential analysis of the difference with regard to grip strength, ESR, and haemoglobin levels, between the figure obtained after taking phenformin and that after taking placebo tablets. For charting purposes, differences of less than 10 mm. Hg in grip, 5 mm. in 1 hour in ESR, and 4 per cent. in haemoglobin concentration were ignored. There was a slight improvement in grip in the phenformin phase, but this was not statistically significant (Fig. 1, opposite).

The main finding was improvement in the ESR, which achieved significance after charting the results of the first sixteen patients (Fig. 2, opposite).

This reduction in ESR bore no relation to increase in haemoglobin level (Fig. 3, opposite).

Fig. 1.—Strength of grip on phenformin and placebo, 10 mm. Hg change considered significant for charting fourteen results in twenty patients.

Fig. 2.—ESR on phenformin and placebo. 5 mm./1st hr difference considered significant for charting eight results in sixteen patients.

Fig. 3.—Haemoglobin levels on phenformin and placebo. 4 mg. per cent. difference considered significant for charting thirteen results in twenty patients.

The four patients with diabetes and rheumatoid arthritis were analysed separately. Three of the four were taking prednisolone; in one the dose of prednisolone was reduced by 2.5 mg. while on phenformin and in the other two the dose remained the same. In three out of four the mean blood sugar fell without increase in insulin on average by 15 mg. per cent. Clinically, two patients improved with regard to their arthritic symptoms while on phenformin as compared with the period on placebo tablets.

Summary and Conclusions

In a double-blind cross-over trial comparing phenformin (Dibotin) with placebo in the treatment of twenty patients with active rheumatoid arthritis, the only statistically significant result was a reduction in ESR. Strength of grip improved a little on

phenformin, but did not achieve significance with the small numbers in the trial. It seems possible that the change in ESR during phenformin administration may not be a true criterion of improvement in the rheumatoid condition, but may reflect the action of the drug on plasma fibrinogen concentration.

Toxicity consisted of nausea and/or diarrhoea; it was responsible for the withdrawal of two patients from the trial and was present in two others.

In cases of active polyarthritis with diabetes, where corticosteroids must be avoided or kept to the minimum dosage, phenformin, preferably used in slow-release capsules, appears to be of some clinical value against both the diseases requiring treatment.

Messrs. Bayer Ltd. kindly provided both the Dibotin and the placebo tablets.

REFERENCES

- Butterfield, J., Fry, I. K., and Holling, E. (1958). *Diabetes*, **7**, 449 (Effects of insulin, tolbutamide, and phenethylbiguanidine on peripheral glucose uptake in man).
- Fearnley, G. R., and Chakrabarti, R. (1964). *J. clin. Path.*, **17**, 328 (Pharmacological enhancement of fibrinolytic activity of blood).
- , —, and Evans, J. F. (1966). *Ibid.*, **2**, 757 (Treatment of rheumatoid arthritis with phenformin plus ethylloestrenol).
- , —, and Hocking, E. D. (1965). *Lancet*, **1**, 9 (Phenformin in rheumatoid arthritis).
- Krall, L. P., and Bradley, R. F. (1959). *Ann. intern. Med.*, **50**, 586 (Clinical evaluation of formamid-inyliminourea, a new biguanide oral blood sugar lowering compound).
- Ungar, R. H., Madison, L. L., and Carter, N. W. (1960). *J. Amer. med. Ass.*, **174**, 2132 (Tolbutamide-phenformin in ketoacidosis-resistant patients.)

Phenformine (Dibotin) dans la polyarthrite

RÉSUMÉ

On compara par la méthode de "double-blind cross-over" la phenformine (Dibotin) à un placebo chez 20 malades atteints de polyarthrite rhumatoïde active. On ne trouva qu'un seul effet statistiquement significatif: la réduction de la vitesse de sédimentation globulaire (VSG). Une légère amélioration de la force de la main chez les malades traités par la phenformine fut en dessous des limites de signification, mais le nombre des cas dans la série fut petit. Il serait possible que l'altération de la VSG au cours du traitement par la phenformine ne soit pas un signe d'amélioration de la condition rhumatoïde mais un résultat de l'action de ce produit sur le taux sanguin du fibrinogène.

La toxicité, se traduisant par des nausées et/ou de la diarrhée, s'observa chez quatre malades et nécessita le retrait de la série de deux d'entre eux.

Dans les cas de polyarthrite évolutive accompagnée d'un diabète, où les corticostéroïdes sont peu indiqués, la phenformine, préférablement sous forme de capsules à dégagement lent, peut être de quelque utilité contre les deux maladies.

Fenformina (Dibotin) en la poliartritis

SUMARIO

Se comparó por el método de "double-blind cross-over" la fenformina (Dibotin) con un placebo en 20 enfermos con poliartritis reumatoide activa y se halló sólo un efecto estadísticamente significativo: la reducción de la velocidad de sedimentación eritrocitaria (VSE). La fuerza de la mano mejoró un poco con la fenformina sin alcanzar los límites de significación en el pequeño número de enfermos investigados. Es posible que la alteración de la VSE durante el tratamiento con la fenformina no sea un criterio de mejoría de la condición sino el efecto de este producto sobre la concentración del fibrinógeno en la sangre.

La toxicidad se manifestó por la nausea y/o la diarrea; de cuatro enfermos afectos dos fueron retirados de la investigación.

En casos de poliartritis activa asociada con diabetes, en los cuales los corticosteroides se ven poco indicados, la fenformina, de preferencia en forma de cápsulas a acción lenta, parece tener un cierto valor clínico contra ambas enfermedades.

CORRECTION

Oreskes, I., et col. *Ann. rheum. Dis.*, 27, 63, lignes 4 et 12:

A la place de "de Waaler-Rose" on doit lire: "d'agglutination utilisant des hematies de mouton tannées".

CORRECCION

Oreskes, I., y col. *Ann. rheum. Dis.* 27, 63, líneas 3 y 11:

En lugar de "Waalser-Rose" se debe leer: "de aglutinación de eritrocitos de cordero curtidos".