

# PRELIMINARY TRIAL OF A POWERFUL NEW SULPHONYLUREA IN MATURITY-ONSET DIABETES—HB419 (GLIBENCLAMIDE)\*

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We have several sulphonylureas from which to choose in the treatment of maturity-onset diabetes. They all act by stimulating insulin output from the subjects' own pancreatic beta cells. It is thus extremely unlikely that a new sulphonylurea will be found to be effective in a large proportion of patients when others have failed, though certainly some are more powerful than others—chlorpropamide is more effective than tolbutamide in some individuals—and the reason for even this limited difference in effectiveness is incompletely resolved. For a new sulphonylurea to be justifiably placed on the market it must therefore fulfil several criteria:

1. It must be at least as effective as the most powerful existing drugs.
2. It must be virtually non-toxic.
3. It must be acceptable by reason of few and minor side-effects.
4. It should not be liable to produce serious hypoglycaemia when correctly used.

The compound HB419, glibenclamide, is a sulphonylurea with a long side-chain. Chemically, it is N- $\left\{ 4-\beta[2\text{-methoxy-5-chlorobenzamido}] \text{-ethyl} \right\}$ -N'-cyclohexyl urea. Its structural formula is shown in Fig. 1.

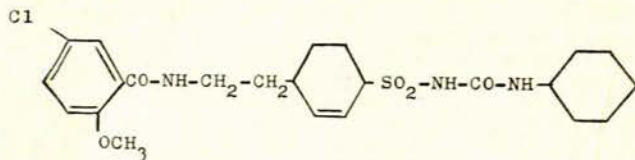


Fig. 1. Structural formula of glibenclamide.

This drug is quite remarkably powerful on a weight basis, being approximately 500 times as potent as tolbuta-

mid and at least 50 times as potent as chlorpropamide.<sup>1-3</sup> This does not necessarily mean that it will be more effective in the treatment of diabetes, but certainly a far smaller dose is required, and this fact might reasonably be expected to reduce or abolish some of the toxic effects pertaining to standard doses of other sulphonylureas. In fact, toxicity studies by the makers have indicated that although the new side-chain has rendered this sulphonylurea much more potent it has not rendered it more toxic, weight for weight, than previous drugs of the same class.<sup>1-3</sup> In view of the very much smaller dose required, HB419 should therefore prove to be virtually safe, except of course that it will occasionally produce hypoglycaemia. It has no antibacterial properties.

The duration of effective action of HB419 is reported as being longer than that of tolbutamide, about 8 hours after a 5-mg. dose, or over 12 hours with larger doses.<sup>1-3</sup> It is reasonable to suppose that a single daily dose will prove adequate to control the majority of sensitive diabetics.

Each tablet of HB419 contains 5 mg. Because of the inherent safety of the drug there is no particular maximum dose level, but more than 4 tablets a day are believed to be wasteful, while it is probable that more than 2 will seldom be necessary.

A small preliminary trial of this drug, ending April 1968, was carried out in Cape Town.

## MATERIAL AND METHODS

### Subjects

In the Diabetes Clinic of Groote Schuur Hospital we used HB419 in 34 diabetics on an outpatient basis. We chose only maturity-onset diabetics, who had all failed to be controlled on diet alone, and who were all receiving other tablets or insulin (one case) at the start of the trial. There were no 'new' cases—most had had dia-

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betes between 5 and 10 years. We also tried to avoid obese subjects; although 12 of our 34 were more than 5% overweight by Broca's index, only 2 were more than 15% overweight. No patients with severe complicating disease were included, though a few had well-compensated heart disease.

Our 34 subjects included 10 men and 24 women; there were 21 White and 13 non-White patients, with an age range of 30-80 years.

#### Methods

Patients already taking tolbutamide or glymidine were first tried on 1 tablet of HB419 daily; patients on chlorpropamide were started on the same number of tablets that they were already taking. Patients already taking a diguanide in addition to sulphonylurea were usually kept on the diguanide. A few patients who had been on combined therapy were initially tried on HB419 alone, but in no case was this successful, and so it was decided thereafter to continue with the diguanide at the same dose.

Patients were seen 2-4 weeks after starting HB419 and then at monthly intervals. At each attendance the patient was weighed with coat removed and was questioned about symptoms and about urine tests performed at home. Several of the more intelligent kept home records on specially printed sheets. Blood was drawn for sugar estimation and several other tests. All subjects had repeated estimations of haemoglobin, total white cells and platelets, blood urea, serum bilirubin, SGOT and alkaline phosphatase. Early morning urine specimens brought to clinics at each visit were tested for sugar and protein by ourselves.

Most patients were observed on HB419 for 5-6 months, some up to 10 months. In 3 cases failure was evident after one month and insulin had to be started.

The maximum or final number of tablets of HB419 used was as follows: 1 daily in 5 cases; 2 daily in 20 cases; 3 daily in 3 cases and 4 daily in 5 cases. One patient required none.

Patients were not considered 'failed' until a diguanide had been used in conjunction with sulphonylurea (except in one case when severe symptoms including weakness and drowsiness developed).

#### RESULTS

Control was judged by the urine tests done by the patients themselves and at the clinics, together with blood-sugar readings taken in the clinic. 'Excellent', 'good' and 'fair' control are terms used as on the maker's test sheets. Thus 'excellent' implies fasting blood-sugar levels below 120 mg./100 ml. (Autoanalyzer, Hoffman method) or postprandial levels below 160 mg./100 ml. with no, or almost no, glycosuria. 'Fair' indicates fasting levels between 150 and 200 mg./100 ml. with frequent glycosuria of moderate degree. 'Good' is between these two.

It should be noted that, especially in older diabetics, the blood-sugar level may be high when glycosuria is absent, because of a high renal threshold. In such cases we have estimated control rather on the basis of the blood-sugar levels, though to maintain really good control with high renal threshold is usually quite impossible or at least impracticable.

The final judgement as regards control is shown in Table I.

TABLE I. CONTROL OF PATIENTS ON HB419

| Degree of control                      | No. of cases |
|--|--------------|
| 'Good' after tolbutamide failed        | 4            |
| 'Excellent' after tolbutamide failed   | 1            |
| 'Excellent' equal to tolbutamide       | 2            |
| 'Fair' equal to tolbutamide            | 1            |
| 'Excellent' equal to chlorpropamide    | 4            |
| 'Good' equal to chlorpropamide         | 3            |
| 'Excellent' better than chlorpropamide | 1            |
| 'Good' better than chlorpropamide      | 1            |
| 'Fair' better than chlorpropamide      | 1            |
| 'Fair' equal to chlorpropamide         | 3            |
| 'Excellent' after glymidine failed     | 1            |
| 'Good' better than glymidine           | 2            |
| 'Failed' equal to chlorpropamide       | 7            |
| 'Fair' better than diguanide alone     | 1            |
| 'Excellent' after poor on insulin      | 1            |
| 'Excellent' also on no tablets         | 1            |
| Total 'Excellent' on HB419             | 10           |
| Total 'Good' on HB419                  | 10           |
| Total 'Fair' on HB419                  | 6            |
| Total 'Failed' on HB419                | 7            |

In a few cases it was possible to test the effect of taking the daily requirement of tablets together in one dose. The recommended time for single-dose therapy was midday, because breakfast is generally a small meal. In 2 instances tablets taken together did not produce as good a control as when taken separately.

There were 9 patients whose diabetes was of over 10 years' duration. Two achieved excellent control with HB419—in one case only after the addition of metformin; 2 achieved good control and 4 failed.

#### Combination with Diguanydes<sup>a</sup>

In 17 cases—i.e. exactly one-half the total subjects—it was necessary to add a diguanide to the HB419 in an attempt to improve control. The diguanide used was phenformin (Insoral TD) in 15 cases, 2 or 3 capsules daily, and metformin (Glucophage) in 2 cases. Final results of combined therapy were 4 failed, 5 fair, 4 good and 4 excellent.

One White woman, aged 65 years, had mild ischaemic heart disease and diabetes that had been present for more than 10 years. Five different sulphonylureas, including HB419, produced no more than a poor 'fair' response. The addition of metformin, 3 tablets daily, to 4 HB419 tablets led to an 'excellent' response.

#### Toxic Effects

There were no toxic effects to HB419. Side-effects were few. One patient complained of headache, and one of fatigue and abdominal pain which did not necessitate stopping the HB419—the relationship of these complaints to the tablets was considered doubtful. (See case 2, below.)

No significant effect in 34 cases was noted on haemoglobin, total white cell count, platelet count, serum bilirubin levels, alkaline phosphatase, SGOT or cholesterol. In 8 cases no effect was seen on blood-urea levels, serum sodium, potassium, chloride, uric acid, thymol turbidity, zinc sulphate test, total proteins or albumin level. In 3 cases the serum amylase levels remained virtually unchanged.

In addition no significant change was seen in body-weight. Hypoglycaemic symptoms were not encountered. Proteinuria was not seen unless already present.

## CASE REPORTS

## Case 1

A White woman aged 66 years, who had been diabetic for 8 years and had been on sulphonylureas since diagnosis, was well controlled on chlorpropamide plus phenformin, but complained of severe flushing and palpitation after taking a small tot of alcohol.<sup>5</sup> On substituting HB419 for the chlorpropamide this complaint was abolished.

## Case 2

A thin White woman aged 55 years, recently diagnosed as diabetic, initially required one tablet (250 mg.) of chlorpropamide for control, and showed glycosuria after discontinuing this. She was equally well controlled on a tablet of HB419, though she said she felt queer and had to draw a deep breath 4 hours after taking it (? mild hypoglycaemia). The dose was reduced to half a tablet and eventually the HB419 was withdrawn, with a continuation of excellent control.

This patient illustrates the fact that recent diabetes may initially need sulphonylurea for control, but subsequently may be controlled quite well without any therapy except a diabetic-type diet, even if the patient is not overweight.<sup>6</sup>

## Case 3

A White woman aged 39 years, of normal weight and a diabetic for 3 years, was taking lente insulin up to 60 units daily and was irregularly controlled, going frequently from hypoglycaemic reactions to gross glycosuria. Control became 'excellent' on only one tablet of HB419 daily, with no insulin.

## Case 4

A Bantu man, aged 45 years and of normal weight, was admitted to hospital in hyperosmolar, non-ketotic diabetic coma.<sup>7</sup> After recovery he was controlled very well on chlorpropamide 2 tablets plus phenformin 3 capsules daily. He remained equally well controlled ('excellent') when 2 tablets of HB419 were taken in place of the chlorpropamide.

## DISCUSSION

HB419 appears to be a well-tolerated drug, approximately equal to chlorpropamide in its ability to control diabetes, tablet for tablet (i.e. 250 mg. chlorpropamide and 5 mg. HB419). Because of the lack of toxicity of the comparatively minute dose of HB419, more than 2 tablets can be given with impunity, and occasionally with improved results. Thus we thought that in 2 subjects the larger dose of 4 tablets produced a distinctly better response than 2 tablets a day. Three cases seemed better controlled on HB419 than on chlorpropamide, and in one the reverse was the case. HB419 appeared to be distinctly more powerful than tolbutamide or glymidine (Glycodiazine).<sup>8</sup>

HB419 combines well with the diguanides. It was possible to save about half the patients who were 'failing' on sulphonylurea alone, including HB419, by adding a diguanide. Thus 8 of 17 cases became 'good' or 'excellent' and another 5 became 'fair'.

'Excellent plus good' results were obtained in 60% of the patients (20 out of 33). This seems quite reasonable in view of the type of subjects selected for the trial. The results were not markedly poorer in patients whose diabetes had been present for over 10 years, though there were 4 failures out of 9 in this group.

The very small dose of HB419 required for control would seem to be an advantage and should reduce or entirely eliminate the serious toxic effects that have been occasionally described with other oral sulphonylureas. In one of our cases sensitivity to alcohol was abolished on changing from chlorpropamide to HB419; another patient vomited when put on chlorpropamide but was able to tolerate HB419 without any side-effects.

Some side-effects must, however, be expected, since they occur also with placebos. Similarly it must be realized that a placebo will lead to 'good control' of diabetes in some 25% of new cases,<sup>10</sup> but that this placebo effect is eliminated when one drug is compared against another, as in this present trial.

It must be understood that this report is concerned with short-term therapy and no mention is made of secondary failure of HB419. This has not yet been encountered, though it is presumably to be expected later. On the other hand, a longer trial may produce better results, since some patients still in the trial may obtain improved control on higher doses of HB419 and/or on combination with diguanides where this has not yet been attempted.

## SUMMARY

HB419 is a remarkably potent sulphonylurea, of which only a few milligrams are effective in sensitive maturity-onset diabetics. In a preliminary trial with 34 patients it appeared readily acceptable, non-toxic and at least as potent as chlorpropamide. It combined well with a diguanide where this was necessary. Other workers have found that hypoglycaemia is a risk that must be taken into account.

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## ADDENDUM

Secondary failure of HB419 occurred in one Coloured female after one year's successful therapy, but good control was again achieved by the addition of phenformin (Insoral TD).

A White female of 55 years was found to require only  $\frac{1}{2}$  tablet of HB419 to produce good control, glycosuria recurring if this was omitted.

At a conference on this drug (Tegernsee-Konferenz über das neue orale Antidiabetikum HB419), held in January 1969, at which results in some 6,000 cases were reported, it became clear that the danger of hypoglycaemia is quite considerable. Great care must be taken in starting treatment in very mild diabetics, particularly in elderly patients.

Apart from hypoglycaemia and various side-effects that may also be seen with placebos, the only adverse reaction definitely attributable to the drug was a very occasional skin rash of sensitivity type.

It was generally agreed that, apart from the natural risk of hypoglycaemia, HB419 is a very safe and well-tolerated drug, with approximately the same power as chlorpropamide for controlling maturity-onset diabetics.

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