CLINICAL TRIAL OF A NEW SULPHONYLUREA IN MATURITY-ONSET DIABETES—HB419 (GLIBENCLAMIDE)*

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In this paper is reported a trial of a new oral sulphonylurea, HB419 or glibenclamide, in the treatment of maturity-onset diabetes. Chemically the substance is N-{4-(β[2-methoxy-5-chlorobenzamido]-ethyl)-benzosulfonyl}-N′-cyclohexyl urea, and its structural formula is shown in Fig. 1.

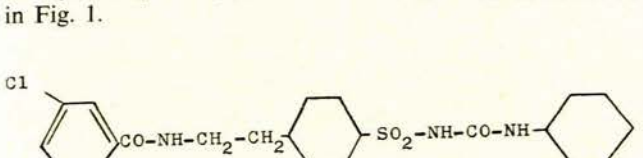

Fig. 1. Structural formula of glibenclamide.

In animal experiments it has been shown to be an extremely powerful hypoglycaemic agent; administered intravenously to normal dogs it was 440 times more active than tolbutamide on a molar basis.[1] Several workers have shown that HB419 stimulates the release of insulin from human beta cells.[2,3] In non-diabetic human subjects the duration of action of the compound varies with dosage, being about 8 hours after a single dose of 2 mg. and up to 12 hours or longer after 5 mg.[4]

In man the biologic half-life in plasma is 5 - 7 hours. After oral administration about 25% is excreted in the urine, mainly in oxidized form, and about 75% is excreted unchanged in the faeces.[4] Acute and chronic toxicity studies in animals, including tests of teratogenicity, revealed a high degree of safety.[4] The agent has no antibacterial properties.[4]

PATIENTS AND METHODS

Eighty-six maturity-onset diabetics were treated at Johannesburg Non-European Hospital on an outpatient basis. There were 54 Indians (28 males and 26 females) who were mainly Moslems, and 32 Bantu (8 males and 24 females). Their ages ranged from 29 to 75 years, with three-quarters of the patients between 40 and 60 years. The majority were overweight. The standards of education and literacy of both Indian and Bantu patients were generally low. The Indians were considerably more affluent than the Bantu, but in both groups it was difficult to impose and maintain a strict dietary regimen, and in the majority of patients the caloric intake was excessive. About one-third of the diabetics were new, while in two-thirds the disease was of variable duration and had been treated previously with other oral agents, mostly sulphonylureas. A number of patients were referred to the hospital by general practitioners because of difficulty in controlling the disease.

New diabetics were started on one tablet (5 mg.) of HB419 daily after it had been established that control by diet alone was inadequate. Patients previously on tolbutamide were also first tried on one tablet daily, while those on chlorpropamide were usually given the same number of tablets that they were already taking.

HB419 was usually taken as a single dose at breakfast, but some patients on more than two tablets daily took the drug 2 or 3 times a day. The duration of treatment was variable: 1 patient received HB419 for 1 week, 14 patients were treated for 1 - 2 months, 9 for 3 - 4 months, 14 for 5 - 6 months, 13 for 7 - 8 months, 18 for 9 - 10 months and 17 for 11 - 12 months.

Patients were seen at weekly intervals to begin with, then fortnightly and thereafter monthly. Records were kept of symptoms, weight, glycosuria, proteinuria and blood-sugar levels (Autoanalyzer-ferricyanide method). Periodically blood was taken for full blood count including platelet number and morphology, serum bilirubin (total and direct), prothrombin index, serum alkaline phosphatase, serum transaminases (glutamic pyruvic and glutamic oxaloacetic), serum lactic dehydrogenase and blood urea. Urine specimens were examined microscopically as well as chemically.

The degree of control was assessed by the blood- and urine-sugar levels, broadly according to criteria laid down in the manufacturers' test sheets:

Excellent: 2-hour postprandial blood-sugar level below 140 mg./100 ml. and no glycosuria.

Good: 2-hour level below 160 mg./100 ml. and slight glycosuria.

Fair: 2-hour level below 200 mg./100 ml. and moderate glycosuria.

Poor: 2-hour level below 260 mg./100 ml. and heavy glycosuria.

Failure: No response to the preparation used.

RESULTS

The responses in the 86 patients were: excellent—21 (24%); good—20 (23%); fair—21 (24%); poor—16 (19%); and failed—8 (10%).

Among the 41 patients whose response was excellent or good, the daily dose was 2·5 mg. in 2, 5 mg. in 19, 10 mg. in 17 and 15 mg. in 3. A single daily dose was used in all except 2 patients who took 5 mg. thrice daily. Among the 21 patients whose response was fair, the daily dose was 2·5 mg. in 1, 5 mg. in 7, 7½ mg. in 1, 10 mg. in 8, 15 mg. in 3 and 20 mg. in 1. Three patients took 15 or 20 mg. in 2 or 3 divided doses. Among the 24 patients whose response was poor or who were failures, the daily dose was 5 mg. in 1, 10 mg. in 13 and 15 mg. in 10. Eight patients took 5 mg. thrice daily.

Response was unrelated to age. There were some differences in efficacy related to sex and race but they were of doubtful significance. Response was related to duration of diabetes as indicated in Table I. Excellent or good results were noted in two-thirds of patients whose dura-

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tion of diabetes was less than one year and who in the main had not been treated previously; of those whose duration of disease was longer and who had been treated with other agents, such results were obtained in one-third.

TABLE I. RELATIONSHIP BETWEEN RESPONSE TO HB419 AND DURATION OF DIABETES

	No. of patients with duration of diabetes of:		
Response	*1 - 12 months*	*1 - 5 years*	*6 - 10 years*
Excellent or good	23 (68%)	11 (34%)	7 (35%)
Fair	5 (15%)	9 (28%)	7 (35%)
Poor or failed	6 (17%)	12 (38%)	6 (30%)
Totals	34 (100%)	32 (100%)	20 (100%)

In 31 patients it was possible to compare, on a tablet-for-tablet basis, the efficacy of HB419 (5 mg.) with that of tolbutamide (500 mg.) or chlorpropamide (250 mg.). In 13 comparisons with tolbutamide HB419 was superior in 2 and equal in 11. In 18 comparisons with chlorpropamide HB419 was inferior in 8 and equal in 10. In 7 comparisons (3 with tolbutamide and 4 with chlorpropamide) in which no difference was found, the results were equally poor rather than equally good.

Side-effects and Toxicity

Most patients tolerated HB419 well. A generalized erythematous rash occurred in 1 case and an itchy maculopapular eruption in another, while a third complained of pruritus. In all 3 the reaction disappeared (topical corticosteroid and calamine lotion were used in the second and third cases, respectively) despite continuing treatment with HB419. One patient developed hypoglycaemia which was relieved by oral sucrose, one became dizzy and one complained of marked nausea and vomiting. Twenty (23%) patients gained between 5 and 16 lb. weight while on HB419 therapy. There was at least one heavy drinker in the series and he did not complain of alcohol intolerance.

Most of the renal, hepatic and haematological investigations yielded normal results. There were slight rises in the levels of serum lactic dehydrogenase in 4 cases, of glutamic oxaloacetic acid transaminase in 4 patients and of glutamic pyruvic transaminase in 2. A mild elevation of the serum bilirubin level occurred in the heavy drinker. Pretreatment levels of serum lactic dehydrogenase, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase and bilirubin were raised in 5, 1, 1 and 2 patients, respectively, and all returned to normal during the course of HB419 therapy. In 2 cases low pretreatment blood neutrophil counts became normal after treatment with HB419 was started.

DISCUSSION

A number of sulphonylureas are available for the treatment of maturity-onset diabetes, and the introduction of a new one should be justified by evidence of superiority in respect of potency, toxicity or side-effects. The minuteness of the dosage of HB419 is interesting pharmacologically but does not necessarily confer therapeutic advantages.

There is no doubt that HB419 is an effective hypoglycaemic agent. In the rather severe test provided by our Indian and Bantu diabetics, excellent or good results were achieved in nearly half the cases and a fair response in a further quarter. Furthermore, it is possible that even better results might have been obtained by using larger doses. Thus the total daily dose did not exceed 5 mg. in a third of patients whose response was classified as fair, or 10 mg. in more than half of those in the poor or failed category.

On the other hand, evidence was not obtained that HB419 has significant advantages over the other sulphonylureas in common use. This was reflected in the relatively small proportion of good results achieved in diabetics of some years' standing, most of whom had previously been treated with other sulphonylureas, and also in the direct comparisons between HB419 and tolbutamide or chlorpropamide. These comparisons were neither randomized nor 'blind', but the results indicated that, on a tablet-for-tablet basis, HB419 was occasionally better than tolbutamide but not uncommonly inferior to chlorpropamide. The toxicity of HB419 appeared to be low, but it was not free of side-effects including hypoglycaemia and weight gain. The latter is a well-recognized accompaniment of sulphonylurea therapy and its frequency in our patients was possibly related to the absence of strict dietary control.

It is possible that with larger doses and in patients more amenable to dietary control HB419 would achieve results better than those reported here. In particular, it needs to be systematically compared with chlorpropamide, the most potent of the sulphonylureas currently in use.

SUMMARY

HB419 or glibenclamide, a new sulphonylurea, was used in the treatment of 86 Indian and Bantu maturity-onset diabetics. The response was excellent or good in 47%, fair in 24% and poor or absent in 29%. Results were better in new diabetics than in older cases previously treated with other sulphonylureas. On a tablet-for-tablet basis it was more effective than tolbutamide in 2 out of 13 patients, but less active than chlorpropamide in 8 out of 18. Toxicity was low, and side-effects were uncommon except for gain in weight. It is suggested that larger doses in patients more amenable to strict dietary control may yield better results.

I should like to thank Prof. James Gear, Director of the South African Institute for Medical Research, where the laboratory investigations were undertaken; Mr G. Winternitz and Dr R. Müller of Hoechst Pharmaceuticals (Pty) Ltd for supplies of HB419 and much valuable assistance; and Dr H. van Wyk, Medical Superintendent of Johannesburg Hospital, for permission to publish.

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