HB419 (GLIBENCLAMIDE) IN THE TREATMENT OF DIABETES MELLITUS*

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Following the introduction of the sulphonylureas as antidiabetic agents in 1955, a succession of these products have found a firm place in the treatment of diabetes mellitus. Response to these drugs has been limited mainly to the maturity-onset group of diabetics, for apart from certain young Bantu and Indian diabetics, few maturity-onset cases in Whites have responded, except for short periods at the onset of the condition. Side-effects have been minimal, but allergic skin manifestations, gastro-intestinal symptoms and blood changes do occur occasionally. As a result, the search for more effective preparations with less sulphonylurea content has continued.

HB419 (glibenclamide†) is a recent addition which has been subjected to clinical trial on the basis of its increased potency in reducing the blood-sugar level and the smaller quantity of highly potent sulphonylurea required. It is a white, odourless, crystalline substance with a chemical formula of N-{4-(β[2-methoxy-5-chlorobenzamido]-ethyl)-benzosulfonyl}-N′-cyclohexyl urea. Its structural formula is given in Fig. 1.

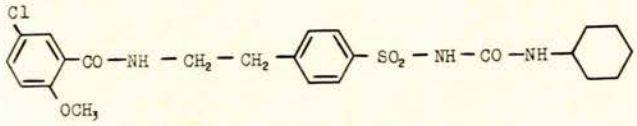

Fig. 1. Structural formula of HB419 (glibenclamide).

Single dose administration on mg. per mg. basis has shown HB419 to be 1,000 times more potent than tolbutamide in the rabbit, 250 times more potent in the dog, and about 500 times more potent in man. Increase in dosage causes prolongation of action up to a certain dosage, above which the blood-sugar level cannot be reduced. The manufacturers state that, in normal human subjects, a dose of 2 mg. per person causes a maximum fall of 30% in blood sugar 2 hours after its administration, with an approximate 8-hour duration of action. A dose of 5 mg. per person reduces the blood sugar by 40% and the effect lasts more than 12 hours, while an increase of dosage to 10 mg. per person produces little further effect.

Studies of animal toxicity—acute, subacute and chronic—have shown the drug to be safe and to have no antibacterial properties. A clinical evaluation of the drug was therefore undertaken at the Diabetic Clinic of Johannesburg Hospital.

SUBJECTS AND METHODS

Ninety-eight maturity-onset diabetic patients were selected for treatment with the new drug HB419. They consisted of 27 males and 71 females, their ages ranging between 37 and 79 years (average 63·8 yrs). The duration of diabetes varied between 1 month and 20 years, with an average of 7·6 years. Fifty-eight were overweight, 35 were normal and 5 were underweight.

A number of associated diseases were present. Sixteen patients were hypertensive, 12 had coronary artery disease, 7 had liver and gallbladder disease, 4 had gastro-intestinal tract disorders and 5 had albuminuria and renal dysfunction, while other disorders were noted in 14 cases.

The duration of treatment was from 1 to 19 months. Seventy-eight cases were treated for from 12 to 19 months, 7 from 6 to 12 months, and 13 for less than 6 months.

Five-mg. tablets of HB419 were employed, and the dose varied between 2½ and 15 mg. daily (½ - 3 tablets). The total dose was administered after breakfast in the cases requiring 10 mg. or less. When this dose was exceeded, the drug was given in 2 or 3 divided doses. HB419 was the only drug used in 59 cases, while diguanides were added in 38 cases and insulin in 1 case.

At the commencement of treatment all patients were seen at weekly intervals. They were instructed to test their urine for sugar 4 times daily and to report immediately if they did not feel well or experienced any side-effects. Blood-sugar estimations, blood counts, platelets, prothrombin indices, liver-function tests, protein electrophoresis, alkaline phosphatase, cholesterol, triglycerides, urea and uric acid estimations were carried out at regular intervals.

The degree of control was assessed by the absence of diabetic symptoms and side-effects, amounts of glycosuria and true blood-sugar levels as measured by the Auto-analyzer. In the 'excellently controlled' group there was no glycosuria in 24 hours, and fasting blood sugar remained below 100 mg./100 ml. One hour postprandially the maximum was 150 mg./100 ml. and 2 hours postprandially the level was 130 mg./100 ml.

In the 'well-controlled' group, fasting blood-sugar levels did not exceed 130 mg./100 ml., with levels of 180 mg./100 ml. 1 hour postprandially and 150 mg./100 ml. 2 hours postprandially.

In the 'fairly controlled' group, fasting blood-sugar levels did not exceed 150 mg./100 ml., with 200 mg./100 ml. 1 hour postprandially and 180 mg./100 ml. 2 hours postprandially.

The 'poorly controlled' group had marked glycosuria, with blood-sugar levels in excess of the preceding.

RESULTS

Control proved to be excellent in 24·2% of cases, good in 19%, fair in 29·5% and poor in 9·5%. The drug failed completely in 6·3% of cases. Deterioration of control while on therapy was noted in 11·5% of cases and occurred between the 24th and 42nd week of treatment. Two deteriorated from excellent to good, 2 from excel-

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†Euglucon—Boehringer Mannheim; Daonil—Hoechst.

lent to fair, 4 from good to fair, one from good to poor and one from fair to failure.

When all the cases were analysed at the end of the trial period, 80% fell into the fair-to-excellent group, with only 20% in the poor-to-failure group.

Comparison with Other Drugs

The hypoglycaemic effect of HB419 was compared in 34 cases with tolbutamide, in 38 cases with chlorpropamide, in 6 cases with glycodiazine, in 4 cases with acetohexamide, in 3 cases with HB113, in 1 case with tolinase and in 5 cases with diguanides. Tablet was compared with tablet, no consideration being given to the amount of active constituent in each tablet.

HB419 proved to be more potent than tolbutamide (0·5-G tablets) in 20 cases, of equal potency in 12 cases and less potent in 2 cases.

Comparison with chlorpropamide (250-mg. tablets) showed HB419 to be more potent in 9 cases, of equal potency in 14 cases and less potent in 15 cases.

The drug was more potent than glycodiazine in 4 cases and less potent in 2 cases. It was more potent than acetohexamide in 2 cases and of equal potency in 2 cases. It was of equal potency to HB113 in 1 case and less potent in 2 cases. It was of equal potency in 1 case to tolinase. HB419 was more potent in 3 cases treated with diguanides, of equal potency in 1 case and less potent in another.

Combined HB419 and Diguanide Therapy

Thirty-eight patients (8 males and 30 females) were treated on a combination of HB419 and diguanides. Two of the patients were underweight, 12 of normal weight, 14 overweight and 10 markedly overweight according to the Broca index.

Twenty-six cases had been previously on combined therapy, (sulphonylurea and diguanide), while 12 had been treated on one drug alone. Sulphonylurea accounted for 11 of these, while phenformin had been the treatment of the twelfth.

HB419 was given to all cases in a dosage of 2 - 3 tablets daily. In 12 cases from 2 to 6 tablets metformin (1,000 - 3,000 mg.) and in 26 cases 2 - 3 capsules phenformin daily (100 - 150 mg.) were added. Treatment was continued for periods up to 19 months (24 cases for 12 - 19 months, 6 cases for 6 - 12 months and 8 cases for less than 6 months). In 31 cases (25 females, 6 males) there was no alteration in weight during therapy. Weight increased in 3 and decreased in 4 females.

Comparison between present and previous treatment shows improvement in control in 4 cases, one case having improved to the excellent group, 2 to the good group and one to the fair group. Where treatment was commenced with HB419 alone, as was done in 23 cases, the addition of diguanides resulted in improvement in 14 cases, with no improvement in the other 9. These 23 cases had been previously treated with other sulphonylureas in combination with diguanides. HB419 alone failed to control their diabetes, and combined therapy was again found necessary. The 9 cases which were unimproved even on combined therapy had previously been poorly controlled on other sulphonylureas with diguanides. Attempts to reduce dosage of diguanides below that used in previous therapy resulted in deterioration of control in all but 1 case in whom 2 tablets of HB419 equalled control with 2 glycodiazine and 2 metformin tablets.

Deterioration in control previously noted with sulphonylureas alone and with combined therapy was again noted in the present series. Eight cases showed deterioration in control after varying periods of treatment. One deteriorated from excellent to good after 36 weeks, 1 from excellent to fair after 36 weeks, 3 from good to fair after 18 - 36 weeks, 1 from good to poor after 36 weeks, and 2 from fair to poor after 36 weeks.

There was no gain in weight in any of these cases.

Side-effects

Side-effects occurred in 23 cases (11 on combined therapy) and they were responsible for discontinuing treatment in 11 cases. This incidence may appear to be unduly high. However, it should be emphasized that most of our patients had participated in previous trials of hypoglycaemic agents and were rather loth to change to a new agent. Moreover, they were specifically asked to report any side-effects, no matter how trivial, and these are all included in our series. Almost all the symptoms occurred during the first 4 - 8 weeks of treatment, and some of the patients decided to discontinue therapy of their own accord and resumed their previous therapeutic regimen. It is our opinion that the majority of their side-effects would have disappeared spontaneously if they had agreed to persist with the new form of therapy.

The side-effects consisted of tiredness and weakness in 10 cases, upper gastro-intestinal symptoms (heartburn, nausea, vomiting and anorexia) in 9 cases, dizziness in 6 cases, headache in 4 cases, body pain in 3 cases, and hot flushes in 2 cases, while tinnitus, impotence and neuropathy accounted for 1 case each. The diguanides may well have been responsible for some of the side-effects.

In only 3 of the 11 cases was there any weight increase during therapy. Reinstitution of former therapy did not necessitate any alteration in previous dosage.

Investigations

Blood tests were performed at monthly intervals at the South African Institute for Medical Research, using the conventional techniques. No significant or permanent changes were detected. A transitory reduction in platelet level, prothrombin index and white cell count was noted in a few cases, but reversion to normal occurred while the patients continued to take the drug.

DISCUSSION

The results obtained in this clinical trial confirm the effectiveness of HB419 (glibenclamide) as a most powerful blood-sugar reducing agent in the treatment of Whites with maturity-onset diabetes.

Eighty percent of cases showed a definite response to the drug, while in only 20% of cases was the drug entirely ineffective. Control has remained excellent in 24·2% and good in 21% of cases. Thus 45·2% of cases have achieved good-to-excellent control, with a further 35·5% showing fair control.

Dietary control was found to be essential with HB419, as with other hypoglycaemic agents.

The effective dose varied between 2½ and 15 mg./day, administered in single or divided dosage. In this trial the maximum dose used was 15 mg., but other workers have used as much as 40 - 80 mg./day. It is our opinion that doses in excess of 15 mg. are seldom required and are unlikely to improve control in the individual case or to increase materially the number of cases adequately controlled.

Combined therapy with diguanides was well tolerated and certainly improved control and increased the percentage of cases which could be well controlled with HB419.

It must be stressed that HB419 may cause hypoglycaemic symptoms even in small dosage. No cases of hypoglycaemic coma were encountered in this series, but reduction in dosage or discontinuance of the drug was necessary in a few cases. The clinician and patient should be alerted to this possibility.

In general, the drug is as well tolerated as tolbutamide and chlorpropamide and no serious side-effects were noted. One patient developed a severe neuropathy which recovered when the drug was discontinued, and better control was established with chlorpropamide. Other side-effects were mild and the majority disappeared if patients persevered with the new treatment.

Although a temporary drop in leucocyte count, platelets and prothrombin index occurred in a few cases, no permanent abnormalities were manifest in repeated laboratory investigations in spite of continuation of therapy.

HB419 is thus a most valuable addition to the practitioner's armamentarium of sulphonylurea drugs. When compared mg. for mg. it is certainly more powerful than any of the sulphonylurea preparations and the patient is, therefore, subjected to a smaller concentration of the active substance.

Individual idiosyncrasy and side-effects will continue to determine the patient's preference for one or other sulphonylurea, and well-controlled patients should, therefore, persist with the treatment which suits them best.

This new drug will occupy an important place in the treatment of diabetes and will certainly increase the number of patients who will be able to benefit from oral therapy.

A further review of the effectively controlled group at the end of 22 months revealed no significant change in our findings.

SUMMARY

The properties of a new sulphonylurea (glibenclamide) are described. Ninety-eight White maturity-onset diabetics have been treated with this drug for periods up to 22 months. It is well tolerated and there are few side-effects, but hypoglycaemia must be guarded against.

No permanent biochemical changes have been noted and 45·2% of cases have achieved good-to-excellent control and 35·5% have achieved fair control. HB419 is an extremely powerful antidiabetic agent.

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