increase in plasma insulin both in the fasting specimen and in response to the glucose load (Fig. 2).

This effect was further investigated after the one-year trial period in five patients who had been treated for 13 to 16 months, and it was then found that there was no significant difference in plasma insulin concentrations at that time as compared with the results at the start of treatment. This aspect of insulin response requires further investigation. Sheldon *et al.* (1966) showed that there was an improvement in plasma insulin response as an early effect of acetohexamide treatment but that this receded rapidly after one to two months. Glibenclamide induced a much more prolonged improvement in plasma insulin response to glucose in diabetic patients.

The significant rises in plasma insulin were not paralleled by as great an improvement in glucose tolerance. It has been pointed out by Chu *et al.* (1968) that there is no evidence to suggest that chlorpropamide had increased insulin secretion independently of usual physiological stimuli. In contrast there is no doubt that the fasting plasma insulin levels on glibenclamide were significantly greater than before treatment, and this must be due to the drug. It appears to have different actions from the other members of the sulphonylurea group in that increased plasma insulin levels are maintained over a long period of time. There was a significant fall in plasma cholesterol in the whole group. Schrade *et al.* (1963) suggested that the level of plasma cholesterol reflected the degree of diabetic control. With their criteria glibenclamide has improved control in our patients.

From this study it is suggested that the initial dose of glibenclamide should be a single tablet of 5 mg. daily, and this can be rapidly increased to 15 mg. daily to attain control. Most patients will respond adequately at this dosage if a good response is going to be obtained. Higher dosages of up to 35 mg. daily produced no improvement over the 15-mg. dose.

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Glibenclamide Therapy in Diabetes Mellitus

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Summary: In an initial trial of glibenclamide in the treatment of maturity onset diabetes mellitus 28 patients were treated for up to one year and no toxic effects or side-effects were encountered. The hypoglycaemic potency of this drug is such that 5 mg. of glibenclamide corresponds to about 1,500 mg. of tolbutamide and 375 mg. of chlorpropamide.

Introduction

The place of oral sulphonylurea drugs in the treatment of maturity onset diabetes mellitus has been well established for over a decade. During this period several modifications to the chemical structure of this group of substances have been introduced, resulting in drugs with different potency, duration of action, and toxicity. The chief experience of most diabetic clinics has been with tolbutamide (biological half-life 5·6 hours, dose 1 to 3 g.) and chlorpropamide (biological half-life 35 hours, dose 0·1 to 0·5 g.) (Hadden and Weaver, 1968).

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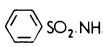
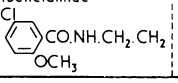
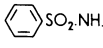
These compounds have a basic formula for effective hypoglycaemic action: R_1-SO_2.NH.CO.NH-R_2. The search for improvement in this family of drugs has shown that insertion of analkylene chain into the R_1 group increased potency. considerably, and substitution of the R_2 radical with a cyclohexyl group was also beneficial. The most potent compound discovered, which also had a suitable duration of hypoglycaemic effect and a low acute toxicity in animal experiments, comparable to that of tolbutamide, was N - 4 - [β - (5 - chloro - 2 - methoxybenzamido) - ethyl] - phenylsulphonyl-N-cyclophexylurea, or glibenclamide (Daonil) (Weber *et al.*, 1969) (Fig. 1).

	R_1		R_2	Biological Half-life (hours)	Dose (G.)
Tolbutamide	CH_3		$CH_2CH_2CH_2CH_3$	5·6	1-3
Chlorpropamide	Cl		$CH_2CH_2CH_3$	35	0·1-0·5
Glibenclamide				5-7	0·0025-0·02

After a dose of 5 mg. of glibenclamide in normal human subjects the peak serum concentration is reached in four hours, and has fallen to less than 5% of this level by 24 hours. No accumulation is found, even after repeated doses. The biological half-life is estimated at five to seven hours (Christ *et al.*, 1969). Animal studies with this compound show a remarkably low toxicity, both acute and chronic (Hebold *et al.*, 1969).

Clinical Studies

Thirty patients with maturity onset diabetes mellitus were asked to take part in the assessment of this new sulphonylurea. The age distribution and duration of diabetes in these patients is shown in Table I. Two patients did not complete the initial investigations. The previous therapy in these patients is shown in Table II. All patients were taking a restricted carbohydrate diet. A group of seven recently diagnosed patients had been under observation with diet alone for a period up to three months and had failed to achieve satisfactory blood glucose levels (mean 272 mg./100 ml.). The remaining patients had been on treatment with other oral antidiabetic agents for a variable period of time: these patients were changed to glibenclamide to establish a basis of comparison of therapeutic potency.

TABLE I.—*Patients Admitted to the Study*

Age (years)	Males	Females	Duration of Diabetes	No. of Patients
Less than 39	1	0	Less than 1 year ..	10
40-49	2	0	1-5 years	9
50-59	4	4	5-10 „	5
60-69	5	4	Over 10 „	6
70-79	1	9		

TABLE II.—*Blood Glucose Values Before and After One Month on Glibenclamide Therapy (5 mg. daily)*

Previous Therapy	No. of Patients	Blood Glucose (mg./100ml.)†	
		Before	After 1 Month
Diet alone	7	272	154
Tolbutamide (1,000-1,500 mg.) ..	5	137	132
Chlorpropamide (125-250 mg.) ..	6	128	125
„ (375-500 mg.) ..	7	142	151
Tolazamide (250 mg.)	1	259	160
Metformin (1,500 mg.)	1	199	105
Chlorpropamide (500 mg.)	1	211*	235*

*Plus metformin (1,500 mg.)
†Mean of the two-and-a-half hour postprandial measurements at 11 a.m. and 9 p.m

A series of biochemical and haematological screening tests were carried out before starting the new drug and at subsequent monthly clinic visits. These tests included white cell and platelet counts, and measurements of haemoglobin concentration, serum bilirubin, zinc sulphate turbidity, alkaline phosphatase, cholesterol, alanine and aspartate aminotransferases, and serum protein electrophoresis. Two blood glucose specimens were taken before each review, about two-and-a-half-hours postprandial, at 11 a.m. and 9 p.m.; the patients attended the hospital for these tests. Blood glucose was measured by the Auto Analyzer ferricyanide reduction technique (modified from Hoffman, 1937), and the other biochemical measurements utilized standard routine laboratory methods.

Results

The range of treatment periods with glibenclamide varied from 1 to 13 months, mean 6·6 months. All patients initially were taking 5 mg./day, and five were later increased to 10 mg./day. The mean of the two blood glucose values immediately before starting glibenclamide, and after one month on 5 mg. of this drug, are shown in Table II.

The seven patients who had not previously had treatment with a hypoglycaemic drug showed a pronounced fall in blood glucose. The 18 patients who had been on a sulphonylurea drug (tolbutamide, chlorpropamide, or tolazamide) showed comparable blood glucose levels for a dose of 1,500 mg. of tolbutamide and 375 mg. of chlorpropamide. The effect of subsequently increasing the dose of glibenclamide from 5 to 10 mg. daily in those patients who did not show a full response to the lower dose was to reduce their mean blood glucose from 200 to 169 mg./100 ml.

Haematological and Biochemical Screening.—No abnormality was detected in the total or differential white cell counts or haemoglobin levels. During follow-up visits no platelet counts below 133,000/cu.mm. have been found. Serum total protein and electrophoretic pattern were unaffected, as was the zinc sulphate turbidity and serum cholesterol. The serum alkaline phosphatase was above the normal laboratory range of 3 to 12 King–Armstrong units in 13 out of 27 patients before beginning glibenclamide (mean 13·0, range 7-25), and after one month's treatment in 9 out of 23 patients (mean 11·6, range 7-27). In those patients followed up for up to one year there was no evidence of deterioration in this index. The mean serum alanine aminotransferase pretreatment was 18·4 units (range 5-40 units) and after the first month 26·8 units (range 7-43 units); the range of normality in this laboratory is accepted as between 6 and 40 units. The serum aspartate aminotransferase values also showed no significant change before and after starting glibenclamide therapy.

Discussion

We have encountered no adverse side-effects in the use of this drug over a one-year period. The results of changing treatment to glibenclamide suggest that 5 mg. is equivalent in clinical practice to about 1,500 mg. of tolbutamide or 375 mg. of chlorpropamide. The initial trial was deliberately arranged to assess the effectiveness of this dose of glibenclamide, and in some cases better control was subsequently established on 10 mg. daily. By comparison with a previous study at this clinic of acetohexamide (Montgomery *et al.*, 1964), which has a similar cyclohexyl group in the R_2 position, the expected therapeutic equivalent for this drug would be about 500 mg. of acetohexamide and 5 mg. of glibenclamide.

The action of all sulphonylurea drugs appears to be similar in the long-term treatment of diabetes mellitus (Rigas *et al.*, 1968). In a previous study (Hadden *et al.*, 1969) of the circadian rhythm of preprandial and postprandial blood glucose and immunoreactive insulin in five patients taking 5 mg. of glibenclamide daily it was shown that there was a similar pattern of raised plasma insulin values to that found with tolbutamide and chlorpropamide. Anderson *et al.* (1970) studied the insulin response to an oral glucose load before and during glibenclamide treatment. They showed a significantly higher level of immunoreactive insulin throughout the test during treatment with glibenclamide.

The tablets of Daonil were supplied by Hoechst Pharmaceuticals, a division of Hoechst U.K. Ltd. We are grateful to Dr. B. Grassick for his advice. Our thanks are also due to the clinical pathology and biochemistry departments of the Royal Victoria Hospital. S.K.B. was in receipt of a Royal Victoria Hospital Fellowship during this study.

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Blood Glucose Variations and Clinical Experience with Glibenclamide in Diabetes Mellitus

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Summary: Thirty patients were treated with glibenclamide for periods up to 16 months. The drug is a potent hypoglycaemic agent, and taken in a single daily dose controls blood glucose levels over a 24-hour period in maturity onset diabetes. A definite dose-effect relationship exists, and the drug may be used in doses of 5 to 20 mg. daily. There were no appreciable side-effects or toxic effects during the period of study.

Introduction

Glibenclamide (Daonil; N-(4-[β-(2-methoxy-5-chlorobenzamido) ethyl] benzosulphonyl)-N′-cyclohexylurea) is a new active hypoglycaemic sulphonamide, one of many synthetic compounds recently studied in an attempt to produce a hypoglycaemic drug with a more potent and prolonged action. Pharmacological studies have already been published (Aumüller *et al.*, 1966) and clinical trials recently completed are being published (Burns, 1969). This report is chiefly concerned with the acute effects of the drug over 24-hour periods in diabetic patients, and with its value as a hypoglycaemic agent in clinical practice.

Patients and Methods

Thirty patients (16 women and 14 men) were studied over a 15-month period. Twenty-eight were more than 40 years old. In 14 the diabetes was recently diagnosed, and no previous therapy had been given. In 14 others control of the diabetes was regarded as unsatisfactory with other oral hypoglycaemic drugs. A further two patients were reasonably controlled on insulin, but had requested a transfer to an oral hypoglycaemic drug. All patients were initially admitted to hospital and put on a standard diet according to their height and weight. After two days on diet alone blood glucose levels were estimated at eight set periods over the 24 hours (fasting, one and two hours after each main meal, and at midnight). A 24-hour urinary glucose estimation was also carried out. Blood and urinary glucose was estimated on the autoanalyser, the glucose-oxidase method being used.

On the next day glibenclamide was begun in a dose of either 2·5 or 5 mg. daily. Over the next few days blood glucose was estimated eight times daily, the dose of glibenclamide being increased as indicated. When optimal control had been achieved (usually within six days) a further 24-hour urinary glucose estimation was carried out and the patients were allowed home. They were readmitted after one, three, six, and nine months, so that profile blood glucose and 24-hour urinary glucose content could be estimated. Where a significant fall in blood glucose occurred, but satisfactory control of diabetes could not be achieved with glibenclamide alone, phenformin was added in a dose of 50 mg. once or twice daily. Combined therapy was necessary in 9 of the 30 patients. Haemoglobin, white cell and differential counts, platelet counts, prothrombin estimation, liver function tests, serum cholesterol, blood urea, and serum proteins were estimated before the drug was begun and then weekly for four weeks, and subsequently after three, six and nine months.

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Results

Assessment of the efficacy of the drug was based on the effects it had on the blood sugar and on the 24-hour excretion of glucose. Control of diabetes was regarded as excellent when two-hour postprandial blood glucose levels were 130 mg./100 ml. or less, good when 130 to 150 mg., fair when 150 to 180 mg., and poor when mean postprandial blood sugars were over 180 mg. (Müller *et al.*, 1969).

Using these criteria on the 30 patients investigated, control was excellent in 12, good in 8, fair in 5, and poor in 5 (Table I). In one of the latter, a patient who had previously been on insulin for several years, the drug had no demonstrable hypoglycaemic effect and was discontinued after one month. Glibenclamide, not unexpectedly, was far more effective in recently diagnosed and previously untreated diabetics than in those in whom other hypoglycaemic agents had been previously tried unsuccessfully.

TABLE I.—*Degree of Clinical Control of Diabetes Mellitus with Glibenclamide in Recently Diagnosed Diabetics and in Those Previously Treated by Other Hypoglycaemic Agents*

Postprandial Blood Sugar Values	New Diabetic Patients	Patients Previously Treated
..130mg./100ml. (excellent control)	10	2
130-150mg./100ml. (good control)	2	6
150-180mg./100ml. (fair control) ..	2	3
·180mg./100ml. (poor control) ..	0	5

Glibenclamide was always given in a single daily dose with breakfast. The blood glucose profiles in the patients when on diet alone and when the optimal dosage of glibenclamide was reached are shown in Fig. 1. It is seen that the drug exerts its hypoglycaemic effects evenly over the 24 hours, and both the midnight and early morning blood glucose levels are strictly comparable to those at other times of the day.

Mean 24-hour glucose levels before treatment was begun and when optimal dosage was reached, are shown in Table II. While the amount of glucose in the urine varied with the