A CLINICAL EVALUATION OF GLIBENCLAMIDE (HB 419, "DAONIL") A NEW ANTIDIABETIC SULPHONYLUREA

By J. S. Cheah

SYNOPSIS

Twenty-eight cases of adult-onset diabetes mellitus (23 males, 5 females; mean age 46.5 years) were treated with glibenclamide (HB 419, "Daonil"), a new oral hypoglycaemic sulphonylurea, for 6 months. Fourteen were of normal weight, 13 were overweight and one was underweight. The average daily dose was 11.4 mg. while the range was 5 to 20 mg. Satisfactory control (relief of symptoms and glycosuria, a fasting and 2-hour postprandial blood sugar levels of 200 mg. or less per 100 ml.) was achieved in 26 cases (89.3%). Hypoglycaemic spells occurred in 3 patients. There were no haematological, hepatic or renal complications during 672 patient-weeks of glibenclamide therapy. It is concluded that glibenclamide is an effective sulphonylurea in the treatment of adult-onset diabetes; its long-term safety remains to be tested. Its advantages are that it is potent and effective and comes in small palatable tablets and it does not cause unpleasant flushing when taken with alcohol. Its disadvantages are its tendency to cause spells of hypoglycaemia in the late morning and it is more expensive than the other sulphonylureas.

Glibenclamide (HB 419, "Daonil"), a new hypoglycaemic sulphonylurea, was developed jointly at the laboratories of Farbwerke Hoechst AG and Boehringer Mannheim GmbH, Germany (Aumuller *et al*, 1966). Its formula, compared to tolbutamide, is shown in Fig. 1, and chemically it is N-4-[β-(5-chloro-2-methosybenzamido)-ethyl]-phenylsulphonyl-N'-cyclohexylurea. It is about

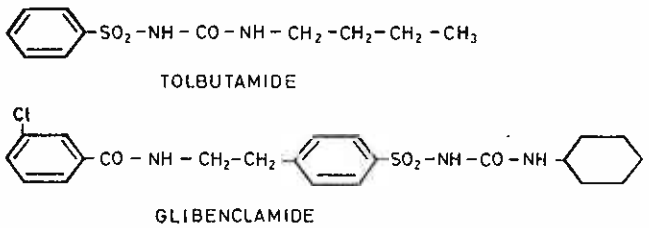

Fig. 1. Structural formula of Glibenclamide (HB 419, "Daonil") as compared to that of Tolbutamide.

250 to 500 times more potent than tolbutamide. Like tolbutamide, it acts by stimulation of the β-cells of the pancreas and has no action in the depancreatectomised dog (Bander *et al*, 1969; Loubatieres *et al*, 1969). Grodsky, Curry and Bennett (1969) has shown that, like tolbutamide, it acts primarily on the release of stored insulin and not on the synthesis of insulin. It is readily absorbed after oral administration, reaches a peak blood level in about 4 hours and has a half-life of about 5 hours (Christ, Heptner and Rupp, 1969). Several short-term trials of its use in the treatment of adult-onset or mild diabetes have shown that it is effective, potent and has no effect on the haematological ,hepatorenal systems and thyroid function (Tegernsee conference, 1969; Martin, Mills and Breidhal, 1969; Davidson *et al*, 1970). Its long-term safety remains to be evaluated (Lancet, 1971). This paper describes our initial experience of the use of glibenclamide.

PATIENTS AND METHODS

Twenty-eight diabetics (15 Chinese, 6 Malays, 4 Indians and 3 Eurasians; 23 males and 5 females) entered the trial. Their mean age was 46·5 years and the age range was 18 to 66 years. Fourteen were of normal weight (normal weight is defined as ±10% of ideal weight; the ideal weight table was that of McFadzean and Yeung, 1968), 13 were

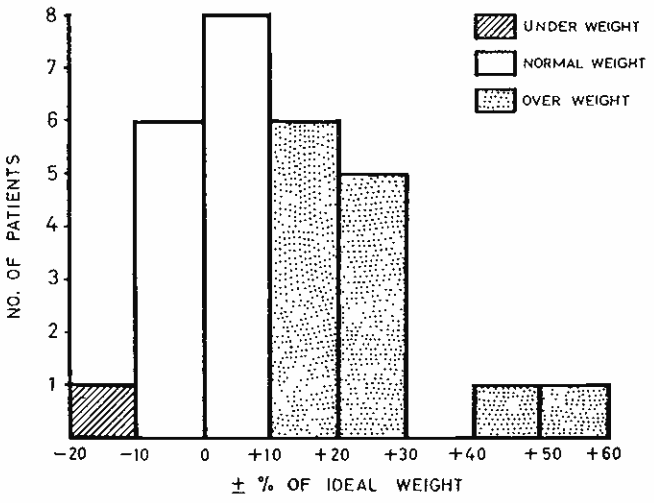

Fig. 2. Weight distribution in the 28 patients in the trail.

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overweight while one was underweight (Fig. 2). The duration of diabetes (from onset of symptoms to time of trial) was less than one year in 18 cases; one to five years in 8 cases and more than 5 years in 2 cases. Ketoacidosis was absent in all the cases. Eight patients had received no previous therapy; 2 were on insulin while the rest were on oral hypoglycaemic therapy (Table I).

TABLE I

PREVIOUS THERAPY OF THE 28 PATIENTS IN THE TRIAL

PREVIOUS THERAPY	NO. OF CASES
NIL	8
GLYCODIAZINE	12
GLYCODIAZINE AND TOLBUTAMIDE	5
INSULIN	2
TOLBUTAMIDE	1
ALL CASES	28

The following investigations were determined before and at the end of glibenclamide treatment: haemoglobin level, leucocyte and platelet counts, total protein in urine, urine microscopy, blood urea, serum cholesterol, serum uric acid, serum bilirubin, serum alkaline phosphatase, serum glutamic-oxaloacetic transaminase and serum glutamic-pyruvic transaminase.

All patients were treated as outpatients and were instructed to take about 100 gm. carbohydrate in their daily diet; those who were of normal weight were instructed to take about 1,500 calories daily while the daily calories were adjusted accordingly in those who were overweight or underweight.

All cases had an oral glucose tolerance test before the start of glibenclamide treatment; during treatment the fasting and 2-hour postprandial blood sugar were done on several occasions. The blood sugar was done using capillary blood by the method of Asatoor and King (1954).

Glibenclamide treatment was started in a dose of 2·5 to 5·0 mg. (one tablet contains 5 mg.) with or just after breakfast. The dose was increased by 2·5 to 5 mg. weekly till satisfactory control was achieved or till a maximum dose of 20 mg. Where the dose was greater than 10 mg., it was given in 2 divided doses, the second dose was given with a late afternoon tea. All the patients tested their urine for sugar 2 to 4 times daily.

Control was assessed as follows: good, when symptoms were relieved, glycosuria was usually absent, the weight approached normality and the fasting and 2-hour postprandial blood levels were 150 mg. or less per 100 ml.; fair, when symptoms were relieved, glycosuria was often absent and the fasting and 2-hour postprandial blood sugar levels were 200 mg. or less per 100 ml. and poor (unsatisfactory) when symptoms were little relieved, glycosuria was usually present and the fasting and 2-hour postprandial blood sugar levels were more than 200 mg. per 100 ml. Fair and good control were regarded as satisfactory.

Initially patients were seen at weekly intervals and later at longer intervals. All the patients were treated with glibenclamide for 6 months.

RESULTS

Good control was achieved in 14 cases (50·0%); fair control in 11 cases (39·3%) and poor (unsatisfactory) control in 3 cases (10·7%). Thus satisfactory (good and fair) control was achieved in 26 cases (89·3%). The mean daily dose in the good, fair and poor control groups was 8·6, 15·0 and 18·3 mg. respectively (Table II). The dosage distribution is shown in Fig. 3.

TABLE II

TYPE OF CONTROL AND MEAN DAILY DOSAGE IN EACH CONTROL GROUP

RESULT OF THERAPY	NO. OF CASES	%	MEAN DOSE IN MG. DAILY
GOOD CONTROL	14	50·0	8·6
FAIR CONTROL	11	39·3	15·0
POOR CONTROL	3	10·7	18·3
ALL CASES	28	100·0	11·4

The mean fasting blood sugar before treatment was 223 mg.; on glibenclamide it fell to 119·0 mg. per 100 ml. The mean 2-hour postprandial blood sugar before and on glibenclamide was 315·6 and 161·3 mg. per 100 ml. (Fig. 4 and Table III). The fall in blood sugar levels was higher in those with good and fair control than in those with poor control (Table III).

Three patients experienced spells of hypoglycaemia; with reduction in the dosage of glibenclamide these spells did not recur. Two patients complained of uncomfortable hunger after glibenclamide in the initial 2 weeks of therapy; this discomfort disappeared after 2 weeks.

The following investigations were not altered significantly after 6 months of glibenclamide

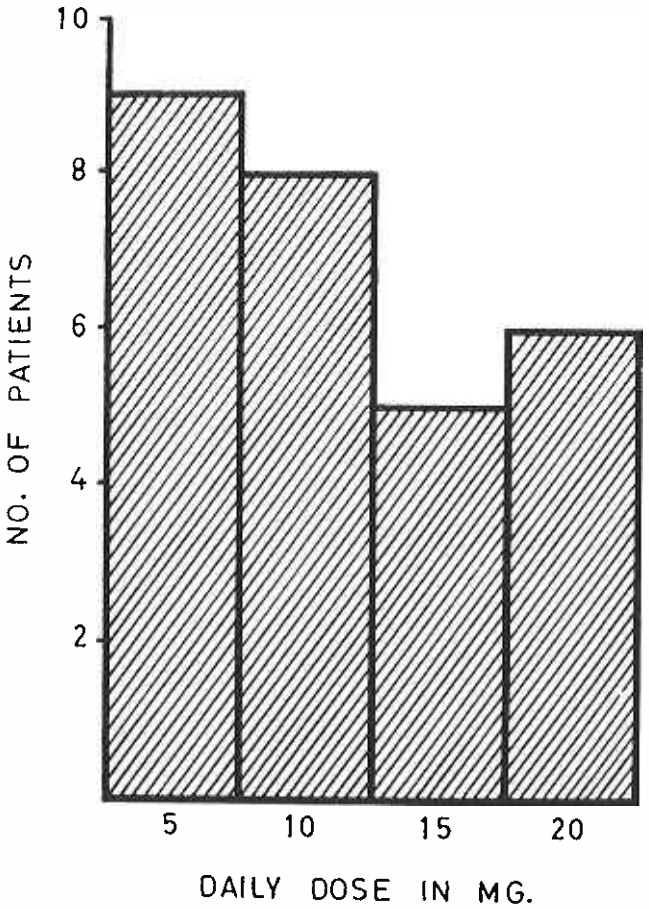

Fig. 3. Distribution of the daily dosage in the 28 patients.

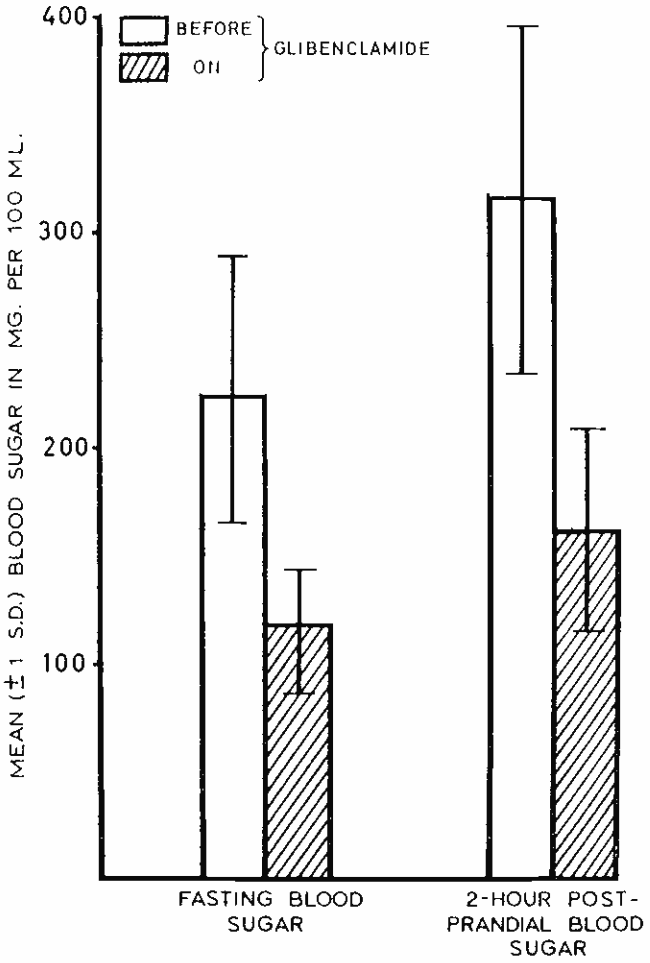

Fig. 4. The mean (± a standard deviation) of the fasting and 2-hour postprandial blood sugar before and while on glibenclamide.

TABLE III

THE FALL IN THE FASTING AND 2-HOUR POSTPRANDIAL BLOOD SUGAR ACHIEVED BY GLIBENCLAMIDE TREATMENT

RESULT OF THERAPY	NO. OF CASES	MEAN FASTING BLOOD SUGAR				MEAN 2-HOUR POSTPRANDIAL BLOOD SUGAR			
		BEFORE DAONIL* IN MG PER 100 ML.	AFTER DAONIL* IN MG PER 100 ML.	FALL IN MG PER 100 ML.	% FALL	BEFORE DAONIL* IN MG PER 100 ML.	AFTER DAONIL* IN MG PER 100 ML.	FALL IN MG PER 100 ML.	% FALL
GOOD CONTROL	14	230·6	111·4	119·2	51·7	314·6	125·5	189·1	60·0
FAIR CONTROL	11	208·0	117·1	90·9	43·7	302·5	180·3	122·2	40·4
POOR CONTROL	3	244·7	161·3	83·4	34·1	401·7	257·7	144·0	35·9
ALL CASES	28	223·2	119·0	104·2	46·7	315·6	161·3	154·3	48·9

* GLIBENCLAMIDE (HB 419; "DAONIL").

treatment: haemoglobin level, leucocyte and platelet counts, total urinary protein, urinary microscopy, blood urea, serum uric acid, serum bilirubin, serum alkaline phosphatase, serum glutamic-oxaloacetic transaminase and serum glutamic-pyruvic transaminase. The mean (± a standard deviation) serum cholesterol before and after glibenclamide was 238·3 (±38·2) and 215·6 (±46·2) mg. per 100 ml. This fall is significant ($p<0·05$) and is probably a reflection of the improvement of the diabetic state.

Two patients had consumed alcohol on many occasions after glibenclamide; there were no episodes of unpleasant flushing.

DISCUSSIONS

In this short-term trial, satisfactory (good and fair) control was achieved in 25 (89·3%) out of 28 patients. Using similar criteria, Martin, Mills and Briedahl (1969) reported satisfactory control in 80% of 75 patients. From the Tegernsee conference (1969) it appears that glibenclamide is very effective in previously untreated maturity-onset diabetics and for those patients that were well controlled with other oral hypoglycaemic drugs. In those that were poorly controlled with other hypoglycaemic drugs, glibenclamide was effective in only a minority of patients.

Muller *et al* (1969), in summarising the clinical result of glibenclamide treatment in 5,053 patients, found that 5 mg. of glibenclamide is approximately equivalent to 1,000 mg. of tolbutamide or 250 mg. of chlorpropamide. Side-effects which necessitated discontinuation of the drug occurred in 1·5% Gastrointestinal upset (nausea, anorexia or sensations of fullness or pressure) were noticed in 0·5%. Allergic skin reactions were seen in 0·5%. No adverse effects on the blood picture, serum enzymes, hepatic and renal functions were reported.

Three of the patients in this series experienced spells of hypoglycaemia: this is a reflection of the potency of the drug. Hypoglycaemia occurs usually in the late morning; to minimise this the drug should be taken during rather than after breakfast (Bloom, 1970).

So far, glibenclamide has not been reported to cause unpleasant flushing when alcohol is consumed at the same time, as may sometimes occur with chlorpropamide, tolbutamide and acetohexamide (Bloom, 1970).

Glibenclamide is more expensive than the other sulphonylureas (Bloom, 1970).

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