Over-all Therapeutic Usefulness of Glybenclamide, a New Hypoglycemic Sulfonylurea

Juan A. Rull, M.D., Heliodoro Gonzalez-Millan, M.D., Ricardo Quibrera, M.D., Mariano Garcia-Viveros, M.D., and Oscar Lozano-Castaneda, M.D., México, D.F.

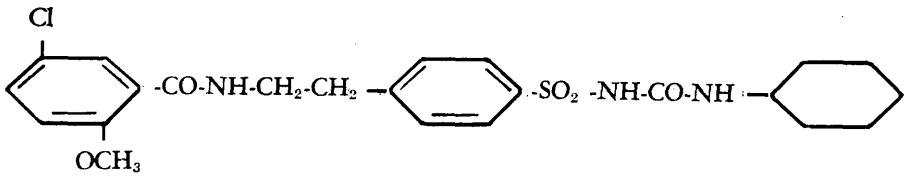
SUMMARY

The over-all therapeutic usefulness of glybenclamide, a new derivative of the hypoglycemic sulfonylureas, was studied in 116 diabetics of all types.

Glybenclamide appears to be a very potent hypoglycemic drug without serious toxicity on short-term trial but its clinical spectrum is similar to that of previously known hypoglycemic sulfonamides. DIABETES *19*:264-70, April, 1970.

A modification of the experimental design recommended by the Committee on the Use of Therapeutic Agents of the American Diabetes Association for the evaluation of new drugs was utilized to study the over-all therapeutic usefulness of glybenclamide.[1]

This drug, N-(4-(4 beta < 2-methoxy-5 chloro-benzamido > ethyl)-benzosulphonyl)-n-ciclohexyl-urea, is a derivative of the hypoglycemic sulfonamides with the structural formula shown on this page.



Glybenclamide is a sulfonylurea and its mechanism of action is similar to that of the other drugs of this group. Extensive studies in animals and normal human subjects have shown that its hypoglycemic effect is several hundred times that of tolbutamide on a mg. per mg. basis. In normal subjects, a 2-mg. oral dose produces a maximal (30 per cent) blood sugar decrease at two hours with a duration of eight hours. Increases of the dose to 5 and 10 mg. are followed by a stronger hypoglycemic effect (40 per cent) and a longer duration of action (twelve hours), but further acute increases have not been related to predictable modifications of hypoglycemic action. No serious toxic manifestations have been found during animal or human studies.[2-6]

From the Diabetes Clinic, Instituto Nacional de la Nutrición, Dr. Jimenez #261, México 7, D.F.

MATERIAL AND METHODS

The present clinical evaluation was conducted in 116 diabetic patients distributed into five groups. The patients were selected from the Outpatient Department of the Diabetes Clinic of the Instituto Nacional de la Nutrición, a nonprofit autonomous federal hospital affiliated with the Universidad Nacional Autonóma de México. Most of the patients belonged to the low and middle-income groups of Mexico City. At the time of selection no acute intercurrent illnesses were present, but concomitant chronic diseases or diabetic complications (arteriosclerosis, urinary tract infections, chronic cholecystitis and cirrhosis) were not a cause of exclusion. All had received dietary instruction prior to their inclusion in the study and had been placed on a diet calculated to attain or maintain their ideal weight. Adherence to diet was insisted upon at every visit.

Group I (table 1) consisted of twenty-four maturity-onset, ketosis-resistant, previously untreated patients. Most patients were or had been obese, and the duration of known diabetes was less than one year in eighteen. All of them had received dietary treatment without

TABLE 1

Clinical characteristics of the patients

Group	Number	Age mean and range	Weight above	Weight ideal	Weight under	Diabetes duration mean and range
I	24	45 years (27-72)	9	11	4	2 years (1 month-10 years)
II	23	54 years (36-70)	16	3	4	7 years (1-14 years)
III	19	52 years (38-88)	7	1	11	9 years (3-18 years)
IV	13	57 years (37-84)	2	5	6	10 years (1 month-20 years)
V	37	32 years (12-60)	9	10	18	5 years (2 months-20 years)

achieving metabolic control, but only some (ten) could be judged "failures" (table 2) to diet therapy. These patients were distributed to one of the following programs (figure 1): glybenclamide-placebo-glybenclamide (Subgroup A) or placebo-glybenclamide-placebo (Subgroup B). A certain degree of bias was introduced in distribution since most of the patients started on placebo were the ones with the better control on diet alone. Each drug or placebo period had a two-month duration. Patients were started on one tablet of placebo or glybenclamide (5 mg. per tablet) given in a single daily dose and increments or reductions were made whenever necessary or possible. The placebo and glybenclamide tablets were identical and the number of tablets was matched when possible.

TABLE 2

Standards utilized for evaluation of results

Degree of control	Fasting blood sugar mg./100 ml.	2-hr. p.p. blood sugar* mg./100 ml.	24-hr. glycosuria gm.
Excellent	<110	<130	0
Good	110-129	130-149	Traces-9
Fair	130-149	150-179	10-19
Poor	150-219	180-249	20-39
Failure	>220	>250	>40

*Two-hour postprandial blood sugar.

Group II (table 1) included twenty-three maturity-onset, ketosis-resistant diabetics under treatment with sulfonylureas: eight were receiving tolbutamide, six chlorpropamide, five tolazamide and four acetohexamide. Two were under excellent control (table 2), nine were under good control, four under fair control and eight were under poor control (this evaluation was done while the patients were taking the indicated sulfonylureas before entering the trial). These patients were randomly placed on one of the following programs (figure 1): placebo-glybenclamide-placebo-previous sulfonylurea (Subgroup A) or placebo-previous sulfonylurea-placebo-glybenclamide (Subgroup B). Each drug period had a three-month duration and each

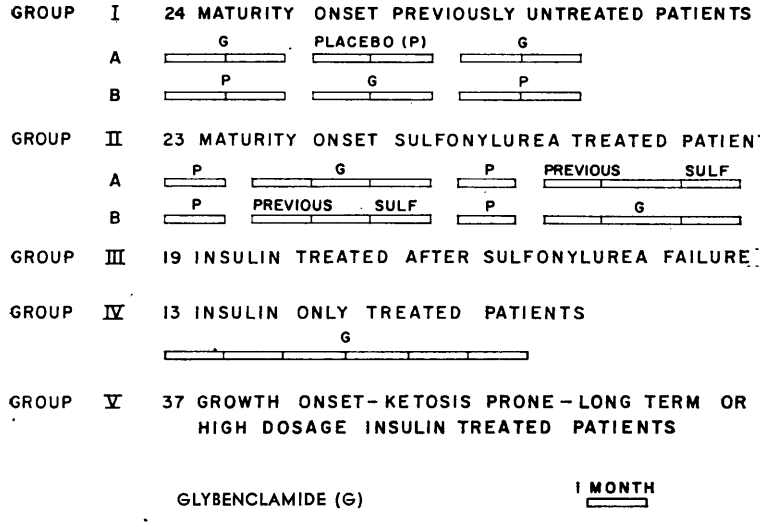


FIG. 1. Experimental design.

placebo period lasted one month. The mean drug dosage in this group was 2.5 gm. of tolbutamide, 2 gm. of acetohexamide, 0.75 gm. of tolazamide, 0.5 gm. of chlorpropamide and 1.5 mg. of glybenclamide.

Group III (table 1) was formed with nineteen diabetics treated with insulin after previous primary or secondary failures to oral treatment. All of them were on less than 30 U. of insulin, but seven had been diabetic for more than ten years and control was poor in eleven (table 2). Insulin was abruptly stopped and glybenclamide was given for six months (figure 1). Initially, most of them were placed on 30 or 45 mg. but after two months the doses were uniformly reduced to 15 mg.

Group IV (table 1) included thirteen insulin-treated patients who had never received a trial of oral treatment. All were on less than 35 U. of insulin, but seven had been diabetic for more than ten years and control was poor in seven (table 2). These patients were treated in the same way as those in Group III (figure 1).

Group V (table 1) was formed with thirty-seven miscellaneous patients who were not candidates for oral treatment. They included growth-onset cases, ketosis-prone adults and insulin-treated patients with insulin requirements in excess of 35 U. or duration of treatment of more than fifteen years. Insulin was discontinued under close supervision (daily contact with one of the senior members of the Clinic staff) and the trial was ended as soon as warranted by the clinical or laboratory findings. In many cases, glybenclamide was given only for a few hours or days.

Patients were seen at least every two weeks during the first two months and then at monthly intervals with determination of fasting blood sugar levels and a twenty-four-hour urine sugar. Every three months in Groups III, IV and V or at every therapeutic change in Groups I and II the following tests were performed: fasting and two-hour postprandial blood sugar level (Hoffman, AutoAnalyzer, whole blood), twenty-four-hour sugar excretion (Nelson-Somogyi), urinalysis, urea (Ormsby), creatinine (Folin), cholesterol (Leppanen), complete blood and platelet counts, bromosuphalein retention (Rosenthal and White), bilirubins (Sepulveda and Osterberg), alkaline phosphatase (Bodansky), glutamic pyruvic transaminase (Reitman and Franckel) and thymol turbidity test (Maclagan).

In Group I, every patient had ten fasting, four postprandial blood sugars and ten twenty-four-hour urine sugar tests; in Group II, eleven fasting, four postprandial blood sugars and eleven twenty-four-hour urine sugar tests; in Groups III and IV, eight fasting, three postprandial and eight twenty-four-hour urine sugar tests.

Results were evaluated by comparing the mean blood sugar levels and mean sugar excretions at the end of each experimental period and by assessing the control status of each patient at the end of the trial. Individual degree of control was determined according to the standards indicated in table 2. When the three measurements fell in different degrees of control, the middle one or the one with two out of three values in it was chosen. In Group II, comparison between glybenclamide and the other drugs was done only with the data referring to the experimental periods.

RESULTS

The hypoglycemic effect of glybenclamide can be seen in Group I (figure 2). In subgroup A, which first

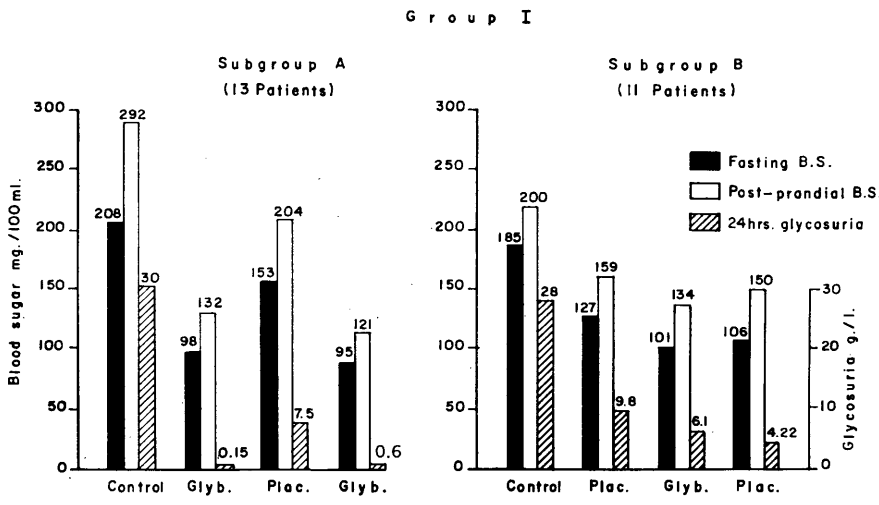


FIG. 2. Mean levels of fasting blood sugar, two-hour postprandial blood sugar and twenty-four-hour urine sugar at the end of each experimental period in Group I (previously untreated patients).

received the active drug, the mean fasting blood sugar, two-hour postprandial and twenty-four-hour urine sugar were close to normal limits after two months of treatment. Substitution of glybenclamide by placebo was followed by a deterioration of all variables measured, although the absolute values were lower than the control figures. On resumption of the active drug, improvement was again observed with almost complete normalization of the mean fasting and postprandial blood sugars. In Subgroup B, the differences between the placebo and drug periods were less pronounced, but the pattern of response was similar and glybenclamide produced improvement of control which was followed by a slight deterioration after substitution by placebo.

In Group II (figure 3) the mean fasting and two-hour postprandial blood sugars and twenty-four-hour urine sugar showed significant decreases during each glybenclamide or "previous sulfonylurea" period. It can be seen that, in both subgroups, the sulfonylurea, glybenclamide or previous drug, given in second term had a stronger hypoglycemic effect.

In Groups III and IV (figure 4) the mean fasting and two-hour postprandial blood sugars and the twenty-four-hour urine sugar failed to show any significant hypoglycemic action of the drug throughout the study. Moreover a slight but progressive deterioration of control was clearly seen in Group III.

All patients but two from Group V were failures and they had to be changed to insulin without completing the trial period. The two successes were obtained in two ketosis-prone, thin, maturity-onset diabetics, never treated previously, who achieved fair control on high doses of glybenclamide (45 and 60 mg.).

In Group I, individual evaluation (table 3) revealed that twenty patients (83.2 per cent) achieved excellent or good control and no failures were observed. The mean glybenclamide requirement was 5 mg.: one patient

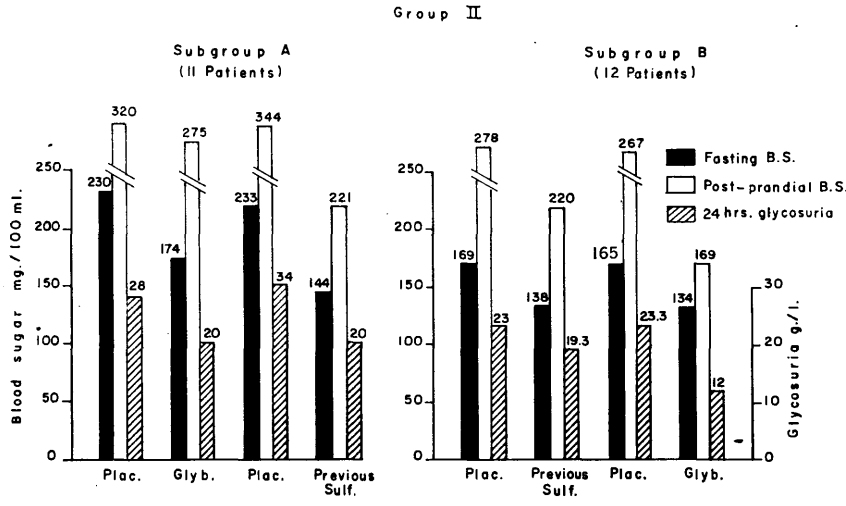


FIG. 3. Mean levels of fasting blood sugar, two-hour postprandial blood sugar and twenty-four-hour urine sugar at the end of each experimental period in Group II (patients previously under treatment with sulfonylureas).

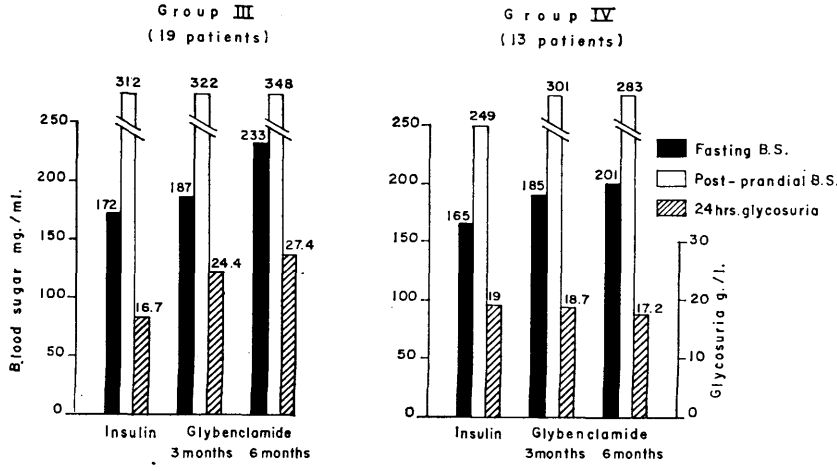


FIG. 4. Mean levels of fasting blood sugar, two-hour postprandial blood sugar and twenty-four-hour urine sugar after three and six months in Groups III and IV (patients previously under treatment with insulin).

TABLE 3

Over-all individual results at the end of the glybenclamide periods

Group	I	II	III	IV	Total
Number of cases	24*	23*	19	13	79
Excellent	16 (66.6)†	4 (17.3)	3 (15.8)	2 (15.4)	25 (31.6)
Good	4 (16.6)	6 (26.0)	0 (0)	2 (15.4)	12 (15.2)
Fair	4 (16.6)	4 (17.4)	1 (5.3)	0 (0)	9 (11.3)
Poor	0 (0)	5 (21.7)	4 (21.0)	4 (30.7)	13 (16.4)
Failure	0 (0)	4 (17.4)	11 (57.9)	5 (38.5)	20 (25.3)
Glybenclamide (mean dose)	5 mg.	15 mg.	15 mg.	15 mg.	

*Combination of results in Subgroups A and B.
†Percentage.

was controlled with less than 2.5; eight with 2.5, twelve with 5 mg. and only three required more than 5 mg. in divided doses.

In Group II, fourteen patients, 60.6 per cent, reached excellent, good or fair compensation while five were poorly controlled and four were failures (table 3). Two patients improved their therapeutic classification when on glybenclamide as compared to the previous sulfonylurea (table 4). The mean glybenclamide requirement was 15 mg. given in three daily doses: only five patients received less than 15 mg. (10 or 5 mg.) and one more (30 mg.).

In Group III, only four out of nineteen patients, 21.9 per cent, achieved sufficient control, three of them with excellent compensation (table 3). Results were similar in Group IV, where four patients out of thirteen, 30.8 per cent, reached excellent or good control. In both groups, the patients who eventually reached satisfactory compensation were the better candidates for oral treatment, i.e., those with the shorter duration of diabetes and with the best control on the lowest doses of insulin. Nevertheless, two of the successes in Groups III and IV reached a better control with glybenclamide than the one they had with insulin. Although high doses of glybenclamide were initially given, after one month all subjects in Groups III and IV were kept on 15 mg. given in three daily doses. As already stated, in Group V, all patients but two were failures. Changes in mean total serum cholesterol and mean body weight were unremarkable.

In one case transient relative neutropenia, probably related to a viral infection, was observed, but otherwise no instances of hematologic toxicity were seen. Although several patients with abnormal control tests of hepatic function and three with well-established liver cirrhosis were included in the study, no further serious abnormalities and no deterioration of previous anomalies were detected. Several patients presented elevations of alkaline phosphatase; however, these changes were transient and they subsided in spite of glybenclamide continuation (table 5). Furthermore, alkaline phosphatase elevations were also seen during placebo administration and they appeared to be related to exacerbations of urinary tract infections. A number of acute exacerbations of urinary infections were seen but no renal function deterioration associated with the drug could be documented.

Mild postprandial hypoglycemia was frequently observed, especially in Group I, but in Group II the frequency and degree of postprandial hypoglycemia was the same with glybenclamide and with previous sulfonylureas. Two patients presented an erythematous rash that disappeared without treatment in spite of glybenclamide continuation. Otherwise, transient and mild digestive complaints in subjects taking high doses

TABLE 4

Comparison of results obtained with glybenclamide and previous sulfonylureas in Group II

Degree of control	Glybenclamide number	Glybenclamide per cent	Previous sulfonylureas number	Previous sulfonylureas per cent
Excellent	4	17.3	4	17.3
Good	6	26.0	4	17.3
Fair	4	17.3	4	17.3
Poor	5	21.7	7	30.4
Failure	4	17.3	4	17.3

TABLE 5

Alkaline phosphatase levels during control, placebo and drug periods. Mean and standard deviation.

Group		Control	Study			
I	A	3.3 ±1.2	Glybenclamide 3.4 ±1.4	Placebo 3.2 ±1.8	Glybenclamide 3.1 ±1.3	
	B	3.0 ±1.2	Placebo 2.7 ±1.0	Glybenclamide 2.9 ±0.8	Placebo 2.5 ±1.0	
II	A		Placebo 4.9 ±1.8	Glybenclamide 3.7 ±1.7	Placebo 3.6 ±1.3	Previous sulfonylurea 3.3 ±1.6
	B		Placebo 5.2 ±3.5	Previous sulfonylurea 4.7 ±2.0	Placebo 3.9 ±2.0	Glybenclamide 3.8 ±2.2
III		4.3 ±1.5	Glybenclamide	3 Months 4.9 ±2.1	6 Months 4.8 ±2.3	
IV		5.0 ±2.2	Glybenclamide	3 Months 5.5 ±3.5	6 Months 4.8 ±2.7	

In Group V only 2 patients completed six months of trial.

(more than 30 mg.) were the only remarkable side effects.

DISCUSSION

Although the recommendations of the Committee on the Use of Therapeutic Agents of the American Diabetes Association are exacting, they were almost completely fulfilled in this study.

In Group I, designed to evaluate the effect of the drug on ideal candidates to oral treatment, the hypoglycemic action of glybenclamide was clearly shown by the different results obtained during the alternating placebo and drug periods in the two sequences. The high rate of excellent and good results and the absence of failures were only to be expected in this type of patient. The same can be said about the frequency of postprandial hypoglycemia and the low requirements of the drug.

Comparison of glybenclamide with other sulfonylureas, as done in Group II, proves that it is a far more potent drug on an mg. per mg. basis, but the over-all results were similar to those obtained with previously known hypoglycemic sulfonamides (table 4). In reference to better results obtained with the sulfonylurea given in second term, glybenclamide or previous drug, during the experimental periods, they probably reflect a residual action of the sulfonylurea given first in spite of the placebo period. This observation must be emphasized since usually all the reported comparative studies follow a single experimental sequence where the drug under study is given in second term. In this trial, most patients received only three tablets of glybenclamide while they took an average of two, three, four, and five tablets of chlorpropamide, tolazamide, acetohexamide and tolbutamide. Thus, from a practical point of view, it appears that the 5-mg. tablet of glybenclamide is more potent than the 0.5 gm. tablet of tolbutamide and acetohexamide, approximately equal to the 250-mg. tablet of tolazamide and slightly less effective than the 250-mg. tablet of chlorpropamide.

A small but significant percentage of insulin-treated patients in Groups III and IV could be controlled with glybenclamide, but this was also observed during earlier studies with two different sulfonamides.[7,8]

As could be expected patients from Group V were all failures with the two aforementioned exceptions, indicating that glybenclamide has a therapeutic spectrum similar to that of previously known hypoglycemic sulfonamides.

No serious hematological, hepatic or renal toxicity, attributable to the drug, was observed during this short-term trial and mild postprandial hypoglycemia was the only remarkable side effect. Surprisingly, a better correlation was found between alkaline phosphatase ele-

vations and urinary infections than with other manifestations of hepatic dysfunction.

From these results it can be concluded that glybenclamide is a potent hypoglycemic sulfonylurea, indeed the most potent of all known hypoglycemic sulfonamides on a mg. per mg. basis. No serious toxicity was apparent on short-term trial, though its clinical spectrum and side effects appear to be the same as those of previously known drugs from this group. It remains to be seen if its low dosage constitutes an asset in long-term treatment.

ACKNOWLEDGMENT

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