Effect of Glycodiazine on Blood Sugar in Diabetes Mellitus

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SUMMARY

Clinical trials were made with glycodiazine, N-(5(2-Methoxyethoxy)-2-Pyrimidinyl) benzenesulfonamide by a technic in which the effects of the drug were compared statistically to those of a placebo in a group of patients with the adult onset type of diabetes mellitus. Glycodiazine was active orally at two dosage levels 0.5 gm. b.i.d. and 0.5 gm. once a day although onset of antihyperglycemic response was slower with the smaller dose. No untoward side effects were noticed. The findings indicate that glycodiazine may be an effective oral antihyperglycemic agent. DIABETES *17*:509-12, August, 1968.

Glycodiazine, N-(5-(2-Methoxyethoxy)-2-Pyrimidinyl) benzenesulfonamide is an antihyperglycemic agent which was synthesized and studied initially in Europe.[1-3,5-10] A 2-sulfonamide-2-alkoxpyrimidine derivative, it differs structurally from both the sulfonylureas and the biguanides (figure 1). In two reported studies in humans glycodiazine has been given for one to two years.[2,6]

The mechanism of the blood sugar lowering action of glycodiazine is similar to that of the sulfonylurea drugs in that it is dependent on the presence of intact islets of Langerhans where it produces degranulation of the beta cells.[1-4] In humans and animals the maximal lowering of the blood sugar level is attained within thirty to sixty minutes after a single oral dose. The antihyperglycemic effect is dose-related, but not related to the route of administration. The maximum blood level of the drug measured after a single dose administered by mouth to humans is also dose-related, about 4 mg. per cent after 0.5 gm. and 15 mg. per cent after 2.0 gm.[5] The peak blood levels decrease by 50 per cent in about 3.8 hours.

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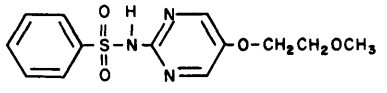
The present investigation was conducted to evaluate glycodiazine by a technic in which the effects of the drug were compared at two dosage levels to those of a placebo in a group of patients with the stable adult-onset type of diabetes.

METHODS

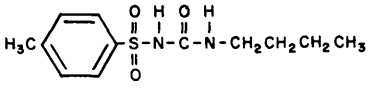
1. *Patients*

Nineteen patients with stable adult-onset type diabetes, admitted as consecutive new patients to the Diabetes Clinic of the Cincinnati General Hospital, agreed to participate. Two withdrew after the twenty-first week;



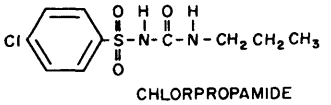
GLYCODIAZINE

N-[5-(2-METHOXYETHOXY)-2-PYRIMIDINYL] BENZENESULFONAMIDE



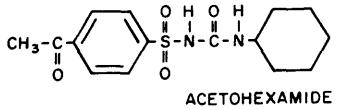
TOLBUTAMIDE

1-BUTYL-3-p-TOLYLSULFONYLUREA



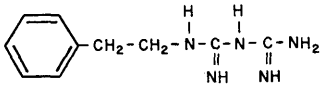
CHLORPROPAMIDE

1-(p-CHLOROPHENYLSULFONYL)-3-PROPYLUREA



ACETOHEXAMIDE

1-[(p-ACETYLPHENYL) SULFONYL] -3-CYCLOHEXYLUREA



PHENFORMIN

PHENETHYLDIGUANIDE

FIG. 1. Oral antihyperglycemic agents.

seventeen continued under observation until completion of the twenty-seven-week study. There were thirteen women and four men. The median age was fifty-six years (range thirty-two to sixty), median weight 171 lb. (range 130-225) and median duration of known diabetes eight months (range three months to twenty years). Nine patients had been treated previously with tolbutamide, one with insulin and seven with diet alone. These treatments were discontinued at least two weeks prior to the beginning of the study.

2. *General care*

The patients were seen in the Diabetes Clinic at planned intervals of two to four weeks. They were instructed to adhere to a prescribed diet of the food exchange type, usually of less than 1500 calories daily since most of the patients were obese. At each clinic visit blood was obtained approximately two hours after breakfast for determination of whole blood sugar in the AutoAnalyzer by a modification of the potassium ferricyanide method.[11] In addition, blood counts, blood urea nitrogen, alkaline phosphatase and glutamic oxaloacetic transaminase (SGOT) concentrations were determined at monthly intervals.

3. *Design of study*

The study was divided into four consecutive treatment periods:

I.	Control. Treatment with diet only	2 weeks
II.	Glycodiazine, 0.5 gm. before breakfast and before supper	12 weeks
III.	Placebo, 0.5 gm. before breakfast and before supper	5 weeks
IV.	Glycodiazine, 0.5 gm. before breakfast only	8 weeks

Blood sugar determinations were made during and at the end of each period. The same diet prescription was continued throughout the study.

4. *Analysis of data*

The mean blood sugar levels of the treatment periods were compared by variance analysis. Two-way classification was used so as to take into account the interaction introduced by the variation of mean levels between patients. The treatment period means were then tested for differences by the method of Tukey.[12] By this approach, it was possible to evaluate trends in mean glycemic levels during the course of the investigation.

RESULTS

1. *Blood sugar response to treatment*

The individual blood glucose concentrations and the mean blood glucose values for treatment periods are given in table 1. The mean treatment period blood sugars that differed significantly from any other mean treatment period blood sugars are shown in table 2. By use of the method of analysis cited previously the minimal significant differences between mean treatment period blood glucose levels for the .05 and .01 levels of probability were found to be 65 and 74 mg. per 100 ml. respectively.

In each of the two weeks of Period I, when diet therapy alone was used, the mean blood glucose levels were 251 and 250 mg. per 100 ml. During Period II, when the patients received glycodiazine 0.5 gm. twice daily in addition to diet, mean blood glucose levels declined significantly from the control levels to a range of 152 to 179 mg. per 100 ml. The decline became significant at less than the 0.01 level of probability at the end of the first week. In Period III, diet plus placebo, mean blood glucose levels rose significantly above those of Period II and were equivalent to those of Period I when no therapy other than diet was applied. Finally, in Period IV, with diet plus glycodiazine 0.5 gm. given before breakfast only, a significant decrease was seen again but not until the eighth week of treatment.

2. *Side effects*

At the end of the study the mean weight change was minus five pounds, and not significant statistically. No patients complained of symptoms suggesting hypoglycemia, and the lowest blood glucose observed during treatment with glycodiazine was 72 mg. per 100 ml. There were no complaints at any time of nausea, abdominal distress, rash, pruritus, diarrhea, dizziness, or palpitation. These complaints were looked for since they had been noted in other studies,[1,3,5,6,8] and they were encountered occasionally, but solely during the first two weeks of treatment, when the drug was given to a few other patients prior to the start of the study.

No changes were noted in serially performed determinations of blood counts, blood urea nitrogen, alkaline phosphatase and glutamic oxaloacetic transaminase although mild leukopenia and transient elevation of SGOT have previously been reported in man.[1,3,5,6]

DISCUSSION

The findings are in agreement with those of previous reports[1-10] and suggest that glycodiazine may be an effective antihyperglycemic agent in adult-onset diabetes.

TABLE 1

Blood sugar values

Patient's No.	Weeks																									
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
1	137	180	174	204		200				272				214	296		218		238		206		155		101		128
2	434	386	374	326		282				276				210	330		360		340		274		270		406		262
3	400	380	94	119		114				107				122	115		240		190		240		266		93		106
4	165	190	93	105		97				98				96	97		121		109		103		114		116		112
5	400	420	362	274		376				220				180	195		236		334		195		180		172		176
6	256	260	288	390		224				294				220	260		280		320		492		293		260		280
7	264	280	198	201		195				215				151	296		316		416		196		246		188		189
8	488	498	174	155		99				225				177	310		276		289		252		256		214		162
9	170	160	106	110		105				110				75	109		160		210		105		100		125		107
10	140	132	80	81		80				72				75	83		120		160		76		80		90		79
11	166	170	99	136		138				182				120	99		190		220		91		101		100		86
12	190	180	116	152		156				94				92	210		322		282		156		276		162		109
13	168	170	122	132		115				148				123	102		102		144		150		139		159		139
14	320	249	162	176		150				234				182	246		260		249		210		198		177		195
15	166	180	145	153		133				196				250	223		242		246		143		221		179		213
16	230	220	142	165		186				149				139	181		183		133		194		174		181		156
17	180	200	128	119		104				147				161	232		298		212		178		217		288		288
Mean	251	250	168	176		162				179				152	199		233		241		192		193		177		164
Std. dev. ±	114	107	90	83		77				70				53	85		70		83		96		68		82		66
Period	I					II											III								IV		
Treatment	Control					Glycodiazine 1 gm./d.											Placebo								Glycodiazine 0.5 gm./d.		

TABLE 2

Significant differences between mean blood sugars

Treatment	Week	I Control 1	2	II Glycodiazine 1.0 gm./d. 3	4	6	10	14	III Placebo 15	17	19	IV Glycodiazine 0.5 gm./d. 21	23	25	27
I Control	1			.01	.01	.01	.05	.01						.01	.01
	2			.01	.01	.01	.05	.01						.05	.01
II Glycodiazine 1.0 gm./d.	3									.05	.05				
	4										.05				
	6									.05	.01				
	10														
	14										.01				
III	15														
	17														.05
	19														.01
IV Glycodiazine 0.5 gm./d.	21														
	23														
	25														
	27														

It is active orally at two dosage levels, 0.5 gm. b.i.d. and 0.5 gm. once a day although onset of antihyperglycemic response in the present cases was slower with the smaller dose.

No untoward side effects were noted in this twenty-seven-week study. In chronic studies in rats no organic lesions have been found,[1] but when six to ten times the blood glucose lowering dose was given to dogs, hematologic changes (leukopenia and granulocytopenia) were seen in some animals.[1] Investigation for teratogenicity in rats and mice has revealed no malfunctions, but survival in the first week among newborn rats was lowered.[1] Long-term observations will be needed to evaluate further the safety of glycodiazine in man.

ACKNOWLEDGMENT

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Dietary Chromium and Eye Lesions

The series of investigations ending with the observation that trivalent chromium could prevent the impairment in glucose tolerance in rats fed a Torula yeast diet has been previously described (Nutrition Reviews *19*: 348, 1961). Further animal experiments, more strictly limiting the possibility of environmental contamination with chromium, have shown that chromium deficiency can also retard growth rate in the rat and lead to an increased mortality rate. These rats may have elevated fasting levels of serum glucose as well as glycosuria. These studies and others suggesting that the derangement in carbohydrate metabolism is related to a decreased responsiveness of tissue to insulin have recently been reviewed by W. Mertz (Fed. Proc. 26:186, 1967).

E. Roginski and Mertz (J. Nutrition 93:249, 1967) have now reported on the induction of corneal opacities in rats raised from weaning on a diet low in chromium (less than 100 p.p.b.). Animals were raised in individual plastic cages covered with vented plastic boards and watered with triple-distilled, deionized water. The diet, a 10 per cent soy protein ration, provided adequate quantities of known nutrients; the chromium supplemented control group received 2 p.p.m. of chromium in the drinking water. All animals were observed at weekly intervals and eye changes were verified with the use of an ophthalmoscope.

Six separate experiments, each lasting ten weeks, were carried out; in all, sixty deficient and forty-five control animals were studied. Among the deficient animals evidence of loss of corneal luster appeared after two to three weeks. In some animals this further developed into a stage characterized by iridal vascular congestion. Ten of the sixty chromium deficient rats ultimately developed corneal opacities.

These fully developed lesions were not reversible by chromium administration nor were they prevented by additional vitamin A in the diets of deficient animals. Opacities were not seen in the chromium supplemented group. That the low protein content of the diets utilized in these studies was a contributing factor to the corneal lesion was suggested by the comment that opacities have been only rarely observed in rats consuming a 30 per cent Torula yeast ration of comparably low chromium content.

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