There was no objective evidence of improvement in the treated or control group as a whole when simple tests of lung function were used. The proportion of individuals showing such improvement was the same in both groups.

Although a higher proportion of patients in the treated group claimed relief from their dyspnoea, a more careful examination of their symptoms suggests that they were moved by gratitude rather than fact.

We think it highly unlikely that the short course of breathing exercises used in this trial is of benefit.

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Glycodiazine in Diabetes Mellitus: a Clinical Trial

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Glycodiazine is the first of the sulphonamidopyrimidines, a new group of orally effective hypoglycaemic drugs, to undergo clinical trial for the treatment of diabetes mellitus. This compound, 2-benzenesulphonamido-5(β-methoxy-ethoxy)-pyrimidine, was selected from a large number of related substances synthesized by Gutsche *et al.* (1964) because it showed potent hypoglycaemic activity in animal experiments. Structurally it somewhat resembles tolbutamide (see Formulae), the chief difference being the incorporation of a pyrimidine ring in place of the urea group. Glycodiazine is also similar to the sulphonylureas in that its blood-sugar-lowering effect depends upon the presence of functioning beta-cell pancreatic islet tissue (Kramer *et al.*, 1964).

Structural formulae of glycodiazine and tolbutamide.

Glycodiazine has now been under clinical trial in Germany and Austria for over three years, and the reports of its use (Leubner, 1964; Robbers *et al.*, 1964; Gutsche and Boenicke, 1964; Bernhard, 1964) have been sufficiently encouraging to justify more widespread trial. This paper presents the results of

treatment with glycodiazine of a small number of carefully observed diabetic patients for periods of up to 14 months.

Patients

Diabetic clinic patients were admitted to the trial during a period of one year. They were chosen if oral hypoglycaemic therapy was indicated, unless they were already satisfactorily controlled on another preparation. Thirteen were newly diagnosed diabetics, 10 had had diabetes for periods ranging from 8 months to 14 years, but control on diet alone or other oral hypoglycaemic agents was unsatisfactory, and two were satisfactorily controlled on insulin. One of these last two patients was taking only 12 units of insulin zinc suspension daily, and although the other was taking 44 units of insulin she had previously been well controlled on tolbutamide. Of the 25 patients 13 were men and 12 women. Their ages ranged from 34 to 74 years; one was under 40, six were 40 to 49, five were 50 to 59, and 13 were 60 and over. Only two patients were more than 10% above standard weight for height, sex, and age (Australian Institute of Anatomy, 1957).

At least four weeks before entering the trial all patients were prescribed a diabetic diet with specific daily allowance of carbohydrate. Glycodiazine treatment was initiated with a dose of 0.5 g. daily taken before breakfast, or 0.5 g. twice daily taken before breakfast and before the evening meal. When necessary the dose was increased to 0.5 g. thrice daily by adding a tablet before the mid-day meal. After three to six months' treatment with glycodiazine the patients were changed to a placebo preparation for at least four weeks. At a different time they were given tolbutamide for a month, the dosage of the latter being the same as the maintenance dose of glycodiazine for that patient.

The patients attended the clinic weekly for the first month, fortnightly for the second month, and thereafter every four weeks. At each visit to the clinic blood was taken from the fasting patients for determination of glucose (Hagedorn and

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Jansen method), urea, uric acid, alkaline phosphatase, and transaminase levels, and for a full blood count. Urine test charts were also examined to detect variations in diabetic control. Diabetic control was assessed according to the fasting blood-glucose-concentration as excellent (less than 100 mg./100 ml.), good (100–120 mg./100 ml.), fair (120–140 mg./100 ml.), or poor (more than 140 mg./100 ml.).

Results

The 25 patients have been taking glycodiazine for a total of 703 weeks. The longest period any patient has been taking the drug is 59 weeks; three others have been taking it for at least 52 weeks, six more for at least 39 weeks, and three more for at least 26 weeks. The shortest period of treatment which has been assessed is six weeks. Three patients left the trial within a month of starting on glycodiazine. One died suddenly, one new patient failed to attend the clinic regularly, and the third, who had previously been treated with insulin zinc suspension (44 units daily), developed severe hyperglycaemia with diabetic symptoms while on oral therapy.

Control of Diabetes.—The remaining 22 patients have continued in the trial and all have been rendered free from thirst, polyuria, and pruritus vulvae, and all urinary tract, skin, and foot infections have cleared. None of these patients now has more than an occasional trace (0.025) of glycosuria. The quality of diabetic control in these patients is shown in detail in Table I. In 12 patients the control can be regarded as fully satisfactory (excellent or good), but although fasting blood-glucose levels are still unsatisfactory (fair or poor) in the other 10 patients, they are all lower than the levels present before glycodiazine therapy was started, and these patients are equally free of symptoms. Of the three patients with poor control two are over 65 years of age and the other is known to eat more than his prescribed diet.

Glycodiazine Compared with Placebo.—Fifteen patients have had placebo tablets substituted for glycodiazine for at least four

TABLE I.—Quality of Diabetic Control in Patients Taking Glycodiazine

Glycodiazine Dose	No.	Excellent	Good	Fair	Poor
0.5 g. daily :					
Initial	8		2	2	4
0.5 g. twice daily :					
Initial	12	4	1	3	4
Unsatisfactory at 0.5 g. daily	6			3	3
0.5 g. thrice daily :					
Initial	2		2		
Unsatisfactory at 1 g. daily	13	2	1	7	3
Control at highest dose	22	6	6	7	3

TABLE II.—Comparison of Fasting Blood Glucose of Patients Taking Glycodiazine With that When Taking Placebo or Tolbutamide

Patient	Fasting Blood Glucose in mg./100 ml.					
	Glyco-diazine	Placebo	Difference	Glyco-diazine	Tolbut-amide	Difference
E.Z.	80	140	+60	80	85	+5
K.S.	95	115	+20	95	115	+20
O.L.				95	130	+35
T.H.				100	110	+10
F.G.	110	95	-15	110	90	-20
M.P.				110	95	-15
K.M.				110	125	+15
M.C.				120	120	0
J.S.	125	150	+25	125	115	-10
A.V.	125	225	+100	160	120	-40
J.G.	140	175	+35	125	150	+25
A.H.	135	195	+60	130	125	-5
R.S.	125	175	+50	130	170	+40
W.D.	140	145	+5	140	135	-5
H.P.	130	160	+30	130	150	+20
C.S.				140	170	+30
E.B.	140	180	+40	150	180	+30
A.B.	170	255	+85	155	205	+50
F.W.	160	235	+75	160	225	+65
F.T.	165	230	+65	175	140	-35
L.P.	170	240	+70			
M.B.				170	185	+15
Mean	134.0	181.0	+47.0 0.01 > P	129.0	140.0	+11.0 0.1 > P > 0.05

weeks during the trial. While taking the placebo all but two showed a definite relapse in the control of their diabetes, with subsequent improvement when glycodiazine was restarted. These results are shown in Table II.

Glycodiazine Compared with Tolbutamide.—Twenty-one patients were changed from glycodiazine to tolbutamide for four weeks. Thirteen had a lower blood-glucose level while taking glycodiazine than while taking tolbutamide, seven had a lower blood-glucose level on tolbutamide, and the other patient showed no difference. For the whole group, the mean blood glucose on glycodiazine was 11 mg./100 ml. lower than that for the patients while on tolbutamide, but the variation was considerable, ranging from 65 mg./100 ml. lower to 40 mg./100 ml. higher while on glycodiazine. These results are also shown in Table II.

Side-effects

Only one patient had a complaint that was directly attributable to glycodiazine. She had generalized pruritus without any rash which came on twice a few days after starting the drug and persisted each time until glycodiazine was stopped. There was no concomitant change in serum alkaline phosphatase or eosinophil count.

Other illnesses suffered by individual patients who were taking glycodiazine were myocardial infarction, cerebral thrombosis, and acute gout, and one patient, a 65-year-old woman, who was started on glycodiazine because her long-standing diabetes mellitus was poorly controlled by dietary restriction alone, died suddenly three weeks later while convalescing after a minor foot operation. Death was presumed to be due to massive pulmonary embolism, but permission for necropsy was refused.

An attack of acute gout occurred in a 51-year-old man who had never previously suffered from arthritis and who had no family history of gout. Despite continuing on glycodiazine and refraining from specific uricosuric therapy, he has had no further arthritis, but his serum uric acid level while on glycodiazine (mean 5.9 mg./100 ml.) is a little higher than while taking placebo (mean 5.0 mg./100 ml.). Thirteen patients had serum uric acid estimations performed while taking glycodiazine, tolbutamide, and placebo. For this group the mean serum uric acid concentration on glycodiazine was 4.5 mg./100 ml., on tolbutamide 4.7 mg./100 ml., and on placebo 4.6 mg./100 ml. There was no evidence that either drug was more often associated with hyperuricaemia than placebo therapy, but it is still possible that glycodiazine may aggravate a tendency to hyperuricaemia in susceptible individuals.

Apart from these, no patient taking glycodiazine from our clinic has complained of any gastro-intestinal disturbance, skin rash, or other symptom which may possibly be attributable to the drug, nor has there been any abnormality detected in the blood count and blood chemical constituents. In particular, there has been no tendency for the serum transaminase or alkaline phosphatase levels to rise while patients are taking glycodiazine. Additionally, one patient who complained of nausea and indigestion while taking tolbutamide has been free of these symptoms since starting glycodiazine in the same dose.

Discussion

The trial has shown that glycodiazine is an effective and well-tolerated oral hypoglycaemic agent. The worsening of hyperglycaemia almost invariably observed when placebo was substituted after several months' treatment with glycodiazine seemed to be more severe in those patients in whom diabetic control was fair or poor than in those in whom control was satisfactory (Table II). Thus it would seem that even those

patients whose diabetic control on glycodiazine was unsatisfactory derived considerable benefit from the drug.

Two of our patients have good control on 0.5 g. of glycodiazine daily, but most are now taking 1 or 1.5 g. every day in divided doses. The maximum maintenance dose of glycodiazine used in clinical trials of this drug in Europe has usually been 1.5 g. daily, with a very few patients taking 2 g. daily (Leubner, 1964; Robbers *et al.*, 1964; Gutsche and Boenicke, 1964; Bernhard, 1964). In two of these trials (Leubner, 1964; Gutsche and Boenicke, 1964) a comparison has been made with the maintenance dose of tolbutamide, which on the average was found to be a little higher than that of glycodiazine. A direct weight-for-weight comparison of the hypoglycaemic effect of these two drugs has been made in our diabetic clinic patients under the usual conditions of out-patient supervision. This comparison has shown glycodiazine to be superior in a larger number of patients (Table II), a finding which is consistent with the conclusions reached by Leubner (1964) and by Gutsche and Boenicke (1964). Gerhards *et al.* (1964) have measured the plasma half-life of glycodiazine and found it to be three and a half hours. Since this is similar to that of tolbutamide (Knauff *et al.*, 1959) this advantage for glycodiazine cannot merely be explained on the basis of a difference in therapeutic duration.

Despite the undoubted efficacy of glycodiazine, satisfactory diabetic control was achieved in only 55% of these patients. This high rate of "failure" can be attributed largely to the type of patient selected for trial and to the comparatively strict criteria used for satisfactory control. Only three (33%) of the nine patients given long-term glycodiazine after periods of unsatisfactory diabetic control on dietary restriction alone or other oral hypoglycaemic drugs now have excellent or good fasting blood-glucose levels, whereas 8 (67%) of 12 newly diagnosed diabetics are well controlled on glycodiazine.

Patients already well controlled on other hypoglycaemic agents were not included in this trial, so that the overall success rate for glycodiazine in our patients is less than that which would be expected in a clinic using glycodiazine preferentially for all patients requiring an oral hypoglycaemic drug. Reviewing sulphonylurea therapy, Marble (1961) thought that satisfactory control can be achieved in 50–80% of selected patients with maturity onset diabetes. This range can be explained by the different criteria of selection and satisfactory diabetic control in the various reported series and the type of dietary restriction practised. Good or satisfactory diabetic control was achieved in 62–84% of patients treated with glycodiazine in the European trials (Leubner, 1964; Robbers *et al.*, 1964; Gutsche and Boenicke, 1964; Bernhard, 1964), but in all these trials the criteria of satisfactory diabetic control were less stringent than those used in our clinic. These preliminary results suggest that glycodiazine will prove at least as successful as tolbutamide, the most widely used sulphonylurea drug, in the management of selected patients with maturity onset diabetes mellitus.

No cases of acquired resistance to glycodiazine were observed in this trial, but the number of patients treated was small and the duration of the trial inadequate to allow an assessment of this possibility. In the European trials late therapeutic failure was encountered in 17 (4.2%) of 407 patients treated for more than six months (Robbers *et al.*, 1964; Gutsche and

Boenicke, 1964; Bernhard, 1964). This incidence is slightly less than the overall secondary failure rate reported for patients treated with tolbutamide (O'Donovan, 1959; Camerini-Dávalos and Marble, 1962), but before valid conclusions can be drawn a closer analysis of contributory factors in individual cases would be required.

In this trial glycodiazine caused pruritus in one patient. Minor symptoms of intolerance such as skin rashes, gastrointestinal disorders, and palpitations have been reported in 34 (5.4%) of 624 patients treated with glycodiazine (Leubner, 1964; Robbers *et al.*, 1964; Gutsche and Boenicke, 1964; Bernhard, 1964). In at least half of these cases the symptoms either disappeared when the dosage was reduced or they failed to reappear when the drug was given again. One patient developed jaundice while taking glycodiazine, but this was thought to have been homologous serum hepatitis. There have been no other reports of serious side-effects such as exfoliative dermatitis, blood dyscrasias, or liver damage. However, true assessment of the frequency of such dangerous reactions cannot be made until the drug has been used for the treatment of large numbers of diabetic patients for longer periods. There is no present evidence to suggest that the intercurrent illnesses suffered by our patients while taking glycodiazine were precipitated by the drug, but the one incident of gout observed does warrant further studies of the effect of this compound on serum uric acid levels.

Summary

A clinical trial of glycodiazine, the first of a new group of oral blood-sugar-lowering agents, the sulphonamidopyrimidines, is described. Of the 25 patients entering the trial 22 have been taking the drug for periods ranging from 6 to 59 weeks. The dose of glycodiazine in most subjects was 1–1.5 g. daily. The quality of diabetic control according to given criteria was excellent in six, good in six, fair in seven, and poor in three. Intolerance to the drug was shown by only one patient, who developed generalized pruritus. Evidence which suggests that glycodiazine is possibly more effective than tolbutamide as a hypoglycaemic agent is presented.

Glycodiazine (Gondafon, Redul) used in this trial was supplied by Schering Pty. Ltd., Sydney, N.S.W.

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