

EVALUATION OF GLYCODIAZINE (LYCANOL) IN THE TREATMENT OF DIABETES MELLITUS

By J.S. Cheah and B.Y. Tan

(Department of Medicine, Outram Road General Hospital, Singapore)

The modern era of oral hypoglycaemic drug therapy in diabetes mellitus began when Franke and Fuchs in 1955 introduced Carbutamide following the pioneer work of Janbon *et al* (1942) and Loubatieres (1957). Carbutamide has been superseded by Tolbutamide, Chlorpropamide, Acetohexamide and Tolazamide: all these drugs belong to the group of oral hypoglycaemic agents designated as sulphonylureas.

Phenformin and Metformin belong to a second group of oral hypoglycaemic drugs termed the biguanides; the effectiveness of Phenformin was first reported by Ungar, Freedman and Shapiro (1957).

Glycodiazine (Lycanol-Bayer) is the first of the sulphonamidopyrimidines, a new group of oral hypoglycaemic drugs to undergo clinical trial. This compound, 2-benzenesulphonamido-5 (beta-methoxy-ethoxy)-pyrimidine, was synthesized by Gutsche *et al* in 1964. Structurally it differs from Tolbutamide in that a pyrimidine ring replaces the urea group (Fig. 1). It has a molecular weight of 331 and it is readily soluble in water and methyl alcohol; its plasma half-life is short (3.8 hours). Its mode of action is similar to that of the sulphonylureas: it stimulates the secretion of insulin by the pancreas of patients who have functioning beta-cells (Kramer *et al*, 1964).

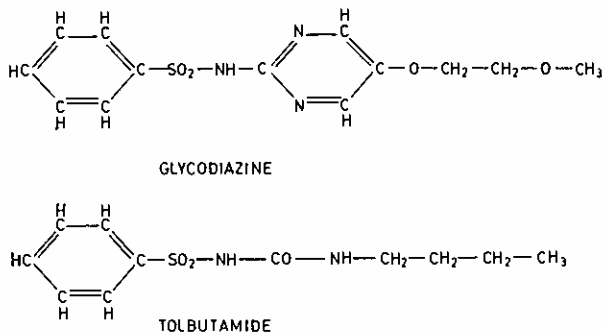


Fig. 1. Structural formulae of Glycodiazine (Lycanol) and Tolbutamide.

Following encouraging results of clinical trials of Glycodiazine in Germany and Austria (Leubner, 1964; Gutsche and Boenicke, 1964; Roberts, Brumby and Traumann, 1964; Bernhard, 1964), reports of more widespread

trials have appeared (Stewart and Anderson, 1965; Bank, Herman and Jackson, 1965; Eisenberg and Cohen, 1966 and Nash, 1968). We report our initial experience of the drug.

PATIENTS AND METHODS

Nineteen previously untreated adult-onset diabetics (9 males, 10 females; 11 Chinese, 4 Malays and 4 Indians) were selected for the trial. Their average age was 56 years; their age and sex distribution are shown in Fig. 2. Six were overweight, 3 were underweight and 10 were of normal weight (normal weight is defined as $\pm 10\%$ of ideal weight according to tables adjusted for height and age, McFadzean and Yeung, 1968). Their weight distribution is shown in Fig. 3. The duration of the diabetes (from onset of symptoms to diagnosis) was less than 1 year in 15 patients; 1-2 years in 3 patients and more than 2 years in 1 patient. The other factors considered in the selection of these patients were an absence of ketoacidosis and a fasting blood sugar of more than 150 mg.% but less than 300 mg.%. These factors are listed in Table I.

Glycodiazine treatment was started with a dose of 1 tablet (0.5 G.) daily taken before breakfast, or 0.5 G. twice daily taken before breakfast and dinner or 0.5 G. thrice daily before meals. The dose was increased weekly to a maximum of 2 tablets thrice daily (3 G.).

The patients attended the clinic weekly for the first month, fortnightly for the second month and thereafter monthly. At each visit symptoms of hypoglycaemia, gastro-intestinal upset and allergic skin reactions were enquired.

The patients were treated with Glycodiazine for 6 months; 4 were on a dose of 0.5 G. daily, 8 were on a dose of 0.5 G. thrice daily and 7 received 1 G. thrice daily. The fasting blood sugars before and after Glycodiazine therapy are shown in Fig. 4. All blood sugars were determined on venous blood using the method of Folin and Wu (1920).

The following investigations were also determined before and 6 months after Glyco-

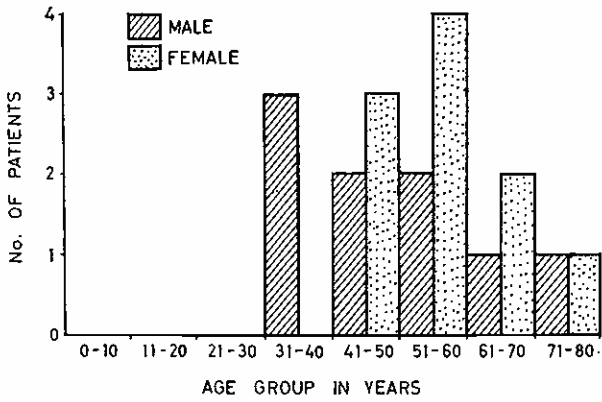


Fig. 2. Age and sex distribution of patients.

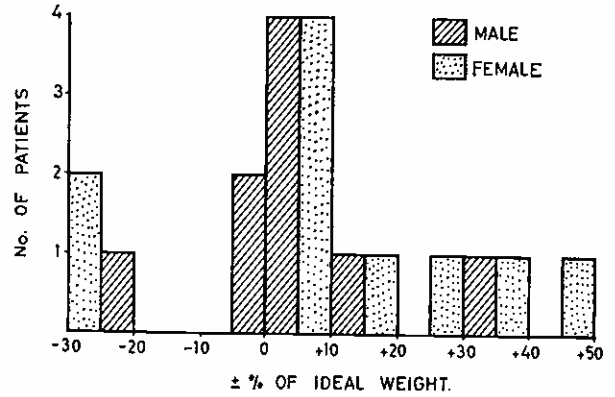


Fig. 3. Weight distribution of patients.

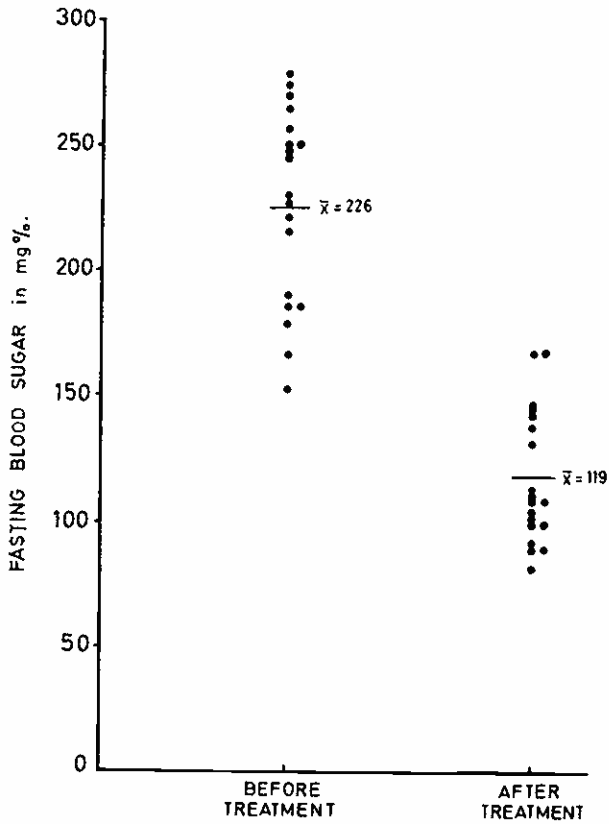


Fig. 4. Fasting blood sugar before and after Glycodiazine (Lycanol) therapy.

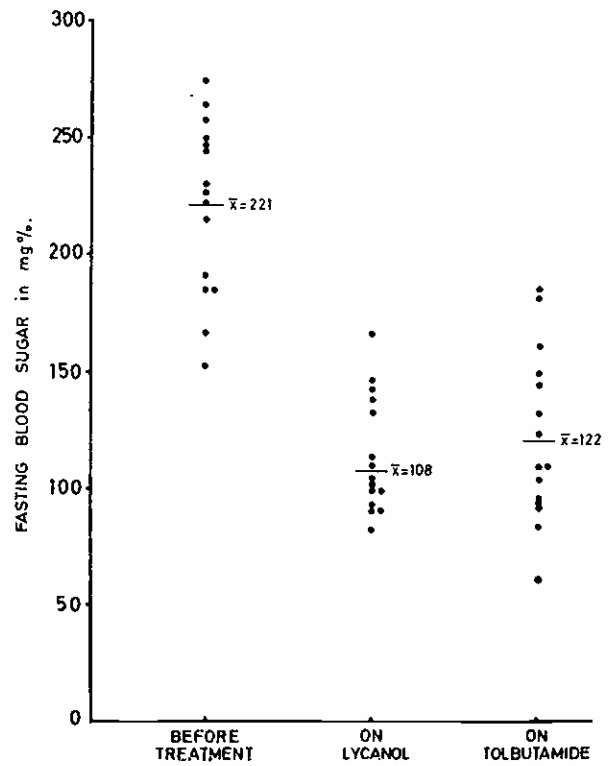


Fig. 5. Fasting blood sugar after Glycodiazine (Lycanol) and Tolbutamide therapy.

TABLE I
CHARACTERISTICS AND RESPONSE OF THE PATIENTS TO
GLYCODIAZINE (LYCANOL)

No.	NAME	AGE IN YEARS	SEX	WEIGHT*	DURATION OF DIABETES IN YEARS	DOSAGE OF LYCANOL IN GMS/DAY	FASTING BLOOD SUGAR IN GM.%. .		RESULT OF THERAPY
							BEFORE TREATMENT	AFTER TREATMENT	
1	P.S.H.	56	F	+27	<1	3.0	222	100	S
2	L.B.	58	F	+4	<1	3.0	230	133	S
3	C.S.H.	65	M	-8	<1	1.5	250	102	S
4	M.F.	45	M	+7	<1	0.5	167	114	S
5	L.S.E.	63	F	-23	<1	3.0	248	138	S
6	K.H.K.	54	F	+4	1	0.5	185	143	S
7	C.A.H.	68	F	+12	<1	0.5	153	100	S
8	I.S.K.	41	F	+10	<1	3.0	227	105	S
9	S.O.	42	F	+40	<1	0.5	179	148	S
10	A.S.	51	M	-28	1	1.5	270	112	S
11	W.C.N.	48	F	+43	<1	1.5	191	147	S
12	M.S.	51	M	-9	<1	1.5	216	91	S
13	T.S.C.	75	M	+7	<1	1.5	185	111	S
14	K.S.	40	M	+8	<1	1.5	277	111	S
15	A.M.	36	M	+40	<1	1.5	274	83	S
16	A.I.	44	M	+9	<1	1.5	264	91	S
17	A.M.	39	M	+20	1½	3.0	246	93	S
18	L.S.	55	F	-24	10	3.0	257	167	NS
19	NS.N.	71	F	+4	<1	3.0	250	167	NS

* : Expressed as \pm % of ideal weight.

S : Satisfactory.

NS : Not Satisfactory

diazine therapy: the peripheral blood picture, urine microscopy, serum cholesterol, serum uric acid, serum glutamic-oxaloacetic transaminase and serum alkaline phosphatase.

After 6 months the patients were taken off drugs for 3-4 weeks and then given Tolbutamide in similar dosage to Glycodiazine. The fasting blood sugars after Glycodiazine and Tolbutamide in 14 patients are shown in Fig. 5.

RESULTS

All 19 patients had a fall in fasting blood sugar: the mean value before therapy was 226 mg.% and during Glycodiazine therapy it was 119 mg.%—a fall of 52.5% (Fig. 4). On the criteria of relief of symptoms and glycosuria and a fasting blood sugar of less than 150 mg.% 17 of the 19 patients (89.5%) had a satisfactory response to Glycodiazine (Table I).

No patient taking Glycodiazine had complained of gastro-intestinal disturbances, jaundice or skin rash. There was no significant change in the blood picture, serum uric acid, serum glutamic-oxaloacetic transaminase and serum alkaline phosphatase after 6 months of Glycodiazine treatment. There was no significant fall of serum cholesterol (mean value before and after therapy were 234 and 223 mg.% respectively; $p > 0.15$).

Glycodiazine was slightly more potent than Tolbutamide as indicated by greater fall in the mean fasting blood sugar following Glycodiazine than following Tolbutamide in similar dosages (Fig. 4).

DISCUSSION

In this short-term trial, Glycodiazine has been found to be a safe and effective oral

hypoglycaemic drug in the treatment of adult-onset, ketosis-resistant diabetic patients. Thus 17 of our 19 patients (89.5%) achieved satisfactory control. Satisfactory diabetic control was found in 52.5-90.5% of patients treated with Glycodiazine in Europe, Australia, South Africa and Isreal (Leubner, 1964; Roberts *et al*, 1964; Gutsche and Boenicke, 1964; Bernhard, 1964; Stewart and Anderson, 1965; Bank *et al*, 1965; Eisenberg and Cohen, 1966). These varying results are probably due to different selections of patients and criteria of response.

These satisfactory control rate achieved by Glycodiazine is comparable to that achieved by the sulfonylureas: thus Marble (1961) in a survey found that satisfactory control can be achieved in 50-80% of selected patients with adult-onset diabetes treated with sulphonylureas. Wasty and Hazell (1966) recorded the treatment of elderly diabetics with Glycodiazine and concluded that it is an effective and safe drug for the elderly mild to moderate diabetic.

No cases of acquired resistance to Glycodiazine were found in this trial. In the European trials secondary failure occurred in 17 (4.2%) of 407 patients treated for more than 6 months (Roberts *et al*, 1964; Gutsche and Boenicke, 1964; Bernhard, 1964).

Leubner (1964) found that Glycodiazine, relative to weight was a more effective hypoglycaemic agent than Tolbutamide. Our results also support this finding.

We did not find any side effects in this short trial. Of the 582 patients treated with Glycodiazine from 4 different clinics (Bernhard, 1964; Gutsche and Boenicke, 1964; Leubner, 1964; Roberts *et al*, 1964), 10 cases (1.7%) developed an urticarial rash, 1 case had severe nausea and vomiting, 2 cases developed abdominal distension, but no blood dyscrasias or disturbances of liver functions were seen. Hypoglycaemic reactions were rare: this was attributed to the short-half-life of the drug. Glycodiazine may produce a slight rise of erythrocyte sedimentation rate (Roe, 1965). One of Stewart and Anderson's (1965) patients developed acute gouty arthritis and Leubner (1964) reported one case of jaundice during Glycodiazine treatment, though both cases were thought not to be associated with the treatment. The toxicity of Glycodiazine seems low and is probably comparable to that of Tolbutamide (Pannekoek, 1968).

The cost of Glycodiazine (Lycanol) is comparable to that of Tolbutamide.

CONCLUSION AND SUMMARY

Seventeen out of 19 (89.5%) previously untreated adult-onset, ketosis-resistant diabetic patients responded satisfactorily to Glycodiazine (Lycanol-Bayer) in a dose of 0.5-3 G. per day in divided doses.

Weight for weight Glycodiazine is slightly more potent than Tolbutamide.

No hepatic, renal, haematological or symptomatic toxic reactions were observed during the total of 456 person-weeks of Glycodiazine therapy.

It is concluded that Glycodiazine (Lycanol) is a safe and effective drug in the treatment of adult-onset diabetic patients and deserves further trials.

ACKNOWLEDGEMENTS

Glycodiazine (Lycanol) was generously supplied by Behn, Meyer & Co. Ltd., Singapore, the local agents for Bayer.

Professor G.A. Ransome, C.B.E., P.J.G., A.M., M.D. (Hon.), M.R.C.S., F.R.C.P. gave permission and encouragement to carry out this trial.

REFERENCES

1. Bank, S., Herman, M. and Jackson, W.P.U. (1965): "A trial of Glycodiazine in the management of adult-onset ketosis-resistant diabetes." *S.A. Med. J.*, 39, 1117.
2. Bernhard, H. (1964): "Oral treatment of diabetes mellitus with Glycodiazine." *Arzneimittel-Forsch.*, 14, 411.
3. Eisenberg, S. and Cohen, A.M. (1966): "Clinical trial of Glycodiazine—a new oral hypoglycaemic drug." *Isreal J. Med. Sci.*, 2, 768.
4. Folin, O. and Wu, H. (1920): "System of blood analysis: simplified and improved method for determination of sugar." *J. Biol. Chem.*, 41, 367.
5. Gutsche, H. and Boenicke, G. (1964): "Glycodiazine, a new oral antidiabetic." *Arzneimittel-Forsch.*, 14, 409.
6. Kramer, M., Hecht, G., Langecker, A.H., Harwart, A., Richter, K.D., and Gloxhuber, Ch. (1964): "Pharmacology of 2-Benzenesulphonamido-5 (beta-methoxy-ethoxy)-pyrimidine (Glycodiazine) a new hypoglycaemic compound." *Ibid.*, 14, 404.
7. Leubner, H. (1964): "Report on clinical trial of a new oral antidiabetic, 2-Benzenesulphonamido-5 (beta-methoxy-ethoxy)-pyrimidine." *Ibid.*, 14, 404.
8. McFadzean, A.J.S. and Yeung, R. (1968): "Diabetes among the Chinese in Hong Kong." *Diabetes* 17, 220.
9. Marble, A. (1961): "Oral hypoglycaemic agents." *Ann. Rev. Med.*, 12, 135.
10. Nash, J. (1968): "Glymidine." *The Practitioner*, 200, 311.
11. Pannekoek, J.H. (1968): "Oral antidiabetic drugs." In *Side Effects of Drugs*, (Meyler, L. and Herxheimer, A., Editors), Vol. 6, 427. The Hague: Mouton & Co.

12. Roberts, H., Brumby, K.H. and Traumann, K.J. (1964): "The therapy of diabetes mellitus with Glycodiazine." *Arzneimittel-Forsch*, 14, 406.
 13. Roe, P.F. (1965): "Trial of a new oral antidiabetic drug Glycodiazine." *J. Irish Med. Ass.*, 56, 183.
 14. Stewart, R.D.H. and Anderson, D.E. (1965): "Glycodiazine in diabetes mellitus: a clinical trial." *Brit. Med. J.*, 2, 682.
 15. Wasty, S.S.H. and Hazell, K. (1966): "The value of Glycodiazine (Gondafon) for elderly diabetic." *Brit. J. Clin. Pract.*, 20, 413.
-