Clinical Evaluation of the Effect of Glycopyramide in Diabetes Mellitus

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A newly synthesized sulfonylurea, glycopyramide (N-*p*-chlorobenzene sulfonyl, N'-pyrrolidinourea) was administered for a long period in 72 diabetic patients, including 25 inpatients and 47 outpatients.

The therapeutic effect of glycopyramide was good in 30 (79%) and fair in 4 of 38 patients of Group I, who had not been treated with any antidiabetic agents. Of 31 patients of Group II, who had not responded to another antidiabetics, 13 (48%) responded excellently and 10 (37%) fairly to the drug. Good control was achieved by glycopyramide in 6 of the 7 diabetics of group III, who had been controlled by insulin less than 25 units daily. These results indicate that glycopyramide gave good response in patients who had not been controlled by other oral antidiabetics, as well as in the patients treated initially with the drug, and that in some of insulin-requiring diabetes insulin could be replaced by glycopyramide.

Glucose tolerance was improved after a long-term administration of glycopyramide. Elevated serum total lipid or cholesterol was decreased by the treatment with glycopyramide. Four patients showed minor side-effects in the gastrointestinal tract. It is proved that the administration of the drug for a long period did not produce any toxic effects on liver function and hemogram.

From this study it was concluded that glycopyramide could be used successfully and safely in the treatment of diabetes mellitus.

Since 1955, when carbutamide was introduced as an antidiabetic agent,¹ drugs of the sulfonylurea series have widely been used for their reliable therapeutic effects. However, because of the occasional side-effects the search continues for a drug whose predictable hypoglycemic action makes secondary failure unlikely, and which is devoid of significant toxicity. A new antidiabetic agent, glycopyramide (Kyorin Pharmaceutical Co., Tokyo), is characterized chemically as N-*p*-chlorobenzene sulfonyl, N'-pyrrolidinourea, and its structural formula is:

The present study is concerned with the clinical evaluation of the effect of this agent in diabetic patients.

MATERIALS AND METHODS

1) Patients

The clinical studies were carried out in 72 diabetic patients at our clinic of the Tohoku University Hospital, consisting of 25 inpatients and 47 outpatients, of whom there were

TABLE 1. *Clinical data of patients and*

Patients	Age and sex	Duration of disease (years)	Body weight index	Glycopyramide administration		
				Initial doses (mg)	Maintenance doses (mg)	Duration (months)
<i>Group I</i>						
M.H.	49 F	5	0.82	1250	1250	3
K.K.	65 M	15	1.12	1000	1000	18
K.A.	61 M	<1	1.08	1250	250	7
M.C.	55 M	<1	0.93	1500	1000	11
I.I.	66 F	1	0.83	1500	1250	1
S.K.	51 F	<1	0.93	750	750	13
T.T.	55 F	<1	1.23	1500	250	10
F.A.	60 F	2	0.98	1000	750	14
H.N.	36 M	7	0.83	750	750	36
K.I.	52 F	<1	1.47	750	250	3
K.E.	64 F	<1	0.98	1000	250	14
I.It.	56 M	5	0.98	500	750	2
S.U.	40 F	2	1.05	750	750	34
T.E.	59 M	6	1.14	750	250	2
K.S.	62 F	<1	0.91	750	500	14
Ki.K.	53 F	<1	1.15	750	500	4
I.K.	60 F	4	0.83	1500	500	3
To.Ta.	31 M	<1	1.15	750	250	10
I.M.	55 F	<1	0.92	750	250	36
C.K.	33 M	<1	0.98	750	500	4
Ta.Ta.	60 M	<1	1.36	500	250	11
N.I.	54 M	<1	1.05	750	500	1
K.O.	57 F	<1	1.11	750	250	5
Y.T.	52 M	<1	0.91	750	500	21
Y.N.	61 F	18	1.14	500	750	12
S.E.	67 F	<1	1.04	750	500	2
S.N.	52 M	2	1.25	750	750	12
Sa.Ko.	53 F	<1	0.92	500	250	2
To.Ta.	42 F	1	1.11	750	250	14
M.C.	46 F	2	1.14	1000	500	6
S.O.	65 M	22	0.98	750	750	2
F.S.	43 F	3	1.14	1000	500	5
A.Y.	52 M	<1	1.07	750	250	46
M.S.	58 F	1	1.16	1000	1000	9
M.H.	49 M	<1	1.22	500	375	13
T.O.	57 M	20	1.40	500	500	1
M.A.	66 M	<1	1.29	750	750	1
S.O.	56 F	<1	1.08	500	250	48
<i>Group II</i>						
T.E.	57 F	1	0.90	1000	1000	22
H.S.	63 M	20	0.97	750	750	12
Y.K.	58 F	1	0.96	750	500	58
S.N.	66 F	3	0.92	500	500	14
T.N.	48 F	1	0.96	1250	750	14
K.Is.	55 M	1	1.20	1000	500	10
Su.Sa.	49 F	1	1.22	750	500	15
To.Ta.	67 M	8	1.00	500	250	5
H.T.	54 M	1	1.02	750	500	48
Sh.S.	46 M	4	1.15	750	750	12
S.A.	55 M	3	1.02	500	250	12
K.Ot.	53 M	8	1.05	1000	1000	29

response to glyclopamide.

Before treatment	Fasting blood sugar (mg %)			Treatment before glyclopamide	Response to glyclopamide
	Maximum	Minimum	Mean		
282	196	99	136	None	Good
282	211	93	145	None	Fair
250	131	68	93	None	Good
235	146	103	133	None	Good
231	138	94	116	None	Good
228	173	113	139	None	Fair
225	216	85	122	None	Good
224	205	124	166	None	Poor
208	161	99	151	None	Fair
205	100	97	98	None	Good
205	128	92	120	None	Good
183	231	139	186	None	Poor
182	178	89	130	None	Good
179	109	76	89	None	Good
177	155	101	129	None	Good
174	165	69	114	None	Good
173	132	95	123	None	Good
169	120	78	96	None	Good
165	130	87	118	None	Good
163	142	110	124	None	Good
161	160	92	118	None	Good
160	112	99	105	None	Good
158	133	87	97	None	Good
153	153	88	117	None	Good
151	210	130	169	None	Poor
151	130	96	109	None	Good
149	135	116	126	None	Good
147	120	81	102	None	Good
147	162	94	111	None	Good
146	124	95	99	None	Good
146	140	76	97	None	Good
146	137	88	115	None	Good
144	154	108	135	None	Fair
143	195	121	149	None	Poor
143	123	92	108	None	Good
142	96	76	83	None	Good
141	123	100	114	None	Good
140	167	103	121	None	Good
226	268	92	140	Tolbutamide	Good
191	213	129	147	Tolbutamide	Fair
181	137	100	125	Tolbutamide	Good
172	212	85	141	Tolbutamide	Fair
165	138	96	128	Tolbutamide	Good
160	175	92	128	Tolbutamide	Good
158	140	73	113	Tolbutamide	Good
154	128	85	89	Tolbutamide	Good
151	170	122	136	Tolbutamide	Good
150	202	118	164	Tolbutamide	Fair
149	140	72	96	Tolbutamide	Good
144	182	118	141	Tolbutamide	Fair

TABLE 1. Continued.

Patients	Age and sex	Duration of disease (years)	Body weight index	Glycopyramide administration		
				Initial dose (mg)	Maintenance dose (mg)	Duration (months)
S.H.	49 F	4	0.94	750	750	11
K.T.	38 M	5	0.91	1500	1500	1
M.W.	48 M	<1	0.98	750	500	34
A.O.	53 F	4	0.81	750	750	26
C.I.	48 F	1	1.04	500	500	25
H.Su.	46 F	1	0.96	750	250	25
Sh.O.	33 M	5	1.20	1000	750	11
T.D.	42 F	3	1.02	750	1000	16
T.K.	53 F	3	1.13	1000	1000	58
E.S.	41 F	5	1.34	750	750	36
Ko.K.	60 M	30	0.95	750	750	31
K.S.	69 F	1	0.76	1000	500	33
Z.T.	56 F	<1	0.89	1000	500	29
A.K.	55 F	<1	0.85	1250	1250	14
Ke.S.	57 M	<1	0.91	1250	1500	1
<i>Group III</i>						
Ka.T.	21 F	2	1.17	1500	500	15
Sh.Sa.	34 M	<1	1.29	750	750	12
Y.K.	63 M	1	1.00	1000	250	17
Ka.Sa.	14 M	1	0.81	1500	250	25
H.G.	62 F	4	1.00	750	750	39
To.Ch.	44 F	<1	0.94	1500	250	10
I.Ich.	32 M	<1	0.67	750	750	6

39 females and 33 males. Inpatients were given dietary treatment under close observation for one or two weeks prior to starting medication. After fasting blood sugar was stabilized, the patients with a blood sugar level above 140 mg% with a urine sugar excretion above 10 g per day were selected for the study. Outpatients were initially prescribed a diabetic diet and observed for about two weeks. When the baseline blood sugar levels were still above 140 mg%, the patients were chosen as test subjects.

The patients studied were presented in Table 1 and divided into three groups, Groups I, II and III. The patients of Group I including 38 diabetics were administered the sulfonyl-urea drug primarily. Twenty-six patients of Group II were those who had been inadequately treated with other oral antidiabetic agents and showing fasting blood sugar above 140 mg%. In seven patients of Group III, insulin was replaced by glycopyramide without any change in dietary therapy only after they had achieved satisfactory control of the disease. Therefore, fasting blood sugar level of the Group III was below 140 mg%.

2) Method of clinical trial

The initial doses of glycopyramide were 1.0 to 1.5 g (4-6 tablets) for patients whose fasting blood sugar exceeded 200 mg% and 0.5 to 0.75 g (2-3 tablets) for those below 200 mg%. Daily dosage was decreased gradually as blood and urine sugar improved. The medication was given in divided doses one to three times daily before meals, and continued for one to 58 months, during which time the fasting blood sugar level of inpatients was determined once a week and their urinary sugar every day. The fasting blood sugar level of outpatients was determined every two to four weeks.

Before treatment	Fasting blood sugar (mg %)			Treatment before glycropyramide	Response to glycropyramide
	Maximum	Minimum	Mean		
201	248	160	217	Chlorpropamide	Poor
181	265	201	243	Tolinase	Poor
160	154	114	132	Tolinase	Good
147	154	101	135	Tolinase	Fair
148	174	109	120	Chlorpentazide	Good
217	149	81	140	Butylbiguanide	Fair
210	167	119	150	Butylbiguanide	Fair
207	201	162	198	Butylbiguanide	Poor
201	198	100	148	Butylbiguanide	Fair
196	257	121	194	Butylbiguanide	Poor
177	180	96	126	Dimethylbi- guanide	Good
174	138	91	125	Butylbiguanide	Good
170	183	112	141	Butylbiguanide	Fair
215	249	117	146	Glycodiazine	Fair
143	143	111	128	Glycodiazine	Good
148	161	109	130	Insulin	Good
132	137	90	112	Insulin	Good
103	119	90	110	Insulin	Good
120	126	69	118	Insulin	Good
118	165	95	119	Insulin	Good
121	159	86	138	Insulin	Good
97	252	114	148	Insulin	Poor

Samples of capillary blood were obtained from the ear lobe and analyzed for blood sugar by Fujita-Iwatake's method,² which showed almost the same blood sugar as obtained by Hagedorn-Jensen's method.³ In our observation, normal fasting blood sugar level ranged between 80 and 120 mg%.

The 50 g glucose tolerance test was carried out in 13 patients prior to and during the administration of the drug by the procedures described elsewhere.⁴

Fasting blood sample was obtained by venepuncture for the determination of serum lipid and liver function tests, and from the ear lobe for hemogram. Total lipid was determined by Bragdon's method⁵ and total cholesterol by Zak-Henly's method.^{6,7} The liver function tests were performed by following methods: thymol turbidity test (TTT) by Maclagan's method,⁸ zinc turbidity test (ZTT) by Kunkel's method,⁹ glutamic pyruvic transaminase (GPT) and glutamic oxaloacetic transaminase (GOT) by the method of Reitman and Frankel^{10,11} and alkaline phosphatase by the method of Huggins and Talalay.¹²

3) Criteria for evaluation of drug effect

In this study the following criteria defined the therapeutic potency of glycropyramide.

- (1) Good—80% of fasting blood sugar measurements below 140 mg%.
- (2) Fair—fasting blood sugar less than 160 mg% and reduced.
- (3) Poor—fasting blood sugar remained above 160 mg%.

Additionally, if fasting blood sugar is controlled below 140 mg% in patients treated with insulin (Group III) and can be remained at the same level by glycropyramide, the effect was evaluated as good.

RESULTS

1) *Effect of glycopyramide on fasting blood sugar*

The effect of glycopyramide on fasting blood sugar was summarized and its change in individual case was shown in Table 1. In Group I, 30 out of 38 patients (79%) showed good response to the drug, while 4 patients of this group showed no response. In Group II, who did not show any good effect with other antidiabetics, 13 patients (48%) responded excellently to the drug and 10 (37%) showed fairly good response, while in 4 patients the drug did not show a good effect. This indicates that glycopyramide is effective in the patients, who have not been treated with any drugs for diabetes mellitus. Also, the results suggest that patients of Group II mostly do not respond to the oral antidiabetic agents. Nevertheless, 10 out of 17 patients who had been treated by sulfonylurea drugs or biguanide other than glycopyramide, showed good response to the latter. This suggests that glycopyramide may be used in the patients who are resistant to other antidiabetics. In 6 patients of Group III, who had been treated with insulin, glycopyramide could substitute for insulin. This result suggests the possibility that the treatment of the patients requiring insulin less than 25 units daily may be controlled with glycopyramide.

In total, 49 (68%) out of 72 patients showed good response to the drug and 14 (19.5%) fairly good response, while 9 (12.5%) responded poorly (Table 2).

In parallel to the change in fasting blood sugar glucosuria was reduced in all inpatients.

TABLE 2. *The relation of drug effect to pretreatment of diabetes*

Group (pretreatment)	Good	Fair	Poor	Total
I (none)	30	4	4	38
II (oral antidiabetics)	13	10	4	27
III (insulin)	6	0	1	7
Total	49(68.0)	14(19.5)	9(12.5)	72(100)

Numbers in parentheses represent percentages.

2) *Relation of baseline blood sugar level to the effect of glycopyramide*

As indicated in Table 3, glycopyramide gave satisfactory results in 76 per cent of 54 patients with baseline blood sugar below 200 mg%. The higher was the fasting blood sugar level, the less effective was the drug. The drug showed good effect in 8 (44%) out of 18 patients with fasting blood sugar above 200 mg% and fairly good effect in 7 patients in this group. Most non-obese diabetic patients with fasting blood glucose 200 mg% usually require the treatment with insulin, but the results described above indicate that oral hypoglycemic agents may also be used successfully in cases with the fasting blood glucose level up to about 250 mg% (Table 3).

3) Influence of age on the effect of glyclopamide

The sulfonylurea drugs are generally more effective in diabetes occurring after age 40, as in 62 patients of our series. However, Table 3 shows that glyclopamide was also effective in 8 of 10 patients at the age of 40 years or less.

TABLE 3. Relation of drug effect to clinical pictures

Group	Drug effect			Total
	Good	Fair	Poor	
Fasting blood sugar (mg%)				
Below 140	5	0	1	6
141--160	23	4	2	29
161--200	13	3	3	19
Above 200	8	7	3	18
Age (years)				
Under 40	6	2	2	10
41--50	10	2	3	15
51--60	22	7	3	32
Over 61	11	3	1	15
Body weight				
Obese	9	0	1	10
Normal	39	14	7	60
Lean	1	0	1	2
Duration of disease (years)				
Less than 1	24	4	1	29
1--5	20	6	7	33
6--10	2	2	0	4
More than 10	3	2	1	6

4) Influence of obesity on the effect of glyclopamide

Patients with body weight index above 1.21 were classified as obese, between 0.81 and 1.20 normal and less than 0.80 lean, based on the calculation from the desirable body weight of Japanese people.¹³ As indicated in Table 3, the effectiveness of glyclopamide treatment was unrelated to the body weight index. Body weight of patients who did not show a good response to the drug was mostly normal.

5) Influence of duration of the disease on the effect of glyclopamide

Twenty-nine of 72 patients had been diagnosed within the preceding one year, and thirty-three, one to five years. The patients with short duration of the disease seem to respond better than the patients with long duration of the disease. Eighty-three per cent of 29 patients with the duration of the disease less than a year, excellently responded to the drug while 61 per cent of 33 patients with the duration of the disease of one to five years responded well. However, there is no statistically significant difference between above two groups ($p < 0.10$).

TABLE 4. *Changes in glucose tolerance*

Patients	Glucose tolerance before treatment (mg%)					
	Before	Minutes after glucose load				Glucose tolerance index*
		30	60	90	120	
K.I.	223	320	334	354	244	295
K.E.	185	280	357	390	370	316
T.E.	161	204	316	280	258	241
N.I.	172	236	292	264	228	238
K.O.	177	222	236	354	292	256
S.E.	151	261	313	290	266	256
M.C.	176	272	292	317	306	273
S.O.	182	239	320	356	320	283
A.Y.	229	358	388	348	316	328
T.O.	142	186	201	203	177	182
Z.T.	212	312	348	340	368	316
K.S.	205	258	356	367	382	319
S.S.	226	368	420	388	362	353
Mean	188	273	321	327	299	281
± SEM	7.9	15.6	30.3	14.7	17.3	12.8

* The mean value of five blood sugar

Moreover, good therapeutic effects were observed in three out of six patients with the disease for more than ten years. This suggests that glycopyramide may be used effectively even in long-standing diabetes (Table 3).

6) *Glucose tolerance before and after glycopyramide*

Oral glucose tolerance test in 13 patients verified the therapeutic effectiveness of glycopyramide, since the blood sugar curve improved in every patient (Table 4). Mean blood sugar values before the treatment were $188 (\pm \text{SE } 7.9) \text{ mg}\%$ at the fasting, $327 \pm 14.7 \text{ mg}\%$ at the peak and $299 \pm 17.3 \text{ mg}\%$ 2 hours after glucose load, whereas during the drug administration they were $111 \pm 6.4 \text{ mg}\%$ at the fasting, $236 \pm 12.4 \text{ mg}\%$ at the peak and $219 \pm 12.6 \text{ mg}\%$ 2 hours after glucose load. In three patients with frank diabetic curve before the treatment the blood sugar curve reverted to 'borderline' after long-term administration of glycopyramide. (The criteria for a diabetic curve is $200 \text{ mg}\%$ or higher at the peak and 2 hour level of $140 \text{ mg}\%$ or more⁴). The mean glucose tolerance index, the mean value of five blood sugar levels during glucose tolerance test, was $281 \pm 12.8 \text{ mg}\%$ before glycopyramide administration and $196 \pm 9.0 \text{ mg}\%$ after the drug therapy. The difference between glucose tolerance indexes before and after the treatment was statistically significant ($p < 0.001$).

7) *Effect of glycopyramide on serum lipid and cholesterol*

Serum total lipids were measured in 28 patients before and after the administration of glycopyramide. Elevated level of serum lipid above $700 \text{ mg}\%$ was observed in 14 out of 28 patients before glycopyramide administration, the

after glyclopypyramide administration

Glucose tolerance after treatment (mg%)					
Before	Minutes after glucose load				Glucose tolerance index*
	30	60	90	120	
100	118	153	174	184	146
93	169	240	280	269	210
146	259	294	282	229	242
99	174	203	201	191	173
107	172	241	217	227	193
97	174	207	231	222	186
148	234	300	309	260	250
99	158	200	226	229	180
90	208	235	262	186	196
123	182	246	165	146	172
147	187	276	271	297	236
120	178	232	258	263	210
79	137	198	196	160	154
111	181	233	236	219	196
6.4	10.2	11.5	12.4	12.6	9.0

levels during glucose tolerance test.

TABLE 5. *Effect of glyclopypyramide on serum total lipid and cholesterol*
 A. *Total lipid (mg %)*

Patients	Before treatment	After treatment
K.A.	1231	536
Y.T.	769	483
Y.N.	728	570
S.E.	1046	929
S.K.	737	731
T.O.	761	582
T.E.	1086	594
H.S.	710	757
S.S.	868	853
T.T.	737	621
Sh.S.	1027	653
A.O.	959	801
T.K.	844	676
Z.T.	768	644
Mean $\pm$ SEM	876.5 $\pm$ 44.1	673.6 $\pm$ 33.8
H.N.	501	658
K.I.	647	685
I.M.	483	536
Ta.T.	620	716
N.I.	690	579
K.Og.	608	825
F.S.	494	505
Y.K.	505	507
S.N.	422	664
Ki.Is.	650	524
H.T.	503	408
S.A.	652	538
Ka.O.	641	522
C.I.	583	819
Mean $\pm$ SEM	571.4 $\pm$ 22.4	609.1 $\pm$ 33.3†

TABLE 5. Continued.

B. Cholesterol (mg %)

Patients	Before treatment	After treatment	Patients	Before treatment	After treatment
K.K.	280	194	H.N.	204	224
K.A.	314	274	S.U.	206	210
K.I.	272	232	I.M.	155	176
Y.T.	298	230	Ta.T.	203	220
S.E.	350	322	N.I.	240	228
S.K.	268	208	K.Og.	210	202
T.O.	276	351	Y.N.	147	170
S.O.	269	232	F.S.	194	172
T.E.	276	216	A.Y.	160	194
T.N.	350	198	H.S.	218	218
T.T.	262	246	Y.K.	141	162
S.S.	260	284	S.N.	150	194
A.O.	308	256	K.Is.	204	180
T.K.	250	234	Su.S.	230	204
A.T.	491	478	H.T.	183	136
Mean	301.6	263.7†	S.A.	214	248
±SEM	15.7	19.1	K.O.	232	246
			C.I.	166	268
			Ha.S.	218	270
			Ko.K.	192	186
			K.S.	170	186
			Z.T.	243	186
			Y.K.	202	210
			H.G.	215	282
			Mean	195.7	207.2
			±SEM	6.2	74†

* The difference is significant ($p < 0.001$).† The difference is significant ($p < 0.01$).

‡ The difference is not significant.

remaining 14 patients showing normal level of lipid. Following the drug therapy, elevated lipids fell in 13 of 14 patients. Total serum lipids of the patients with initial value below 700 mg% became normal after the treatment with glycopyramide in all patients except three, whose total lipids rose above 700 mg% after the drug therapy. The mean level of total lipids in the patients whose initial level of lipid exceeded 700 mg% was 876.5 ± 44.1 mg% before the drug administration and fell to 673.6 ± 33.8 mg% after the medication. This decrease in total serum lipids was statistically significant ($p < 0.001$) (Table 5-A).

Total serum cholesterol was measured before and after glycopyramide in 39 diabetics, of whom 15 patients showed the total cholesterol level above 250 mg% and 24 patients below 250 mg% before the drug therapy. Serum cholesterol fell after the drug therapy in 13 of 15 patients with high level of initial cholesterol. Cholesterol level changed normal in all patients with cholesterol below 250 mg% except for two patients whose cholesterol elevated after the drug therapy. The mean cholesterol level of the patients with initial high value was 301.6 ± 15.7 mg% before therapy and fell to 263.7 ± 19.1 mg% after the drug therapy (Table 5-B). The decrease in total serum cholesterol was statistically significant ($p < 0.01$).

These results suggest the possibility of improvement in serum total lipids and cholesterol by the glycypyramide treatment.

8) Toxicity of glycypyramide on liver and hemogram

Liver function tests were done in 20 patients before and during the administration of glycypyramide. Complete blood counts were carried out in 12 patients before and during the drug administration. No abnormality developed in either the liver profile (Table 6) or the hemogram (Table 7).

TABLE 6. *Effect of glycypyramide on liver function test**

Patients		I.I	TTT	ZTT	GOT	GPT	Al.P.
M.H.	B	5.5	2.8	12.7	30	18	22.5
	A	5.8	4.0	13.8	23	14	18.0
I.K.	B	7	0.6	2.6	8	11	6.2
	A	7	1.1	3.1	12	6	5.6
N.I.	B	5.6	2.0	6.5	29	37	22.5
	A	6	1.0	6.6	22	19	16.0
K.O.	B	8	1.7	3.6	8	8	
	A	8	4.5	10.4	37	29	14.2
Sa.Ko.	B	3.9	0.7	6.1	13	5	6.6
	A	8.2	1.1	4.8	12	20	4.5
M.C.	B	7	3.0	7.8	8	10	10.9
	A	7	3.7	6.0	11	12	9.2
S.O.	B	9.6	2.2	3.4	17	6	7.3
	A	4.0	1.7	3.4	13	23	5.1
A.Y.	B	4	0.2	3.6	24	33	4.4
	A	4	1.9	6.6	7	5	4
T.O.	B	5.5	0.9	6.6	17	12	10.0
	A	5.7	1.3	7.8	15	10	11.7
M.A.	B	10.	8.4	5.1	11	3	8.4
	A	6	3.1	7.2	19	14	8.2
Sa.O.	B	4	0.2	1.6			
	A	5.4	1.4	7.2	15	10	6.3
T.N.	B	5.2	0.6	3.3	10	8	7
	A	6	1.6	5.0	10	6	6.3
Sh.S.	B	6.2	2.2	5.2	19	16	5.0
	A	6.8	2.4	4.4	13	38	5.1
T.K.	B	7.5	2.0	4.4	12	11	12.8
	A	6.5	1.7	3.6	19	14	8.2
Z.T.	B	6.1	2.6	7.5	20	6	6.3
	A	6.0	3.4	8.2	20	6	7.5
K.S.	B	6	1.2	6.6	5	4	6.2
	A	6	1.0	6.2	5	3	5.9
Ka.T.	B	7.2	0.7	3.6	11	9	5.0
	A	5	0.8	4.6	10	3	6.0
Sh.Sa.	B	6	0.1	1.6	12	16	5.4
	A	5	1.1	3.4	22	32	7.1
Y.K.	B	5	0.6	1.8	19	15	6.7
	A	5	2.5	5.2	13	10	5.6
I.Ich.	B	5	1.2	6.2	39	37	14.3
	A	8.2	1.5	8.0	40	34	17.0

* I.I., icterus index; TTT, thymol turbidity test; ZTT, zinc turbidity test; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; and Al.P., alkaline phosphatase. Numbers express the unit in each measurement. B and A, mean before and after the treatment with glycypyramide, respectively.

TABLE 7. *Effect of glycopyramide on hemogram*

Patients	White blood cell		Red blood cell (million)	Hemoglobin (%)
M.S.	B*	8225	4.54	70
	A	9,250	4.26	89
T.E.	B	10,000	3.71	94
	A	10,700	3.94	82
N.I.	B	5,000	4.83	98
	A	4,500	4.54	96
S.K.	B	6,200	4.28	85
	A	6,500	4.56	90
M.C.	B	5,200	3.93	83
	A	5,045	4.91	94
S.O.	B	4,700	4.32	110
	A	7,600	4.84	94
T.N.	B	6,600	4.28	80
	A	5,900	4.17	78
Sh.S.	B	7,000	5.10	116
	A	6,375	4.25	92
Z.T.	B	5,800	4.91	88
	A	6,400	5.02	90
K.S.	B	5,250	4.23	80
	A	7,200	4.10	86
Sh.Sa.	B	8,050	4.65	102
	A	8,150	5.05	110
Y.K.	B	6,750	4.10	100
	A	7,200	4.20	90

* B and A mean before and after the treatment with glycopyramide, respectively.

9) *Side-effects of glycopyramide*

Four of 72 patients developed minor side effects. Three individuals developed gastrointestinal symptoms, including constipation, mild abdominal pain and distention. The other patients experienced general malaise. The drug was not discontinued in these cases. All side-effects manifested themselves within a week after starting the administration of glycopyramide.

DISCUSSION

A newly synthesized sulfonylurea, glycopyramide, showed good effect in 68 per cent of 72 diabetic patients, and fair effect in 20 per cent of them. A survey of the reports on glycopyramide published in Japan¹⁴⁻²⁰ shows that good response to the drug was observed in 175 out of 206 diabetic patients, although the criteria for the evaluation of the drug effect varies more or less in different reports. These results, including our own, indicate that the drug produced the same effect as other sulfonylurea drugs widely used.

From the analysis of the relationship of the drug effect to clinical pictures, patients with mild diabetes or short duration of the disease usually showed good response. However, it should be noted that glycopyramide exerted good effect on the patients whose fasting blood sugar was higher than 200 mg% or in those who were

failed to respond well to other antidiabetic agents. Furthermore, insulin was successfully replaced by glycopyramide in 6 out of 7 diabetic patients who were treated with 25 units or less of insulin per day.

Blood sugar lowering effect of glycopyramide might be due to increased secretion of insulin from the pancreas. In other experiments with a group of four anesthetized dogs,²¹ venous blood sugar fell to the mean nadir of 72 mg% from the baseline level of 105 mg% following the injection of glycopyramide in a dose of 50 mg per kg of body weight. Plasma insulin concentration of the upper pancreaticoduodenal vein abruptly rose within 15 minutes after the drug administration. The result in one dog is shown in Fig. 1. Plasma insulin concentration in the upper pancreaticoduodenal vein rose much higher after the injection of glycopyramide in a dose of 50 mg per kg of body weight in comparison with the results obtained in a dog injected the same amount of tolbutamide. These results are compatible with the observation of Oda *et al.*¹⁴ that the potency ratio of glycopyramide against tolbutamide was 2.66 based on the hypoglycemic effect in rats.

Fig. 1. Effects of the intravenous administration of glycopyramide in a dose of 50 mg per kg body weight upon blood sugar and plasma insulin in the pancreatic vein and the femoral vein of an anesthetized dog.

The drug, when administered by mouth at fasting, is absorbed very slowly as described elsewhere.²¹ Plasma concentration of glycopyramide in healthy volunteers rose gradually and reached the peak 60 minutes after the administration of one gram of glycopyramide, the high level being maintained during three hours. When one gram of glycopyramide was given at fasting with 2 g of sodium bicarbonate,

glyclopypyrimide was absorbed rapidly and its concentration in plasma reached the peak during first 30 minutes. It is supposed that the plasma concentration of glyclopypyrimide can be maintained in the long-term administration of the drug by following possible reasons; (1) diet ingestion enhances the absorption of the drug through the rise in pH and the increased solubility (2) glyclopypyrimide can be absorbed easily through the change in the intestine by long-term administration of the drug, and (3) accumulation of the drug in blood by slow absorption. Glyclopypyrimide is broken down in the body to chlorobenzene sulfonamide, pyrrolidine and urea which are excreted into urine (T. T. Irikura, unpublished). It is indicated from the results of experiments with rabbits and human subjects that half life time of glyclopypyrimide is about three hours in the body.^{14,21}

As described above, there are few minor side-effects but no toxicity on the liver function or hemogram was observed. In the reports by various authors in Japan, there were described only few side-effects such as disturbance in the gastrointestinal tract.¹⁴⁻²⁰ From these facts it may be concluded that glyclopypyrimide is a therapeutically effective oral antidiabetic agent which can be used with safety.

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