Diabetologia, Suppl. to 9, 348—350 (1973)

Clinical Study with Glipizide, a New Oral Antidiabetic Drug

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Received: April 5, 1973, and in revised form: July 9, 1973, accepted: July 9, 1973

Summary. Nineteen patients, of whom ten had been previously treated with and failed on other oral antidiabetic drugs, were included in a cross-over trial in order to compare the efficacy of glipizide with placebo in the case of the newly diagnosed patients and with previous therapy in established diabetics. Glipizide was more effective than placebo in all cases and provided excellent or good control in eight out of the nine newly diagnosed patients. In three out of the ten previously treated patients, glipizide improved control. The drug was well tolerated.

Key words: Maturity onset diabetes, glipizide, hypoglycemic sulphonamides, oral antidiabetic drugs, sulfonylureas.

Glipizide is a sulfonylcyclohexylurea derivative and its mode of action has been described by Ambrogi *et al.* [1, 2, 3]. The drug has proved to be a potent hypoglycemic agent. No toxic effects were observed during long-term treatment in animals with doses up to 60 times the optimal therapeutic dose. Neither have any teratogenic effects been observed.

Clinical material

19 patients, 9 women and 10 men, have been treated with glipizide. All were out-patients. The material was divided into two groups.

Group I

7 women and 3 men, average age 56 years, had earlier been treated with sulfonylurea drugs. Four of these had been treated with a combination of phenformin and sulfonylurea. Nine of the patients were so-called secondary failures. One patient had nausea with the previous therapy.

Group II

2 women, 7 men, average age 55 years, with newly diagnosed diabetes, not controlled by diet alone.

Methods

The glipizide trial was performed as a cross-over study. In group I glipizide was compared with placebo and earlier antidiabetic agents given according to one of two alternatives:

1. placebo/4 weeks/ — glipizide/3 months/ — placebo/4 weeks/ — earlier used drug/3 months/, or

2. placebo/4 weeks/ — earlier used drug/ 3 months/ — placebo/ 4 weeks/ — glipizide/3 months/.

Group II was treated according to one of the following 2 alternatives:

1. diet/3 weeks/ — glipizide/2 months/ — placebo/2 months/ — glipizide/ 2 months/, or

2. diet/3 weeks/ — placebo/2 months/ — glipizide/2 months/ — placebo/2 months/.

All patients had received diet instruction and remained on the same calorie consumption during the whole study. Patients on treatment with digitalis, diuretics and/or antihypertensives remained on the same dose during the whole trial period. Patients treated with phenformin remained on the same dose even during "placebo periods".

Glipizide was given as a single dose up to 10 mg and thereafter in 2 doses morning and evening. The patients were examined fasting in the morning, initially every week and then at intervals of 2—3 weeks. At every visit fasting blood glucose (acc. to Marks -59 [4]), urine glucose (tested with Clinitest, Ames) and body weight were checked. Determinations of blood picture, liver and kidney functions, serum electrolytes, serum cholesterol (acc. to Huang [5, Ness [6] and serum triglycerides (acc. to Laurell 66 [7]) were performed. In addition, the fundi were inspected and an ECG performed.

Results

In group I (Table 1) "good control" was obtained in 3 patients who had failed on other antidiabetic therapy. In 4 patients glipizide treatment resulted in impaired control. In three of these patients [3, 5, 10] insulin therapy is now necessary. In group I there are no statistically significant differences between blood and urine glucose during the different periods.

In group II "excellent control" was obtained with glipizide in 5 patients, "good control" in 3 patients

Table 1. *Group I. Previously treated patients*

Pat. No	Sex	Age	Length (cm)	Other therapy	Previous therapy							Placebo					Glipizide							Side effects	Remarks
					Drug	Dose	FBG mg/ 100 ml	UG g/24 h	Chol. mg/ 100 ml	TG mMOL	Weight (kg)	FBG mg/ 100 ml	UG g/24 h	Chol. mg/ 100 ml	TG mMOL	Weight (kg)	Drug	Dose	FBG mg/ 100 ml	UG g/24 h	Chol. mg/ 100 ml	TG mMOL	Weight (kg)		
1	F	72	160	Digitalis Tiazide Hydralazine	C F	375 100	162	5	210	3.48	69.4	358	100	212	3.96	67	Gli F	20 100	260	10	220	1.49	62.3	0	—
2	F	72	155	Digitalis	T	1.5	178	18	280	2.31	59	200	125	286	2.16	57.8	Gli	20	182	46	319	2.26	58.2	0	—
3	M	71	170	Digitalis	T	1.5	190	50	175	1.00	85.8	253	50	147	0.97	83.7	Gli F	20 100	260	50	175	1.10	75	0	Changed to Insulin 52 IU A few months later op. for cancer of pancreas
4	F	40	161	—	C F	375 100	322	150	202	0.66	71.6	345	100	223	0.98	71	Gli F	20 100	230	0	211	0.60	74	0	—
5	F	40	162	Tiazide Clonidin	C	375	144	0	270	1.02	89	300	24	260	4.33	88.4	Gli	20	160	5	238	2.10	90	0	Now changed to Insulin
6	F	61	162	Tiazide	C F	375 100	201	10	260	2.01	81.2	205	110	239	1.94	76.9	Gli F	20 100	290	36	282	2.25	73.5	0	—
7	F	60	162	—	Gb	5	187	0	267	0.97	78	200	20	235	0.66	77.2	Gli	10	130	0	265	0.86	78	0	—
8	F	70	161	Digitalis	C F	375 100	294	22	233	2.12	76	300	30	340	3.42	75	Gli F	20 100	230	10	254	1.83	74	0	—
9	M	38	186	—	C F	375 100	175	10	348	0.62	130	290	10	309	7.21	130	Gli F	20 100	255	10	300	4.33	130	0	—
10	M	38	182	—	Gb	15	200	0	204	0.47	74.2	200	2.5	216	0.29	73.5	Gli	20	322	75	213	0.27	72.1	0	Changed to Insulin 32 IU
X							205.3	26.5	244.9	1.47	81.5	265.1	57.2	246.7	2.59	80.1			231.9	24.2	247.7	1.71	78.7		
S.E.M.							18.08	14.53	15.98	0.96	5.98	19.59	14.72	17.37	0.68	6.09			18.75	8.17	14.15	0.37	6.32		

C = Chlorpropamide, F = Phenformin, T = Tolbutamide, Gb = Glibenclamide, Gli = Glipizide, FBG = Fasting blood glucose, UG = Urine glucose, Chol. = Cholesterol, TG = Triglycerides

Table 2. *Group II. Newly diagnosed patients*

Pat. No	Sex	Age	Length (cm)	Without therapy					Placebo					Glipizide							Side effects	Other therapy	Remarks
				FBG mg/ 100 ml	UG g/24 h	Chol. mg/ 100 ml	TG mMOL	Weight (kg)	FBG mg/ 100 ml	UG g/24 h	Chol. mg/ 100 ml	TG mMOL	Weight (kg)	Drug	Dose	FBG mg/ 100 ml	UG g/24 h	Chol. mg/ 100 ml	TG mMOL	Weight (kg)			
1	M	66	178	160	5	358	1.96	64	152	2.5	308	1.30	61	Gli	5	135	0	314	1.86	61.8	(+) 0	—	At one occation slight hypoglycaemia
2	M	52	167	322	100	383	11.93	73.8	196	10	229	2.33	75.8	Gli	5	92	0	197	1.15	77	0	—	—
3	M	51	180	176	9	259	0.85	81.5	138	0	298	0.96	79	Gli	2.5	108	0	284	0.82	78	0	—	—
4	M	34	173	180	60	194	0.36	79	142	0	216	0.77	72.9	Gli	5	98	0	202	0.94	74	0	—	—
5	M	65	168	220	20	340	2.84	78.5	203	34	389	2.05	81	Gli	15	110	0	339	2.19	79	0	—	—
6	M	63	168	240	100	227	4.03	90	216	140	230	3.04	88.5	Gli	5	116	0	239	1.30	85	0	—	—
7	F	42	169	184	25	239	2.12	130	180	10	264	1.98	130	Gli	15	160	0	232	2.18	130	0	—	—
8	M	70	172	300	60	240	2.01	122	303	25	220	0.82	114	Gli	20	128	0	239	1.46	120	0	Furosemide Prednisolon (5 mg)	—
9	F	66	164	293	75	232	0.64	83.3	253	0	225	1.36	84.6	Gli	20	231	0	198	0.88	83.8	0	Levaxine	—
X				230.56	50.44	274.66	2.97	89.12	198.11	24.61	264.33	1.62	87.46			130.89		249.33	1.42	87.62			
S.E.M.				20.39	12.40	22.45	1.18	7.39	18.09	14.97	19.32	0.22	22.61			14.27		17.31	0.18	7.46			

FBG = Fasting blood glucose, UG = Urine glucose, Gli = Glipizide, Chol. = Cholesterol, TG = Triglycerides

and "fair control" in 1 patient. With diet and placebo "good control" was achieved only in 2 patients, and in the remaining cases satisfactory control was not obtained (Table 2).

In group II there are significantly lower blood glucose values on glipizide therapy than on placebo ($0.01 < p < 0.001$). Urine glucose disappeared during glipizide therapy in all cases.

Side effects

After 2 weeks treatment with glipizide at a dose of 5 mg, one man in group II had hypoglycemic side effects approximately 3 h after breakfast and glipizide. Rapid relief was obtained following the intake of food. With the same dose of glipizide the patient has subsequently been subjectively well. Consecutive blood glucose determinations up to 3—4 h after breakfast have not shown any excessively low values. Glipizide was well tolerated by the remaining patients in both groups. Gastrointestinal side effects have not been observed.

Blood picture, liver and kidney function as well as electrolytes have remained unchanged. Serum cholesterol and serum triglycerides and also blood pressure have shown a tendency to decrease during treatment. The appearance of the fundi and ECG have remained unchanged.

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