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Glipizide versus Tolbutamide in Maturity-Onset Diabetes, an Open Comparative Study

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Summary. The preliminary results of an open comparative study of the oral antidiabetic glipizide and tolbutamide have shown that in all patients, except for 1 [2] of 16 glipizide cases and [2 [1] of 12 tolbutamide cases, an adequate control of the diabetes could be achieved. There were no side effects besides clinical signs of hypoglycaemia in 4 patients on Glipizide.

Key words: Sulfonylureas, naturity-onset diabetes, glipizide, tolbutamide, hypoglycaemic sulphonamides, oral antidiabetic drugs, lipids.

Glipizide, a new and potent sulphonylurea derivative has been compared with tolbutamide in an open comparative study in terms of dosage, efficacy, toleration, incidence of primary and secondary failures and effect on the parameters of lipid metabolism.

Glipizide is a sulphonylcyclohexylurea with the following structural formula:

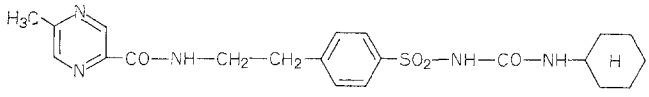

Fig. 1

The chemistry, pharmacokinetics, and clinical results obtained with glipizide have been described in a series of recent papers [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11].

Method

1. Prior to the onset of treatment with either trial drug both newly diagnosed cases and patients previously treated with oral antidiabetics were maintained on diet alone for a period of 3 to 7 days.
Diagnostic criteria:

- Fasting level of blood glucose over 120 mg%
  (Glucose-Oxydase-Perid Method)
- Postprandial values over 180 mg%
- Glucosuria
  (qualitative: strips B-M-Test Glucose
  quantitative: polarimetry)
- Clinical symptoms of diabetes mellitus

Diet: 1500—2000 cals/day
according to situation of patient
carbohydrates: 150—220 g/day
about 45% carbohydrates
about 35% fat
about 20% protein

2. The starting dose of glipizide was 2.5 mg and 5 mg, respectively. Dosage adjustments were made every 3 to 7 days up to 20 mg/die (maximum 30 mg).

The daily dosage was either given as a single dose or, if this appeared to be necessary, as multiple doses. The dosage range of Tolbutamide was 500 mg to 4000 mg.

3. The following parameters were measured before treatment, weekly during the first month of treatment and then at monthly intervals: blood glucose levels (enzymatic) fasting and 1 and 2 h after a test meal (breakfast consisting of 27 g CHO = 113 cals); 24 h urinary glucose excretion; blood pressure and pulse in lying and standing position; and body weight.

4. Total cholesterol, free cholesterol, non-esterified fatty acids, triglycerides, alkaline phosphatase, BUN, uric acid and the serum electrolytes Na^+ and K^+ were determined before treatment and then every 3 months.

Fundus examination and ECG were performed before treatment and will be repeated after 12 months therapy.

5. *Criteria of Assessment*: a) *Clinical* (Cl): Clinical assessment according to the overall picture based on the evaluation of all laboratory values as well as the patient's state in respect of feeling of well-being, ability to do his work, absence of more severe hypoglycaemic episodes and other data.

1 = excellent, 2 = good, 3 = fair, 4 = poor, 5 = negative

This assessment reflects the personal judgement of the author, taking into account the patients professional and private situation.

b) *Chemical 1* (Ch_1): according to blood glucose values during therapy.

The following limits were arbitrarily selected as reference values:

This arbitrary selection is considered to be justified by the following points:

Table 1

		fasting	1 h after loading	2 h after loading
Range	low	< 100	< 160	< 120
	medium	100–130	160–220	120–150
	high	> 130	> 220	> 150

Only three ranges (low, medium, high) are defined by these values, thus simplifying evaluation and not overstressing minor differences.

Fasting and 2 h values are lower, 1 h values higher compared with criterion Ch_2 (see below), thus rendering the selected ranges more appropriate to the blood glucose values actually observed.

These values selected for the evaluation of results coincide with the values recommended for the diagnosis of diabetes [12, 13]. The evaluation is based on the position of the arithmetic means of the blood glucose concentrations in this reference system (fasting value and 1 and 2 h after loading). The mean values were calculated from the blood glucose concentrations measured at the monthly assessment visits.

According to the distribution of these individual three mean values (fasting, 1 h, 2 h) for each patient under therapy, assessment is accomplished in the following way:

Table 2

	Distribution of mean blood glucose values (monthly assessments):
1 = excellent	three values in low range or two values in low range and one value in medium range
2 = good	three values in medium range or two values in medium range and one value in low or high range
3 = fair	one value in medium range and two values in high range
4 = negative	three values in high range

Assessment Scale

c) *Chemical 2* (Ch_2): in terms of blood glucose values according to table:

The most unfavourable value was decisive for the evaluation according to Ch_2.

6. Patient Selection: 40 patients with maturity-onset diabetes were allocated to one of the treatment groups (according to a randomization list) so that 20 patients were treated with glipizide and 20 patients with tolbutamide.

Patients were excluded for the following reasons:

- hypersensitivity to one of the trial drugs,
- ketoacidosis (plasma HCO_3^- below 17 mEq/l),
- juvenile and brittle diabetes,
- renal and/or hepatic insufficiency,
- pregnancy,
- patients treated with insulin in excess of 40 U daily,
- severe complications such as gangrene, tuberculosis, etc.

Preliminary Results

Patient Information

Duration of diabetes: Average: 3.3 years (range 3 months to 11 years) glipizide-patients: 3.2 years (3 months to 10 years) tolbutamide-patients: 3.5 years (4 months to 11 years).

Previous antidiabetic treatment: All patients but one had been treated previously with different sulphonylureas, sometimes in combination with biguanides. Three of the glipizide-patients had previous insulin treatment ($\leq$20 U/day).

Body weight: Measured by the ratio

$$\frac{\text{Weight (kg)}}{\text{Height (cm)} - 100},$$

half of the patients were 20% or more overweight (8 of 16 in glipizide-group and 6 of 12 in tolbutamide-group).

Average weight changes from initial pretreatment values to values at last assessment visit were minimal (glipizide + 0.4%, range − 4.0% to + 5.5%, tolbutamide + 0.7%, range − 3.1% to + 7.3% of initial value).

Glucosuria at monthly assessments:

Glipizide

41 assessments none
2 assessments 2 g/24 h
1 assessment 4 g/24 h
2 assessments 5 g/24 h
2 assessments 6 g/24 h

Tolbutamide

33 assessments none
1 assessment 3 g/24 h
2 assessments 12 g/24 h

In the following the results obtained in 28 patients (16 glipizide, 12 tolbutamide) with a total of 84 monthly assessments (48 glipizide. 36 tolbutamide) are reported (see Tables 4, 5, 6).

Summary of the assessments according to the criteria under point 5.

The mean values of all patients (with standard error) prior to treatment and during therapy (mean values of monthly assessments) with the trial drugs glipizide and tolbutamide are shown in Fig. 2.

For ready orientation, the reference values (Ch_1. see method 5) are also shown in this figure.

There were no side effects, besides clinical signs of hypoglycaemia in 4 patients on glipizide.

In patients No. 1, 5, 7, 15 a state with clinical signs of hypoglycaemia (tachycardia, increased perspiration, tremor) was observed approximately 5 h after lunch and about 9 h after intake of the daily dose of 2.5 mg glipizide. Blood glucose values taken at this stage were not within the hypoglycaemic range (No. 1: 64 mg%, 68 mg%, No. 5: 63 mg%, No. 7: 58 mg%, No. 15: 79 mg%). These manifestations appeared in patient No. 1 twice and in patients No. 5 and 7 once after 3 months of treatment. Patient No. 15 showed these symptoms after about 2 weeks of therapy. In all cases it was regarded as a typical relative hypoglycaemia [14, 15] and could be controlled by oral carbohydrate.

In 1 patient [26] tolbutamide was discontinued prior to the first monthly assessment and treatment continued with diet alone. This patient is not included in Tables 4 and 6.

In 3 patients [5, 7, 20] the metabolic state improved under glipizide to such an extent that the patients could be transferred to diet alone after 3 months of treatment. Table 5 shows the values during glipizide therapy only.

Table 3.

Therapeutic results	Glycaemia (values in whole blood)		
	fasting	1 h p.p.	2 h p.p.
excellent	≤110 mg/100 ml	≤150 mg/100 ml	≤130 mg/100 ml
good	≤130 mg/100 ml	≤180 mg/100 ml	≤150 mg/100 ml
fair	≤150 mg/100 ml	≤200 mg/100 ml	≤180 mg/100 ml
poor	≤220 mg/100 ml	≤280 mg/100 ml	≤250 mg/100 ml
negative	> 220 mg/100 ml	> 280 mg/100 ml	> 250 mg/100 ml

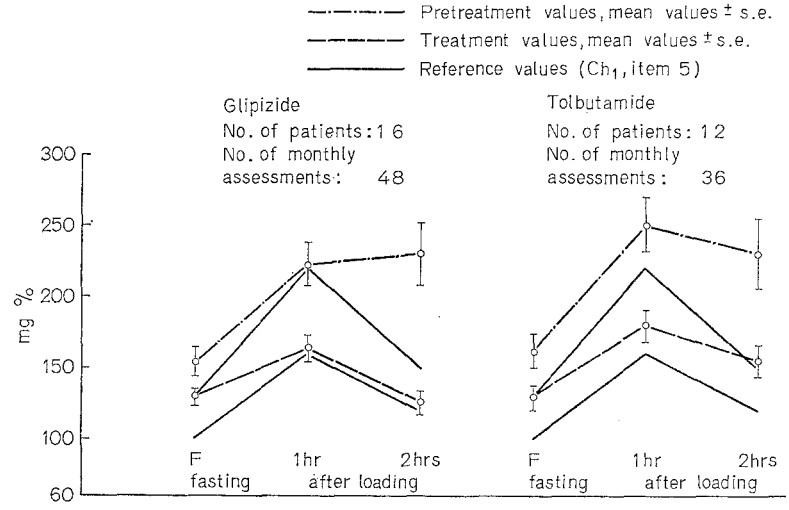

Fig. 2. ·-·-· pretreatment values, mean values ± s.e. – – – treatment values, mean values ± s.e. —— reference values (Ch_1, point 5)

Table 4

	Glipizide			Tolbutamide		
	Cl	Ch_1	Ch_2	Cl	Ch_1	Ch_2
Excellent	7	7	3	1	5	3
Good	4	6	7	7	3	2
Fair	4	1	3	0	2	3
Poor	0		3	2		3
Negative	1	2	0	2	2	1

Discussion

Because of the small number of patients and the short period of observation, only preliminary results can be presented. Since the blood glucose values recorded at the assessment visits constitute an essential, though not the only, criterion of evaluation and as there exists no generally accepted reference standard for the "chemical" evaluation [16], the results were graded according to clinical criteria (Cl) as well as two different "chemical" criteria (Ch_1, Ch_2; see criteria of assessment, point 5, and Tables 4, 5, 6).

Taking into account that with the criterion Ch_1 a four-grade scale, and with the criteria Cl and Ch_2 a five-grade scale is used for classification, the results can be considered as more or less concordant. Where this is not the case, as in patient No. 29 (Table 5), the more flexible clinical classification is better suited than the calculation of mean values of longer periods and the classification according to rigid evaluation patterns.

In the case of patient No. 29 frequent assessments and inquiries have shown that this patient had reduced the dose on her own. After the patient had observed the dosage recommended, the quality of control could be rated as moderate from the clinical point of view.

to the results of Emanueli *et al.* [9]. These authors stated that favourable control according to different criteria was possible in 76—83% of several hundred patients.

Considering the fact that the initial mean value one

Table 5. *Glipizide*

Patient No.	Age	♂	♀	Mean daily dose mg	Pretreatment val. F	1 h	2 h	Mean values of monthly assessments: F	1 h	2 h	Number of monthly assessments:	Evaluation Cl[a]	Ch_1[b]	Ch_2[a]
1	58	x		2.5	123	179	136	79	134	100	3	1	1	1
2	58		x	6.25	139	197	218	123	170	126	4	2	2	2
4	75		x	6.88	119	210	186	126	163	129	4	3	2	2
5	64		x	3.12	122	154	115	122	148	72	3	1	1	2
7	75		x	3.54	135	159	221	96	119	100	3	1	1	1
11	70	x		15.63	226	340	450	136	184	163	2	2	3	3
13	72	x		18.75	146	228	252	124	174	122	3	2	2	2
15	71		x	3.13	129	234	259	113	139	83	2	1	1	2
17	55	x		5.0	127	181	198	130	144	96	3	3	1	2
18	70		x	7.08	176	183	234	149	185	138	3	2	2	3
20	37	x		1.72	132	228	147	101	105	67	2	1	1	1
23	78		x	11.41	146	268	330	104	214	178	4	1	2	4
24	64	x		22.81	199	263	241	196	249	208	4	5	4	4
28	70	x		7.19	248	350	350	121	152	100	4	1	1	2
29	76		x	23.75	169	223	226	220	251	191	2	3	4	4
30	68		x	2.5	125	175	115	132	197	99	2	3	2	3
	Mean values:				154	223	230	129	164	126				
	Standard error:				9.87	14.57	22.33	5.71	8.68	7.64				

Key: [a] 1 = excellent, 2 = good, 3 = fair, 4 = poor, 5 = negative.
[b] 1 = excellent, 2 = good, 3 = fair, 4 = negative.

Table 6. *Tolbutamide*

Patient No.:	Age	♂	♀	Mean daily dose mg	Pretreatment val. F	1 h	2 h	Mean values of monthly assessments F	1 h	2 h	Number of monthly assessments	Evaluation Cl[a]	Ch_1[b]	Ch_2[a]
6	71		x	3167	230	350	350	94	166	106	3	2	1	2
8	59	x		2750	138	256	278	166	191	170	3	4	3	4
9	62		x	3000	194	208	275	122	183	164	1	2	2	3
10	53	x		2000	118	269	227	104	128	111	3	2	1	1
12	68		x	1833	191	370	274	131	192	143	3	2	2	3
14	76		x	1750	158	278	335	156	222	234	2	5	4	4
16	70	x		500	126	199	122	68	110	76	3	1	1	1
19	76		x	1000	148	268	192	91	148	127	3	2	1	1
21	75		x	500	121	159	113	116	169	91	4	2	1	2
22	69		x	1000	138	158	118	118	166	154	4	2	2	3
25	61		x	3000	181	248	284	142	172	210	4	4	3	4
27	69		x	3333	203	246	206	244	329	308	3	5	4	5
	Mean values:				162	251	231	129	179	155				
	Standard error:				10.59	18.88	23.76	7.87	9.85	11.45				

Key: [a] 1 = exellent, 2 = good, 3 = fair, 4 = poor, 5 = negative.
[b] 1 = excellent, 2 = good, 3 = fair, 4 = negative.

When the criteria "excellent", "good" and "fair" (Table 4) are combined, it can be stated that in 80—90% of patients on glipizide and in 65—85% of patients on tolbutamide a reasonable degree of control could be achieved.

The results obtained with glipizide are comparable

hour after load of patients on tolbutamide is somewhat higher than the corresponding value for glipizide-patients it can be stated that the blood-glucose lowering effect of glipizide is at least equal to that of tolbutamide.

After completion of a 12 month treatment course

in 40 patients (20 glipizide, 20 tolbutamide) further results, including also the parameters of lipid metabolism and other laboratory values, will be reported.

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