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Glipizide versus Tolbutamide, an Open Trial

Effects on Insulin Secretory Patterns and Glucose Concentrations

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Summary. An open parallel trial with glipizide or tolbutamide was carried out in a cohort of 29 comparable maturity-onset diabetic patients. Eighteen of these individuals were studied in detail. During six months of active drug therapy the mean decrease in fasting serum glucose levels on glipizide was 25 ±2% versus 17±2% on tolbutamide ($p < 0.025$). Decreases in post prandial glucose levels were 12.2 and 10.4%. Glucose disappearance rates (Kg) during the sixth month of treatment with both drugs increased significantly: on glipizide from 0.47±0.04%/min to 0.85±0.08%/min ($p<0.005$), and on tolbutamide from 0.47±0.08%/min to 0.70±0.11%/min ($p<0.01$). Early and late insulin release (summed increases over basal for 2–10 min and 10–60 min) during intravenous glucose tolerance testing increased during glipizide, but not during tolbutamide therapy. Post prandial insulin increments over basal during an oral glucose tolerance test also increased during glipizide, but not tolbutamide therapy. Both drugs were comparable with regard to efficacy and safety; however, only glipizide had chronic effects upon insulin secretion.

Key words: Glipizide, glucagon, insulin, insulin sensitivity, maturity onset diabetes, oral hypoglycaemic agents, tolbutamide.

The chronic hypoglycaemic effects of the sulphonylureas depend upon the presence of the drugs in the circulation as well as the secretion of insulin [1]. It has however been difficult to demonstrate that such agents chronically alter insulin secretion or secretory dynamics [2, 3]. Contradictions concerning the presence or absence of long term effects on insulin may be due to use of differing secretogogues, routes of administration, or differences in drug action. Drug effects upon monocyte receptors and glucagon responsiveness to a protein stimulus have also been reported [4, 5, 6]. The purpose of the present studies was to explore the hypoglycaemic mechanisms of an established (tolbutamide) and newer (glipizide) sulphonylurea in two comparable groups of maturity onset diabetic patients.

The former has not been shown to have chronic effects on insulin secretion [7] while the latter has been shown to be the most potent sulphonylurea on a weight basis as well as having marked effects upon insulin in short term studies [8]. An open, parallel, comparative trial of tolbutamide and glipizide was carried out in patients with persistent fasting hyperglycaemia during a four week diet-placebo period. During active drug treatment, fasting and two hour post prandial serum glucose levels were assessed at monthly intervals throughout a six month treatment program. Insulin secretion and dynamics and glucose disappearance rates (Kg) were studied before and at the end of the sixth month of therapy.

Materials and Methods

A. Patient Selection

Patients included in this study were male and female adults (who used contraceptives or were unable to bear children) above 30 years of age whose life expectancy was estimated to be at least five years. Such individuals had documented maturity onset diabetes as confirmed by an oral glucose tolerance test (OGTT) on admission to the diet screening phase of the study. United States Public Health Service criteria were used for oral glucose tolerance testing as adapted for serum glucose [9]. Informed consent was obtained at the first visit and an estimate was made of the patient's capability to comprehend and adhere to diet and medication schedules. Exclusion and inclusion criteria for the diet screening phase of the

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Table 1. Inclusion and exclusion criteria[a]

Inclusion	*Exclusion*
1. Over age 30	1. Juvenile-onset or unstable diabetes mellitus
2. Diagnosis confirmed by OGTT	2. Hepatic or renal insufficiency
3. Life expectancy of five years or more	3. Use of diabetogenic drugs
4. Ability to adhere to diet and medication regimens	4. History of drug abuse or non-compliant behaviour
	5. Previous sulphonylurea therapy failure

[a] Abbreviation used: OGTT, oral glucose tolerance test

study are summarized in Table 1. Twenty-nine individuals were maintained on either tolbutamide or glipizide. Eleven individuals had missing data, were lost to follow-up, had to discontinue drug, and/or declined to continue in the study for its full duration. Eighteen completed the study and are described in detail. Patients were recruited from the population of the diabetes clinic of the Boston City Hospital and studied in the ambulatory facility of the Thorndike General Clinical Research Center for Boston University Medical Center at Boston City Hospital.

B. Experimental Design

The study consisted of a diet screening-placebo phase, a baseline evaluation, drug titration, and maintenance periods, and a final evaluation. The screening phase lasted six weeks or less and encompassed a maximum of seven weekly visits. At the first visit patients discontinued any diabetic medications. At that visit they underwent a 100 g oral glucose tolerance test (OGTT) and were then placed on a diet designed to achieve and maintain ideal body weight (±5%) (Metropolitan Life Insurance Co.). The diet consisted of 45% carbohydrate, 20% protein and 35% fat. After receiving a supply of placebo drug the patients were instructed to take one tablet daily before breakfast. At each diet screening visit, fasting and two hour post prandial serum glucose concentrations were determined. The patient's weight was recorded, urinalysis performed for glucose and acetone and an interim history obtained. Serum obtained at these visits was frozen and saved for determination of insulin concentrations. Patients were admitted to the drug titration phase when they exhibited three fasting serum glucose concentrations, of greater than 130 mg/dl and less than 230 mg/dl, the last two of which were consecutive. Before being given active drug, patients underwent a baseline evaluation and an intravenous glucose tolerance test (IVGTT). Specimens were subsequently analyzed for glucose, insulin and glucagon concentrations. Patients then entered the active drug titration phase and were assigned consecutive numbers which were matched with a corresponding list of computer generated random drug assignments.

The drug titration phase lasted until maximum control of fasting hyperglycaemia was obtained, or a maximum tolerated dose was reached. The largest daily doses of glipizide and tolbutamide prescribed were 40 mg and 3 g. Glipizide was supplied as scored 5 and 10 mg tablets, tolbutamide as 500 mg tablets. The drugs were administered in divided doses. During the drug titration phase patients were seen weekly, when fasting and two hour post prandial glucose concentrations were obtained (after a 100 g glucose load). Laboratory screening was done at every other visit beginning with the second titration visit. This consisted of a complete blood count, serum alanine and aspartate aminotransferases bilirubin, albumin and globulin, electrolytes, cholesterol and triglyceride concentrations.

After maximum control or maximum dose was reached for two consecutive weekly visits, the patient entered the drug maintenance phase. Patients were seen at two week intervals for the first two maintenance visits and thereafter monthly. The active drug phase lasted for a total of six months or until discontinuation for other reasons. At each maintenance visit, fasting and post prandial glucose concentrations were obtained as described above. Active drug was administered after obtaining fasting blood specimens and prior to glucose administration. Laboratory screening was carried out after the second week and second month on drug maintenance and at the final visit of the study. ECG and ophthalmologic examinations were performed before and after six months of drug. At the termination visit of the study an IVGTT was also done.

C. Laboratory and Data Analysis

During the OGTT serum samples were obtained for glucose and insulin concentrations at 0, 30, 60, 90, 120 and 180 min. Koladex® (120 ml), which contains 100 g of glucose, was drunk over a 10 min period. The IVGTT in the study utilized 0.375 g glucose/kg body weight injected IV over 2 min [10]. Samples were collected from a vein of the opposite arm at 0, 2, 4, 6, 10, 20, 30, 40, 60, and 90 min after beginning glucose injection. Whole blood (2 ml) was collected in iced EDTA tubes to which 1000 units of aprotinin had been added [11]. This specimen was then centrifuged at 4° C and the plasma frozen at −20° C for glucagon analysis. Blood samples (3 ml) were placed in dried tubes to clot at 4° C. After separation, the serum was separated and frozen at −20° for determination of insulin. At titration and maintenance visits patients had samples obtained for analysis of fasting and two hour postprandial serum glucose and insulin levels. Serum glucose was measured at each visit by means of a Beckman Glucose Analyzer. Glucagon and insulin samples in a given patient were run in the same assay by previously published methods [12, 13]. The minimum detectable glucagon concentration in this assay is 25 pg/ml (5 pg/tube) and the coefficient of variation is 10% at 50 pg/ml and 5% from 100 to 1000 pg/ml. Unger's 30 K antiglucagon serum was used. ^{125}I insulin and glucagon were obtained from New England Nuclear, Boston, Massachusetts, U.S.A. Glucose disappearance rates were determined by calculation of the slope of log. glucose concentrations in mg/dl from the 10th through 60th min after beginning glucose injection [14].

Baseline glucose and insulin concentrations referred to in the text are the means of concentrations obtained during the screening period. Each mean was derived from a minimum of three observations. Statistical analysis was carried out by paired t tests. When noted, non-parametric techniques were used [15].

Results

The two drug groups were well-matched for age, sex, and previous therapy (Table 2). The difference in duration of diabetes was 4.8 versus 9.4 years for glipizide and tolbutamide groups. The longest duration in the former was 15 years whereas two individuals in the latter group had diabetes for 20 years. %/ideal body weight also differed with five of the glipizide group and three of the tolbutamide group exceeding 115%. However the differences between

Table 2. Baseline characteristics[a]

Tolbutamide group

No.	Age (years)	Sex	Duration of diabetes (years)	% ideal body weight	Previous therapy
01	61	M	3	114	Tolbutamide
02	47	M	12	113	Insulin
03	83	F	20	125	Tolazamide
04	67	M	6	132	Tolbutamide
11	75	M	7	95	Tolbutamide
13	60	M	10	92	Insulin
17	71	F	20	102	Tolbutamide Phenformin
20	63	M	11	98	Diet
23	53	M	3	118	Tolbutamide
27	60	M	2	106	Diet
Mean±SEM					
	64±3		9±2	110±4	

Glipizide group

No.	Age (years)	Sex	Duration of diabetes (years)	% ideal body weight	Previous therapy
05	67	M	15	126	Diet
07	75	M	2	150	Chlorpropamide
12	45	M	5	112	Tolbutamide/ Phenformin
14	58	F	1	129	Insulin
18	48	F	1	115	Diet
19	67	M	7	116	Tolbutamide
21	65	M	3	118	Diet
26	65	M	4	107	Diet
Mean±SEM					
	61±4		5±1	122±5	

[a] Mean and SEM are rounded to the nearest whole number

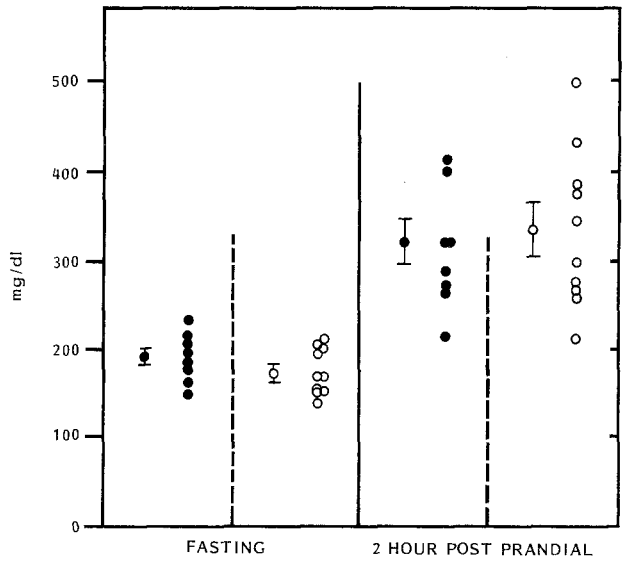

Fig. 1. Baseline (pre-drug) serum glucose concentrations in mg/dl. Mean concentrations are given for the individuals to be treated with glipizide (closed circles) or tolbutamide (open circles). Mean values for each group ± SEM are also shown to the left of each set of data

groups were not significant using the Mann-Whitney U test. Data was also reanalyzed in both groups with the heaviest individual (150% of ideal weight) eliminated from the glipizide group and the two individuals with diabetes of the longest duration excluded from the tolbutamide group. The results and conclusions reached were not changed by such reanalysis.

Mean pre-drug fasting and two hour post-prandial serum glucose concentrations for both the glipizide and tolbutamide subjects were virtually identical (see Fig. 1). Fasting serum levels of glucose were 190±7 and 173±8 mg/dl respectively. Post-prandial concentrations of glucose were 318±25 and 336±28 mg/dl.

Mean % change from baseline glucose concentrations for fasting and two hour post prandial glucose concentrations are shown in Table 3. During the second month of therapy, one tolbutamide treated individual who was responsive during the first month of therapy had an increase in glucose levels of >10% over basal. Therefore data with regard to fasting and 2 h post-prandial plasma glucose levels were deleted for this patient from the second to sixth months of therapy. Tolbutamide was continued since the patient refused insulin therapy and was stable. The mean overall decrease in fasting glucose concentrations on glipizide was 25±2% ($p<0.001$) which was significantly greater than the reduction while on tolbutamide of 17±2% ($p<0.025$).

Overall decreases in two h post-prandial glucose levels were similar for both sulphonylureas: 12% and 10% for glipizide and tolbutamide respectively. Decreases in fasting glucose levels were greater than decreases in post-prandial levels for both groups ($p<0.001$ and <0.025, respectively).

Glucose disappearance rates (Kg) for individuals and for the groups before treatment and while on drugs are shown in Figure 2. Mean Kg for the glipizide treated patients increased from a pre-drug value of 0.47±0.04%/min to 0.85±0.08%/min on glipizide. In the tolbutamide treated patients, Kg increased from a baseline value of 0.47±0.08% to 0.70±0.11%/min. Both increases were highly significant ($p<0.005$ and <0.01).

Early insulin release (Fig. 3a) in response to the IV glucose load was assessed by summing the change in insulin concentrations over fasting levels at 2, 4, 6, and 10 min after beginning a 2 min injection of glu-

Table 3. Percent decrease in glucose concentrations during drug therapy[a]

Fasting							
Month	1	2	3	4	5	6	Mean
Glipizide	20±7	30±2	31±5	23±7	24±6	21±8	25±2
p[b]	0.025	0.001	0.001	0.01	0.005	0.025	0.001
Tolbutamide	7±4	16±5	21±4	24±4	16±6	20±5	17±2
p[b]	NS	0.01	0.001	0.001	0.025	0.005	0.001
Two hour post oral glucose							
Glipizide	9±10	11±9	23±9	9±8	6±6	16±5	12±3
p[b]	NS	NS	0.024	NS	NS	0.01	0.01
Tolbutamide	10±4	8±4	13±5	10±6	12±6	9±5	10±1
p[b]	0.01	0.05	0.025	NS	0.05	NS	0.001

[a] Patient 002 of the tolbutamide group was excluded from analysis for the second through sixth months since his glucose concentrations rose to 10% above baseline levels during this period

[b] Probability that mean glucose concentrations have decreased significantly from the placebo-diet control period NS indicates $p>0.05$

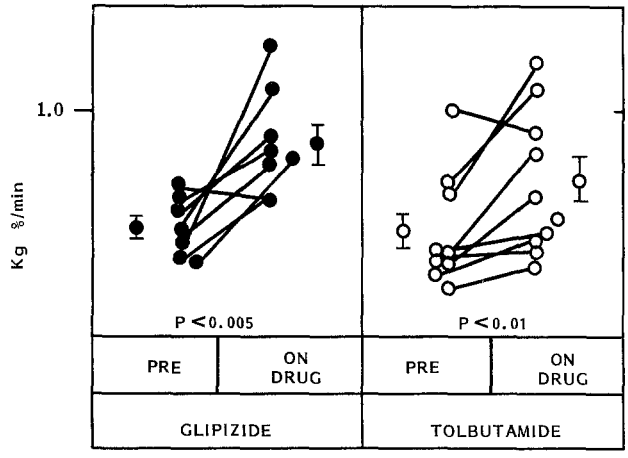

Fig. 2. Glucose disappearance rates (Kg) observed during IVGTT. Individual and mean values are given for each cohort. In the tolbutamide group, one individual had an indeterminate Kg during the baseline study and is therefore omitted from analysis

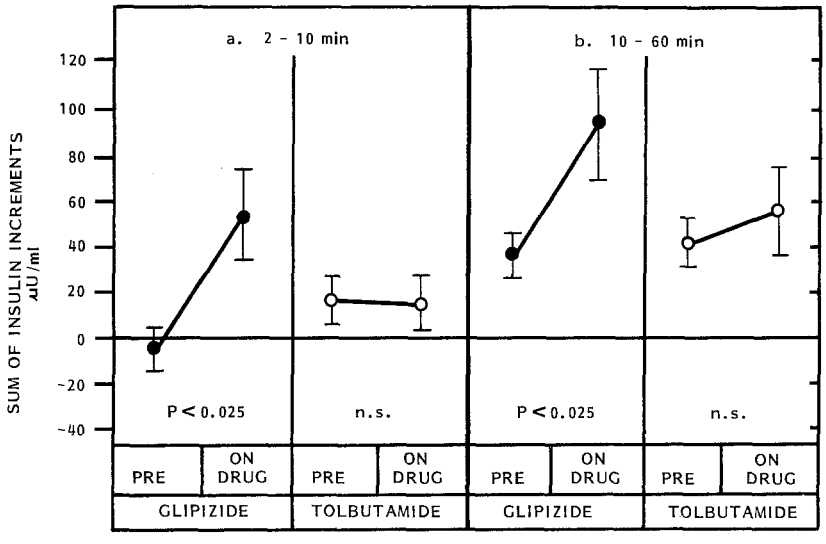

Fig. 3a Early insulin release after glucose injection. The sum of insulin increments over basal (Δ insulin 0–10 min) in μU/ml before treatment and while on drugs is shown. **b** Late insulin release after glucose injection. The sum of insulin increments over basal (Δ insulin 10–60 min) in μU/ml before treatment and while on drugs is shown

cose. Glipizide subjects had no detectable early insulin release relative to fasting prior to drug therapy. Differences in early insulin secretion between the two drug groups prior to active agent were not significant. During drug therapy, early insulin release over fasting increased to 54±20 μU/ml in the glipizide group ($p<0.025$). In contrast, tolbutamide treatment did not alter early insulin release significantly, 17 versus 16 μU/ml. Late release was also increased significantly by glipizide, but not tolbutamide (Fig. 3b). For glipizide, the mean pretreatment late insulin increment was 37±10 μU/ml increasing to 95±24 μU/ml ($p<0.025$) after treatment. Mean fasting and two hour post-prandial insulin concentrations before and while on drug are shown in Table 4. Neither drug altered fasting plasma insulin levels significantly, and tolbutamide did not alter insulin release after an oral glucose load. When analyzed in paired fashion, individuals treated with glipizide increased their 2 h serum insulin concentrations over fasting from 52±9 μU/ml to 69±4 μU/ml, ($p<0.025$). Mean weight loss for these groups was virtually identical, −0.91 kg for the glipizide and −1.09 kg for the tolbutamide treated individuals.

Glucagon suppressibility by hyperglycaemia during IVGTT was studied in two tolbutamide and five

Table 4. Serum insulin concentrations μU/ml

	Glipizide			*Tolbutamide*		
	Before	On drug	p[a]	Before	On drug	p[a]
Fasting	16±3	17±3	NS	10±2	9±5	NS
Two hour post glucose meal	69±11	86±7	NS	54±9	62±10	NS
Insulin increment	52±9	69±4	0.025	44±1	52±10	NS

[a] Probability that insulin concentrations on drug differ from those measured during the placebo-control period: $p>0.05$ indicated by NS

glipizide treated individuals. Prior to therapy, there was a small but significant ($p<0.025$) decrease in plasma glucagon concentrations during the IVGTT. The maximum suppression in glucagon concentrations was 33%. Mean fasting plasma glucagon concentration prior to drug was 119±13 pg/ml and while on drug was 115±24 pg/ml. On drug, mean suppression of glucagon levels was not significant for any time period.

Three of sixteen individuals treated with glipizide had to discontinue therapy. One patient, although normal on baseline evaluation, sustained a transient increase in serum alanine and aspartate transaminases. This abnormality may have been related to a previous history of liver disease. Two individuals had nausea, vomiting, and diarrhoea. All symptoms resolved within 48 h of discontinuation of the drug. Eight of the remaining individuals completed the entire experimental protocol and are included in this report. Of the thirteen patients treated with tolbutamide, none had symptoms requiring discontinuation of drug. Ten tolbutamide treated individuals completed the protocol. There were no individuals in either group who demonstrated progression of retinopathy. Serum triglycerides and cholesterol concentrations remained unchanged.

Discussion and Conclusions

Glipizide was first proposed to be an effective oral hypoglycaemic agent by Ambrogi and co-workers [16]. The dynamics of insulin secretion after a single acute dose of glipizide orally was shown to be similar to that observed after tolbutamide; others demonstrated that peak concentrations of the drug were reached at a similar time after ingestion [17, 28]. The studies presented here provide evidence that long-term alterations in insulin secretion are observed with glipizide, but not tolbutamide.

Both glipizide and tolbutamide were effective in reducing fasting serum glucose concentrations. This could not be explained by alterations in fasting insulin levels. The decrease in fasting serum glucose concentrations with tolbutamide therapy was clearly less than that for glipizide during the first three months while on drug therapy. However, for the fourth, fifth and sixth months the fall in fasting glucose concentration was similar. The explanation for this difference is not obvious and after six months of therapy these two drugs were equivalent. The overall decrease in two hour post-prandial serum glucose concentrations for both drugs were similar.

In the case of glipizide, post prandial hypoglycaemic activity may be attributable in part to alterations in insulin secretion. This was similar to observations made by Hecht in chlorpropamide treated individuals [2]. However, alterations in insulin secretion are clearly not an absolute necessity for the decrease in glucose concentrations, since in both groups glucose concentrations fell in the absence of changes in fasting serum insulin levels. The recent demonstration that diabetic individuals are characterized by decreased insulin binding to monocytes [6, 19] and that treatment with sulphonylureas can enhance binding to such cells, provides a possible explanation for enhanced insulin sensitivity in the absence of changes in insulin concentrations.

A defect in early insulin release after an IV glucose load is a regular feature of diabetes mellitus and has been proposed as a possible causative factor in defective carbohydrate handling [20, 21]. Both tolbutamide and glipizide enhanced glucose disappearance rates during therapy. However, tolbutamide did not alter either early or late insulin release. Glipizide, on the other hand, significantly enhanced both early and late insulin release. Tolbutamide and glipizide possess the capacity to alter sensitivity to endogenous insulin, but only one of these agents alters the magnitude of insulin secretion during chronic therapy.

In unpublished data from our laboratory we have noted that the early insulin release in normal individuals, when analyzed as outlined, exceeds late insulin release by a ratio of at least 2 : 1. In diabetic individuals this ratio is less than 1 : 1. This abnormal pattern of insulin release is not altered by sulphonylurea therapy. Both in the case of glipizide and tolbutamide treated patients, late insulin release over basal, both before and on drug was greater than that of early release. Therefore, despite differences between the two drugs in quantitative effects upon insulin release, neither restored insulin secretory patterns to normal.

The mechanism of failure in glucagon suppressibility by hyperglycaemia in diabetes seems related to both a deficiency of insulin per se and also an abnor-

mality in glucose receptors of the beta cells [22]. The individuals studied in this report had relative preservation of insulin secretion in contrast to the first patients who were described in the literature. Therefore, it was not surprising that these individuals demonstrated suppressibility of glucagon concentrations during hyperglycaemia prior to drug. No consistent changes in glucagon suppressibility were induced by either drug in the small number of individuals studied.

Tolbutamide and glipizide increased insulin sensitivity to endogenous insulin; however, only glipizide had a chronic effect upon insulin secretion. Tolbutamide seems to act primarily by enhancement of sensitivity to endogenous insulin whereas glipizide enhances insulin secretion and may act by both mechanisms.

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