Evaluation of Efficacy and Safety of Gliclazide in NIDDM Patients Who Failed to Respond to Glibenclamide Therapy

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Gliclazide is also a second generation sulphonylurea having hypoglycaemic activity along with hemorrhological properties. Like glibenclamide it increases the secretion of insulin in the early phase of therapy.

Abstract

The safety and efficacy of gliclazide, 80 mg twice daily was evaluated in NIDDM patients who failed to respond to 10mg or more of glibenclamide. Two hundred and twenty seven patients were evaluated in eight centres. Fasting blood glucose was reduced by >20% in 36% and HbAlc by more than 12.5% in 74% of patients at the end of 12 weeks of treatment. The responders to both a reduction of fasting blood glucose > 20% and HbA_{1c} by more than or equal to 12.5% were 32% of patients. There was a significant reduction in total serum cholesterol ($p < 0.001$), triglycerides ($p < 0.05$) and LDL ($p < 0.01$) at the end of 12 weeks, The incidence of side effects was 6.2%.

Introduction

Non-insulin-dependent diabetes mellitus (NIDDM or type 2 diabetes mellitus) accounts for more than 75% of patients with diabetes seen in clinical practice[1]. Patients who fail to respond to dietary control and exercise eventually require pharmacological treatment, usually beginning with an oral hypoglycaemic agent[2]. The ideal pharmacological agent should correct the factor(s) causing the metabolic dysfunction and also reduce the risk of associated macro and microvascular disease.

Glibenclamide is now one of the most widely used oral hypoglycaemic drugs in the management of NIDDM. It is probably the most potent second generation sulphonylurea having short term and long term pharmacological actions that are common to all sulphonylureas. The drugs act initially by augmenting insulin secretion from pancreatic islet beta cells. However, the long term hypoglycaemic action is attributed to extrapancreatic effects including reduction of hepatic glucose output[3-5].

Gliclazide is also a second generation sulphonylurea having hypoglycaemic activity along with hemorrhological properties. Like glibenclamide it increases the secretion of insulin in the early phase of therapy. The glycemic control is partly medicated by extrapancreatic effects such as increased peripheral responsiveness or increased sensitivity to insulin.

The haemobiological actions of gliclazide are seen as reduction in platelet adhesiveness[6] and aggregation[7]. The anti-platelet activity of gliclazide is comparable to that of aspirin and superior to that of dipyramidole[6].

A similar proportion of NIDDM patients are satisfactorily controlled with glibenclamide as compared to other sulphonylureas[8]. Glibenclamide is effective in controlling hyperglycaemia in NIDDM patients who have failed to respond to other sulphonylureas[4,9]. The converse may also occur. Therefore, we studied the efficacy and safety of gliclazide in NIDDM patients who failed to respond to glibenclamide therapy.

Materials and Methods

Two hundred and thirty four patients with NIDDM were enrolled in an open multicentric study in eight centres which had institutional review board approval. Patients of either sex having NIDDM according to WHO criteria for more than

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three months and aged between 30 and 80 (excluding women with child bearing potential) years were recruited. They did not respond adequately to 10 mg or more of glibenclamide as assessed by a HbA_{1c} level of 8% or more. A written informed consent was obtained from each patient. Patients were excluded with chronic hepatic or renal disease with serum creatinine > 1.5 mg/dl, decompensated heart failure (NYHA III/IV), unstable angina or myocardial infarction within the last 12 months, uncontrolled hypertension (SB ≥200 mmHg and/or DBP > 120 mmHg) and those using concurrent drugs known to influence blood glucose levels.

The study subjects were examined thoroughly, including a fundoscopic examination. At the pre-admission visit the following investigations were done; fasting plasma glucose, serum insulin, c-peptide, creatinine, lipid profile, liver function tests and complete blood count. Glibenclamide was discontinued. At the admission visit (not more than three days from pre-admission screening), fasting plasma glucose was done and gliclazide was dispensed for four weeks each, for a total of 12 weeks. Patients were instructed to take one tablet half an hour before breakfast and one half hour before dinner. Fasting plasma glucose was repeated at the end of four and eight weeks. All investigations done at the pre-admission visit were repeated at the end of 12 weeks. Side effects if present were recorded at each visit.

Efficacy assessment

The response of each patient to the study medication was assessed by monitoring the fasting plasma glucose and HbA_{1c}. The responders were those patients who showed a reduction of 20% or more in FPG and 1% (i.e., percentage reduction of 12.5) or more reduction in HbA_{1c}.

Safety assessment

Blood biochemistry was monitored before and at the end of the study. Adverse reactions along with their severity were recorded.

Statistical analysis

The data from all the centres was pooled and analyzed by applying the paired 't' test.

Results

Among the 234 patients enrolled from eight centres, 14 were excluded from efficacy analysis (seven patients dropped out due to the following reasons: 1 took less than 10 mg of glibenclamide, 1 had dental abscess, 1 was unhappy with the treatment and four failed to follow-up. The remaining seven had side effects). Two hundred and twenty patients were analyzed for efficacy. One hundred and twenty four were men and 96 were women. Mean age was 51.93 ± 9.7 years, weight 63.2 ± 9.5 kg, body mass index 24.32 ± 4.3 kg/m. Duration of diabetes was 81.96 ± 61.7 months and duration of using glibenclamide was 47.29 ± 49.25 months (Table 1).

Table 1. Patient profile (n = 227)

Age (years)	51.93±9.7
Sex M/F	125/96
Height (cm)	160.48±8.7
Weight (kg)	63.20±9.5
BMI (kg/m)	24.37±4.3
Duration of NIDDM (months)	81.96±61.7

Clinical efficacy

Gliclazide reduced the FPG by >5% in 117 patients, by ≥10% in 96 and >20% in 41 patients at the end of four weeks. At the end of eight and 12 weeks there was >5% reduction in FBG in 122, 137, ≥10% reduction in 102, 122 and ≥20% reduction in 70 and 79 patients, respectively (Table 2 and Figure).

Table 2. Blood glucose response (n = 227)

	Follow-up (no. of patients)		
Parameters	Visit 1	Visit 2	Visit 3
Reduction in FBS			
≥5%	117	122	137
≥10%	96	102	122
≥20%	41	70	79
Reduction in HbA1c ≥1%			163
Reduction in FBS ≥20% and HbA1c ≥1%			70

Gliclazide reduced the HbA_{1c} by >1% in 163 patients at the eend of the trial period (Table 2). The responders to gliclazide as measured by reduction in FBS by ≥20% at the end of the trial were 79 patient (36%) or for reduction in HbA_{1c} by ≥1% were 163 patients (74%). The responders to both reduction in FBG by ≥ 20% HbA_{1c} ≥ 1% were 70 patients (32%).

Safety evaluation

Out of 227 patients who were evaluable for safety 14 (6.2%) had side effects due to the treatment. Seven had side effects due to which the test drug had to be discountinued. In the rest of the seven patients the treatment was continued as the side effects were mild and did not warrant withdrawal of the test drug. The side effects recorded were: headache in

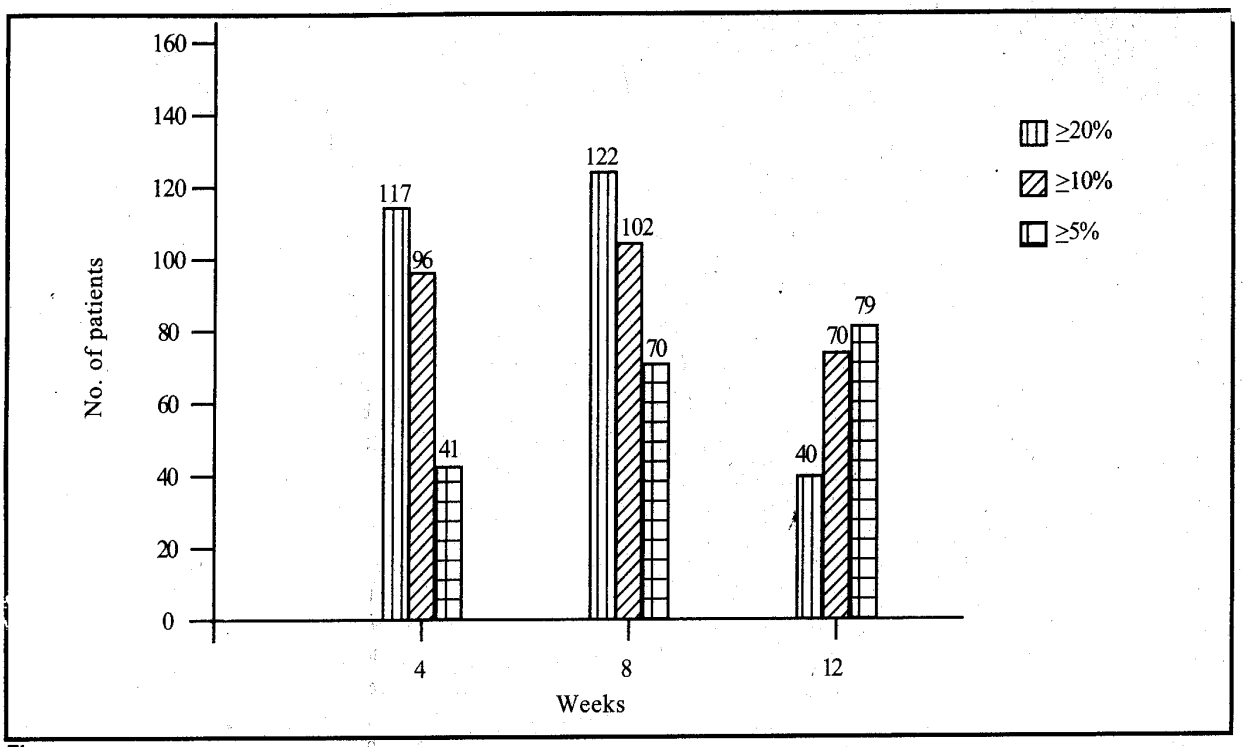

Figure.

five patients, fever in two, nausea and vomiting in three, drowsiness and lethargy in one patient, itching and rash in two patients, hepatitis in one and diarrhoea in two patients (Table 3).

The biochemical parameters are shown in Table 4. The mean serum cholesterol before the study was 199.8 ± 33.09 mg/dl and at the end of the study it was 191.73 ± 33.72 mg/dl ($p < 0.001$). The mean triglycerides and LDL before the study were 183.59 ± 82.93 mg/dl and 117.02 ± 39.48 mg/dl and at the end of the study they were 172.02 ± 69.47 mg/dl and 111.62 ± 36.39 mg/dl respectively ($p < 0.05$ and 0.01 respectively). There was no significant difference in the other biochemical parameters shown in Table 4.

Table 3. Adverse drug reaction (n = 227)

	No. of patients
Headache	5
Fever	2
Nausea and vomiting	3
Drowsiness and lethargy	1
Rash and itching	2
Hepatitis	1
Diarrhoea	2

Discussion

Efficacy of gliclazide 160 mg was studied in the treatment of NIDDM patients who failed to respond to 10 mg or more of glibenclamide. Gliclazide reduced the fasting blood sugar by more than or equal to 20% in 36% of NIDDM patients at the end of three-month treatment, as compared to previous studies where the reduction in fasting blood glucose was 12-62% with 40-320 mg/day of gliclazide[10-12]. However Shaw, et al.[13] showed that there was only 2% decrease in blood glucose levels after treatment with gliclazide in patients who had failed to respond to previous glibenclamide treatment.

Earlier studies showed that the percentage reduction of glycosylated haemoglobin with gliclazide range from 7.9- 37.9[11,14,15]. In this study a percentage reduction of more than 12.5 in glycosylated haemoglobin was seen in 74% of patients.

Several studies reported a significant decrease in total cholesterol of 2-16% in patient with NIDDM treated with gliclazide 20-320 mg/d for 3-36 months[12,16-20]. In the present study there is a significant decrease of 4.1% of serum cholesterol at the end of 3-month treatment with gliclazide 160 mg/day. Colliel et al.[12] showed a significant decrease in plasma triglyceride levels by 18-30%. Similarly a significant decrease in plasma triglyceride levels by 6.3% was seen in our study. In this study there was also a significant percentage reduction of 4.6 in LDL cholesterol compared to 19% in an earlier study[17].

Table 4. Response of other biochemical parameters

	Before	After
SGPT (U/L)	23.8±10.1	24.4±12.5
Alkaline phosphatase (U/L)	122.7±55.7	122.8±51.9
S. cholesterol (mg/dl)	199.9±33.1	191.7±33.8***
S. triglycerides (mg/dl)	183.6±82.9	172.0±69.5*
HDL (mg/dl)	40.2±7.7	40.2±7.4
LDL (mg/dl)	117.0±39.5	111.6±36.4**
S. creatinine (mg/dl)	1.0±0.2	0.9±0.2
S. insulin (mIU/L)	18.5±16.7	17.0±12.8
C. peptidue (nmol/ml)	1.2±1.5	1.3±1.5

*p < 0.05; **p < 0.01; ***p < 0.001.

Holmes et al.[16] have shown an overall incidence of 7.6% of adverse drug reactions with gliclazide. The major reactions were gastrointestinal in 1.7% and skin reactions in 0.7%. In this study the overall incidence of side effects was similar (6.2%); with GI disturbances in 1.3% and skin reactions in 0.9.

References

1. Campbell DB, Laviele R and Nathan C. The mode of action and clinical pharmacology of gliclazide. *Diab. Res. Clin. Pract.* 1991;14(Suppl. 2):S21-S36.
2. Campbell IW. Management of type 2 diabetes mellitus with special reference to metformin therapy. *Diabetes and Metabolism* 1991;17:191-196.
3. Kolterman OG, Gray RS, Shapiro G, Scarlett JA, Griffin J and Olwefsky JM. The acute chronic effects of sulphonylurea therapy in type 2 diabetc subjects. *Diabetes* 1984;33:346.
4. De Fronzo RA and Simonson DC. Oral sulfonylurea agents suppress hepatic glucose production in non insulin dependent diabetes individuals. *Diabetes Care* 1984;(Suppl. 7):72-80.
5. Simonson DC, Ferranini E, Bevilacqua S, et al. Mechanism of improvement in glucose metabolism after chronic glyburidetherapy. *Diabetes* 1984:33:838-845.
6. Desnoyers P and Saint Dzier D. Gliclazide: Haemobiological properties. A synopsis with emphosis on inhibition of plateletcoagulant factors. Royal Society of Medicine International Congress and Symposium series 1980;20:19-27.
7. Ponari O, Civardi E, Mesha S, Pini M, Portioli D and Dettori AG. Antiplatelet effects of long treatment with gliclazide in diabetic patients. *Thrombosis Research* 1979;16:191-203.
8. Hatao K, Kaku K, Matsuda M, Tsuchiya M and Kaneko T. Sulphonylureas stimulate fructose-2, 6 biphosphateformation in proportion to its hypoglycaemic action. *Diab. Res. Clin. Pract.* 1985;1:49-53.
9. Kolterman OG, Prince MJ and Olefsky JM. Insulin resistance in non insulin dependent diabetes mellitus; impact of sulphonylurea agents in vivo and in vitro. *Am. J. Med.* 1983;74(1A):82-101.
10. Page RCL, Harden KE, Walravens NKN, Onslow C, Sutton P, et al. "Healthy living' and sulphonylurea therapy have difference effects on glucose tolerance and risk factors for vascular disease in subjects with impared glucose tolerance. *Q. J. Med.* 1993;86:145-154.
11. Chang TC, Wang LM, Cheng CY, Kyo HF, Lui PC, et al. The action of gliclazide on insulin secretion and insulin sensitivity in non-obese non-insulin dependent diabetic patients. *Chinese Med. J.* 1990;46:79-85.
12. Collier A, Watson HHK, Patrick AW, Ludlam CA and Clarke BF. Effect of glycemic control, metformin and gliclazide on platelet density and aggregability in recently diagnosed type 2 (non insulin dependent) diabetic patients. *Diabete et Metabolisme* 1989;15:420-425.
13. Shaw KM, Wheeley MSG, Campbel DB and Ward JD. Home blood glucose monitoring in non insulin dependent diabetes: The effect of gliclazide on blood glucose and weight control, a multicentre trial. *Diabetic Med.* 1985;8:484-490.
14. Noury J and Nandeuil A. Comparative three month study of the efficacies of metformin and gliclazide in the treatment of NIDDM. *Diabete et Metabolisme* 1991;17:209-212.
15. Johnson AB, Argykaki M, Thow JC, Jones Jr, Broughton D, et al. The effect of sulphonylurea therapy on skeletal muscle glycogen synthase activity and insulin secretion in newly presenting type 2 (non insulin dependent) diabetic patients. *Diabet. Med.* 1991;8:243-253.
16. Homes B, Heel RC, Brogden RN, Speight TM and Avery G. Gliclazide. A preliminary review of its pharmacodynamic properties and therapeutic efficacy in diabetes mellitus. *Drugs* 1984;27:301-327.
17. Fu ZZ, Yan T, Chen YJ and Sang J. Thromboxane/prostacyclin balance in type 2 diabetics: Gliclazide effects. *Metabolism* 1992;(Suppl. 1):33-35.
18. Gram J, Jespersen J and Kold A. Rise of plasma t-ty in a group of maturity onset diabetic patients shifted from a first generation (tolbutamide) to a second generation sulphonylurea (gliclazide). *J. Int. Med.* 1989;225:241-247.
19. Kilo C, Dudley J and Kalb B. Evaluation of the efficacy and safety of diamicron in non insulin dependent diabetic patients. *Diab. Res. Clin. Pract.* 1991;14(Suppl. 2):S79-S82.
20. Zurro Hernandez J and Lavielle R. Is sulphonylurea therapy effective long term? A3 year study with gliclazide. *Curr. Med. Res. Opinion* 1986;10:351-358.