Glimepiride - A Short Term Trial of the Clinical Efficacy

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Diabetes is a common disorder and is reaching epidemic proportions especially in the third world. In the last few years new drugs have emerged targeting at better pharmacokinetic and low side effect profile. Among them have been various insulin sensitizers and newer sulfonylurias. Glimepiride with an impressive tract record offered more benefits and improved quality of life. The clinical efficacy in relation to the commonly used or traditional sulfonylurias was thus evaluated in this short term open trial involving 48 patients. The objective was to determine the clinical efficacy, tolerability, side effect profile and the equivalent dose of glimepiride compared to conventional sulphonylurias. The advantages of this new second generation sulfonyluria are discussed.

Key words: Diabetes, glimepride, efficacy

Diabetes is a common disorder and is reaching epidemic proportions especially in the third world. In the last few years new drugs have emerged targeting at better pharmacokinetic and low side effect profile. Among them have been various insulin sensitizers and newer sulfonylurias. Glimepiride with an impressive tract record offered more benefits and improved quality of life. The clinical efficacy in relation to the commonly used or traditional sulfonylurias was thus evaluated in this short term open trial involving 48 patients. The objective was to determine the clinical efficacy, tolerability, side effect profile and the equivalent dose of glimepiride compared to conventional sulphonylurias. The advantages of this new second generation sulfonyluria are discussed.

Material and Methods

A total of 48 patients were put on glimepiride who had type-II Diabetes and were on oral hypoglycemics alone or in combination with biguanides. It was ascertained that there was no other significant coexisting illness like liver or renal disease and that they were not taking treatment for these. Non of the patients had any serious complication in relation to Diabetes. All patients were otherwise healthy on regular therapy with dietary regulation. None of the patients had diabetes of more than 10 years standing. Patients with persistent proteinuria, advanced retinopathy, neuropathy or heart disease were not included in the study. The patient population was chosen from the outdoor setting of Pakistan Medical Research center, Diabetic department in Fatima Jinnah Medical College, Lahore, Masood Hospital, Faisal Hospital and Akram Medical Complex Lahore from November 1998 to June 1999.

The following parameters were determined before starting glimepiride.

HBA_{1C}	repeat after every 2 months
BSF	repeat on each visit.
Urea and ceratinine	repeat after every 2 months
Blood c/e	repeat after every 2 months
Urine c/e	repeat after every 1 month
Electrolytes	repeat after every 2 month
Cholestrol	repeat after every 2 months
Weight in Kg	repeat after every 1 month

Results

The patients were called for review with the specified tests at the following intervals. (w=week & m=months).

Parameter	1 w	2 w	1 m	6 w	2 m	3 m	4 m
BSF mg%	124	126	118	116	114	116	116
HBA_{1C} %	8.6				8.2		7.9
Urea/Cr	29/0.9				27/0.9		30/0.9
Blood c/e	NAD				NAD		NAD
Urine c/e	-pr		-pr		-pr	-pr	-pr
Electroyte	NAD				NAD		NAD
Cholestrol	244				240		238
Weight Kg	68		68		67	66.5	67.5

(NAD = nothing abnormal detected, pr = protein, values of cholestrol urea and creatinine are in mg%)

Range of BSF was 74-158mg% at start of treatment (mean value of 124mg%) and this range of BSF was bought down to 69-130mg% at end of treatment with a mean of 116mg%. Range of HbA_{1C} was 7.2-11.5% at start of treatment (mean of 8.6%) which changed to 6.8-10.1% at end of treatment with a mean valve of 7.9%. Similarly the cholesterol level ranged between 188-302mg% at start of treatment (mean value of 244mg%) which changed to 166-257mg% at end of treatment with a mean value of 238mg%.

A total of 56 patients were originally included in the study but only 48 completed the study period with 7 patients dropping out or lost to follow-up. One patient had to be taken off the treatment due to hypoglycemia. Thus among the 48 patients who were selected in the study there were 28 males and 20 females. The age ranges from 41 to 68 years with a mean age of 49 years. At the beginning of the study the average HbA_{1C} was 8.6 which fell to 7.9 at the end of the study at the end of 4 months. The 48 patients were taking various oral hypoglycemics as detailed. 18 patients were on glibenclamide in a dose range from 1 to 3 tablets per day or in two divided doses. 14 patients were on gliclazide 80mg in a dose ranging from 1 to 3 tablets per day or in divided doses. 9 Patients were on metformin in a dose ranging from 1 tablet twice daily to 2 tablets thrice daily. 3 patients were on glipizide

in a dose ranging from 1 tablet once daily to 1 tablet twice daily. 4 patients were on a combination of once daily sufonyluria with twice daily metformin.

As a starting substitute dose each oral hypoglycemic tablet in the sulfonyluria group was substituted with glimepiride in the following manner: For every 5 mg of glibenclmide, 80 mg of gliclazide and 5mg of glipizide 1 mg of glimepiride was substituted. For every 1 or 1.5g of metformin 1 mg of Glimepiride was substituted. In this way a 1-3mg of glimepiride was given to the patients and the dose increased as necessary upto a maximum of 4mg per day to achieve satisfactory control. This control was defined a fasting blood sugar of less than 130mg% and at any random time less than 180mg%.

Glimepiride was very well tolerated with hypoglycemia reported as the only side effect. In total there were only 3 patients with episodes of hypoglycemia and 1 patient had to be admitted to the hospital for recurrent hypoglycemia at the start of therapy and on the second day he had to be taken off the treatment. The other two cases had mild symptoms of hypoglycemia that cleared with self-treatment. The effect on the lipids was a decrease in the total level of cholesterol from a mean of 244mg% to 238mg% at the end of treatment period of 4 months. Out of a total of 48 patients 35 showed a decrease (3-15%) in the level of cholesterol, while it remained the same (change less than 3%) in 9 patients and increased (5%) in 4 patients. The drug did not show any untoward effect on common laboratory parameters like urine complete examination, serum electrolyte, urea and serum creatinine. The effect on weight in the total patient population was a slight loss of 1.5 kg in 4 months. In the breakup of these patietns in 24 patients the weight remained constant, in 16 it decreased more that 0.5 kg & in 8 patients it increased more than 0.5 kg.

Discussion

Glimepiride is a new generation oral sulfonyluria[1] which acts on different receptor that the traditional sulfonylurias[2,3]. The binding protein of glibenclamide (140 kDa subunit) and Glimepride (65 kDa subunit) involved in the regulation of ATP dependent K^+-channels and binding affinities are different[4]. This means that in some cases it may also be added to the other sulfonylureas to potentiate the effect - although this remains to be clinically proven. Mechanism of sulfonylurea which stimulates insulin release is supposed by binding to a regulatory subunit of plasma membrane ATP-sensitive K+ (KATP) channel. The consequent closure of KATP channel leads to depolarization, opening of voltage-dependent Ca2+ channels, Ca2+ influx, and a rise in intracellular [Ca2+], resulting in insulin secretion[5]. However, it has been suggested that sulfonylurea may have an additional action on secretion, independent of changes in intracellular [Ca2+] but dependent on the activity of protein kinase C (PKC)[5]. Glimepiride is eliminated by the formation of a hydroxy-metabolite (hydroxy-gli) which exhibits some hypoglycemic effect and a carboxymetabolite (carboxy-gli) which does not have any such activity[6]. The average decrease in sugar is around 10%[6]. In our study it showed an average decrease of 8mg% in the fasting blood sugar levels over and above previous levels while these patients were on other oral hypoglycmics.

Glimepiride is a "second-generation" sulfonylurea agent which stimulates pancreatic beta-cell insulin secretion, lowers blood glucose and improves tissue insulin sensitivity in non-insulin-dependent diabetic subjects. Its insulinotropic effect is comparable with that of glibenclamide but may diminish in the presence of normoglycaemia[7]. This may mean that patients may be less prone to hypoglycemia and may be a more logical choice in patients taking active exercise. The normal response of reduction in insulin production with exercie is maintained while on glimepride[8]. In our study only three patients suffered from hypoglycemia.

Sulfonylureas have extrapancreatic activity and glimepride has the strongest extrapancreatic activity among the sulfonylureas[9]. This activity is due to dephophorylation and activation of key enzymes of glucose transport and metabolism induced by glycosyl-phosphatidylinositol specific phospholipase C[9] .Sulfonylureas may also influence glucagon secretion via ATP dependent K^+ channels with sulfonylurea binding sites in alpha cells of the pancreatic islets[10]. Clinically extrapancreatic effect may be due to stimulation of peripheral glucose disposal and inhibition of glucose production. This effect means that the hyperinsulinemia may be less marked with this drug resulting in lower tong term complications - this however remains to be clinically proven.

In general sulfonylureas are suspected to have adverse cardiovascular effects[11]. One of the mechanisms may be via ATP dependent K+channels in caradiomyosites[12] and smooth muscle cells of blood vessels[13]. Under physiological conditions most channels are closed but open up under ischemic conditions[14]. By inhibiting the ATP dependent K+ channels in the smooth muscles of the coronaries, sulfonylureas reduce the coronary blood flow[15], and by inhibiting these channels in the caradiomyosites sulfonylureas delay myocardial repolarization time causing an arrhythmogenic potential[16]. The anti-athrogenic effect of glimepride is thought to be mediated via action on platelets[17] and inhibition of cyclooxygenase pathway[18]. Whether this effect relates into clinically useful reduction of microand macrovaasculara complications remains to be seen.

It is a safe drug and in our study the only problem was hypoglycemia observed in 3 patients and mild headache in 2 patients requiring simple analgesic paracetamol for 5 days in one patient and 8 days in the second patient. In another study the incidence of headache with glimepiride is about 5%[19]. Out of these one patient had severe hypoglycemia and had to be admitted. We feel this was an idiosyncratic reaction with a hyper-responsive reaction to the drug. In the other two cases the hypoglycemia was mild and controlled by self medication

by the patient and continued with the drug without further problems. In another study fewer hypoglycaemic reactions occurred with glimepiride than with glibenclamide (105 versus 150 episodes[20]. No other side effect was reported by the 48 patients over a period of 4 months. Therefore in conclusion as far as the side effect profile is concerned in our small sample of patients, glimepiride is very safe except for the rare hyper-responsiveness shown by one patient.

It is an effective drug and works well to control blood sugar levels. The safety and efficacy of glimepiride have been confirmed in studies involving over 5000 patients with type 2 diabetes[21]. When we switched patients controlled on other oral hypoglycemics to glimepride, the average blood sugar fasting over a 4 months period in our study was reduced from 124 to 116mg. In one study glimepiride lowered FPG by 46 mg/dL, hemoglobin A_{1C} (HbA_{1C}) by 1.4%, and 2-hour postprandial glucose by 72 mg/dL more than placebo[22]. In another study once-daily doses of 1-8 mg reduced fasting plasma glucose from baseline by 43-74 mg/dL more than did placebo ($p < 0.001$)[21]. The glycosylated hemoglobin was reduced in our study from 8.6 (while on other sulfonylurias) at start of therapy to 7.9 at the end of 4 months of therapy with glipepiride. In another study (Hb) A_{1C} values decreased by 1.2-1.9% more than with placebo ($p < 0.001$)[21]. The rank order of potency of the oral hypoglycemic agents we tested: glibenclamide = glimepiride > tolbutamide > chlorpropamide >> metformin[23]. The greatest blood glucose lowering effects of glimepiride occur in the first 4 hours after the dose. The newly developed glimepiride has a marked insulin secretory effect both in vitro and in vivo, and is capable of increasing plasma insulin levels with approximately 50% in type 2 diabetes subjects[24]. Glimepiride has fewer and less severe effects on cardiovascular variables than glibenclamide (glyburide)[25]. Glimepiride was similar in efficacy to glibenclamide and glipizide in 1-year studies. However, glimepiride appears to reduce blood glucose more rapidly than glipizide over the first few weeks of treatment[25].

Although glimepride has certain important advantages over the conventional sulfonlurias namely. Insulin friendly i.e. has extra-pancreatic effects (inulin sparing effect).

1. Once daily therapy from 1 to 8 mg with 24 hour action.
2. Different receptor binding site.
3. Reduced chance of hypoglycemia after exercise.
4. Lower risk of hypoglycemia.
5. Improves tissue sensitivity to insulin.
6. Potential to cause a slight reduction in weight.
7. Cardiovascular friendly with less arrhythmia.
8. Preventative action.

Whether this translates into clinical usefulness remains to be seen in long term controlled studies.

Conclusion

Glimepiride is a safe and effective new oral sulfonyluria with favorable clinical profile. Glimepride in a dose of 1mg produces almost the same amount of lowering of sugar as 5 mg of glybenclamide, 80mg gliclazide and 5 mg of glipizide. Among the biguanides 1mg of glimepiride is roughly equal to the effect of 1.5 gm of metformin. Long term studies are required to translate the theoretical advantages like insulin sparing, different receptor binding and physiological release into clinical usefulness.

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