



Once Daily Sulfonylurea Efficacy and Safety

Manoj Chadha

Consultant Endocrinologist, P.D. Hinduja Hospital and Research Centre, Mumbai 400016.

57

The thrust in oral drug therapy of type 2 diabetes mellitus has been to make it safer (fewer adverse effects), convenient (once daily administration) and at the same time delay development of secondary failure to sulfonylureas. Sulfonylureas have been used for type 2 diabetes mellitus for over 50 years and are still the leading class of oral hypoglycemic agent. Concerns about cardiovascular events have come up time and again. However data from UKPDS and others have confirmed the safety of sulfonylureas. The first sulfonylurea was introduced in the early '50s in the management of type 2 diabetes mellitus (and needed to be administered with each meal). Glibenclamide, glipizide and gliclazide were subsequently added and glimepiride (once daily sulfonylureas) was added to the armamentarium in the mid '90s. Thereafter there have been developments in drug delivery technology so that the shorter acting sulfonylureas can be also administered once daily.

The existing sulfonylureas are classified into

1st generation sulfonylureas

Tolbutamide

2nd generation sulfonylureas

Glibenclamide/ Glipizide/ Gliclazide

3rd generation sulfonylureas

Glimepiride

Ideal sulfonylureas should have the following characteristics:

It should control fasting and postprandial hyperglycaemia

It should not produce hypoglycaemia

It should be effective in once a day dosing

It should not produce hyperinsulinaemia and weight gain

It should not interact with other drugs

The search for the ideal sulfonylurea continues.

The 1st and 2nd generation sulfonylureas act through a common receptor on the beta cells. Sulfonylureas bind to these receptors and bring about closure of the K_{ATP} channel leading to depolarization of beta cells and subsequent insulin release. Sulfonylureas bind also to cardiovascular K_{ATP} channels, although less well than to beta cell K_{ATP} channels. Extra-pancreatic action of these classes of sulfonylureas has been postulated.

A considerable body of evidence has been amassed regarding the use of glimepiride in type 2 diabetes mellitus since its introduction. Glimepiride is available as 1, 2, 3, and 4 mg tablets. The recommended dose is 1 to a maximum of 8 mg per day. It differs from other sulfonylureas in a number of respects. It acts on a 64K sulfonylurea receptor different from the regular sulfonylurea receptor. Glimepiride therapy ameliorates the relative insulin secretory deficit found in most patients with type 2 DM. It is a direct insulin secretagogue; indirectly, it also increases insulin secretion in response to fuels such as glucose. It acts by binding to a high affinity sulfonylurea receptor, which results in closure of ATP-sensitive potassium channels in the beta-cells of the pancreas. The question has been raised whether insulin secretagogues by acting on vascular or myocardial potassium channels may prevent ischaemic preconditioning, a physiological adaptation that could affect the outcome of coronary heart disease. There is evidence against this concern being applicable to glimepiride. Extra pancreatic action of glimepiride has been clinically documented. Its extra-pancreatic action is due to decrease in insulin resistance along with increased expression of GLUT-4 transporters. In clinical studies, glimepiride was generally associated with a lower risk of hypoglycemia and less weight gain than other sulfonylureas. Results of other studies suggest that glimepiride can be used in older patients and those with renal compromise. Its convenient once daily dosing may enhance compliance for diabetic patients who often also require medications for other co-morbid conditions, such as hypertension, hyperlipidaemia and cardiac disease. Glimepiride is approved for monotherapy, for combination with metformin and with insulin. Clinically, its reduced risk of hypoglycaemia makes it preferable to some other insulin secretagogues when attempting to achieve recommended glycemic control ($HbA_{1c} < 7\%$). Using bedtime/ supertime NPH with morning glimepiride in overweight diabetic patients achieves glycemic goals more quickly than insulin alone and with lower insulin doses.

Tsung-Ming Lee and Tsai-Fwu Chou demonstrated for the first time in humans with IHD that diabetes mellitus per se has an independent direct effect on the ability of the myocardium to tolerate ischemia. They tested the effect of glibenclamide and glimepiride in 20 non-diabetic and 23 diabetic persons on ischemic preconditioning during the course of repeated

therapeutic balloon dilatation of coronary arteries. Three different ways of assessing myocardial adaptation to prior ischemia were used: subjectively reported anginal pain; ST segment change and lactate balance across the coronary bed. With no drug pretreatment or glimepiride pretreatment in the non-diabetic group, or with pretreatment in the diabetic group, clear improvements of pain score, ST-segment shift and net coronary lactate production were all seen after preconditioning. It reconfirms that some sulfonylureas have an independent direct effect on the ability of the myocardium to tolerate ischemia. Acute and chronic administration of glibenclamide but not of the pancreas specific glimepiride induce potentially harmful cardiovascular effects in both diabetic and non-diabetic patients with coronary vascular disease. Glimepiride offers some promise for diabetic therapy while minimizing undesirable side effects in cardiac tissue.

Glipizide is a second generation sulphonylurea agent that is available in a Gastrointestinal Therapeutic System (GITS) extended-release formulation. *Glipizide GITS* provides more stable plasma drug concentrations than the immediate-release formulation and the once-daily regimen may optimise patient compliance. Glipizide is available as 5 and 10 mg sustained release tablets. The recommended dose is 5 to a maximum of 20 mg per day. In patients with type 2 diabetes mellitus, glipizide GITS is at least as effective as the immediate-release formulation of glipizide in providing glycaemic control, and may have a greater effect on fasting plasma glucose levels. In a preliminary report ($n = 40$) glipizide GITS provided better glycaemic control and produced less fasting insulinaemia than glibenclamide. The incidence of hypoglycaemic symptoms with glipizide GITS is low ($< \text{or} = 3\%$). Two prospective, randomized, double-blind, placebo-controlled, multicenter clinical trials were performed in 347 patients with type 2 diabetes mellitus (aged 59 ± 0.6 years; BMI, 29 ± 0.3 kg/m²; known diabetes duration, 8 ± 0.4 years) to investigate the efficacy, safety, and dose-response characteristics of an *extended-release preparation of glipizide* using the gastrointestinal therapeutic system (GITS) on plasma glucose, glycosylated hemoglobin (HbA_{1c}), and insulin secretion to a liquid-mixed meal. Each trial was conducted over duration of 16 weeks. In the first trial, once-daily doses of 5, 20, 40, or 60 mg glipizide GITS were compared with placebo in 143 patients. In the second trial, doses of 5, 10, 15, or 20 mg of glipizide GITS were compared with placebo in 204 patients. HbA_{1c}, fasting plasma glucose (FPG), insulin, C-peptide, and glipizide levels were determined at regular intervals throughout the study. Postprandial plasma glucose (PPG), insulin, and C-peptide also were determined at 1 and 2 h after a mixed meal. All doses of glipizide GITS in both trials produced significant reductions from placebo in FPG (range 57 to 74 mg/dl) and HbA_{1c} (range 1.50 to 1.82%). Pharmacodynamic analysis indicated a significant relationship between plasma glipizide concentration and reduction in FPG and HbA_{1c} over a dose range of 5-60 mg, with maximal efficacy achieved at a dose of 20 mg for FPG and at 5 mg for HbA_{1c}. PPG levels were significantly lower, and both postprandial insulin and C-peptide levels significantly higher in patients treated with glipizide GITS compared with placebo. The percent reduction in FPG was comparable across patients with diverse demographic and clinical characteristics, including those with entry FPG ≥ 250

mg/dl, resulting in greater absolute decreases in FPG and HbA_{1c} in patients with the most severe hyperglycemia. Only 11 patients in both studies discontinued therapy because of hypoglycemia. Glipizide GITS did not alter lipids levels or produce weight gain. The once-daily glipizide GITS lowered HbA_{1c}, FPG, and PPG over a dose range of 5-60 mg, maintained its effectiveness in poorly controlled patients (those with entry FPG ≥ 250 mg/dl), was safe and well tolerated in a wide variety of patients with type 2 diabetes mellitus and did not produce weight gain or adversely affect lipids.

Gliclazide modified release (MR) is a new formulation of the drug gliclazide and is given once daily. Gliclazide is available as 30 and 60 mg modified release tablets. The recommended dose is 30 to a maximum of 120 mg per day. The hydrophilic matrix of hydromellose-based polymer in the new formulation brings about a progressive release of the drug which parallels the 24-hour glycemic profile in untreated patients with type 2 diabetes mellitus. The formulation shows high bioavailability and its absorption profile is unaffected by coadministration with food. After single oral administration of a 30 mg MR tablet, gliclazide was completely absorbed both under fasted and fed conditions. A consistent and optimal release of gliclazide from this formulation leads to a low to moderate overall variability of its pharmacokinetic parameters. Gliclazide MR is associated with an unsurpassed efficacy:acceptability ratio, with the potential additional advantages inherent in reduced dosage and once-daily administration. Mean plasma glucose levels are significantly reduced over a 24-hour period in patients with type 2 diabetes mellitus treated with gliclazide MR once daily, in both fasting and postprandial states. No cardiovascular ATP-sensitive potassium channel interaction has been observed at therapeutic concentrations of gliclazide MR. In a randomised, double-blind, multicentre study, gliclazide MR 30 to 120 mg once daily showed similar efficacy to gliclazide immediate release (IR) 80 to 320 mg/day (in divided doses for doses >80 mg) in patients with type 2 diabetes mellitus over a 10-month period, reducing glycosylated haemoglobin (HbA_{1c}) and fasting plasma glucose to a similar extent. The drug appeared most efficacious in patients who had previously been treated by diet alone, where significant reductions in HbA_{1c} from baseline of 0.9% and 0.95% were seen at 10 and 24 months. Gliclazide MR was well tolerated with an adverse effect profile similar to that of gliclazide IR. The most commonly observed adverse events were arthralgia, arthritis, back pain and bronchitis (each $<5\%$). The safety of Gliclazide MR and Gliclazide was equally high. The incidence of hypoglycemia was particularly low (0.2 hypoglycemia/100 patient months) in the elderly population, which represented almost 40% of the included patients. Bodyweight remained stable. In this study no episodes of nocturnal hypoglycaemia or hypoglycaemia requiring third party assistance were observed during treatment with gliclazide MR. Episodes of symptomatic hypoglycaemia were infrequent, occurring in approximately 5% of patients.

Efficacy and safety of gliclazide MR has been compared to that of glimepiride in the GUIDE study. Eight hundred and forty five type 2 diabetics (on dietary modification alone or on metformin/ alpha glucosidase inhibitor) were randomized to either of the two drugs as monotherapy or in combination with their current medication. The study extended over 27 weeks.

During the titration period the dose of study medication was increased every 3 weeks till metabolic control was achieved (FPG 5.0-7.9 mmol/L) or till dose 4. Patients were instructed on self-glucose monitoring and were trained to recognize symptoms of hypoglycemia. HbA_{1c} decreased from a mean of 8.3% equally in both groups. Nearly 50% of the patients in both groups achieved HbA_{1c} < 7% and 25% < 6.5%. However the incidence of hypoglycemia requiring external assistance (< 3 mmol/L) was lower in the gliclazide MR (3.7%) treated group as compared to the glimepiride group (8.9%).

Glibenclamide has been the gold standard against which new sulfonylureas are compared. However it is losing out to newer sulfonylureas on grounds of multiple daily dosing and higher incidence of hypoglycemic episodes. This may discourage compliance. Effects of glibenclamide when used once daily and when used in split doses were compared to determine if it is appropriate to consider dosing it less frequently. The number of hypoglycemic episodes occurring with both regimes was compared. Thirty type 2 diabetics on multiple daily glibenclamide were enrolled. Their regimens were changed over to once daily. Blood for glucose, insulin, lipids, HbA_{1c} and glibenclamide and body weight measurements were determined before and after the crossover period. No major difference in the sugar and insulin profiles with the two regimens was found. Lipid profile and plasma glibenclamide were also similar. The HbA_{1c} levels and body mass index and number of minor and major hypoglycemic episodes and hospital admissions for hypoglycemia also did not differ. Single daily dosing of glibenclamide was equivalent to multiple daily dose regimens. It can be used to an advantage to improve patient's compliance.

Once daily sulfonylureas can be used safely and with the desired efficacy to control type 2 diabetes mellitus. Various studies have confirmed the efficacy and safety of once daily

glimepiride, gliclazide MR and glipizide MR. Data suggests that dosing frequency exerts a greater impact on patient adherence and persistence than number of tablets per dose. Better patient compliance translates into better control of diabetes mellitus. *The safety factor becomes all the more important in view of the recommendations of ADA (HbA_{1c} < 7.0%) and AACE (HbA_{1c} < 6.5%) for strict control of Diabetes mellitus.*

REFERENCES

1. Drouin P. Diamicon MR once daily is effective and well tolerated in type 2 diabetes: a double-blind, randomized, multinational study. *J Diabetes Complications* 2000;14:185-91.
2. Harrower A. Gliclazide modified release: from once-daily administration to 24-hour blood glucose control. *Metabolism* 2000;49(10 Suppl 2):7-11.
3. McCall AL. Clinical review of glimepiride. *Expert Opin Pharmacother* 2001;2:699-713.
4. McGavin JK, Perry CM, Goa KL. Gliclazide modified release. *Drugs* 2002;62:1357-64.
5. Rosenstock J, Samols E, Muchmore DB, Schneider J. Glimepiride, a new once-daily sulfonylurea. A double-blind placebo-controlled study of NIDDM patients. Glimepiride Study Group. *Diabetes Care* 1996;19:1194-9.
6. Scherthaner G, Grimaldi A. GUIDE study: double blind comparison of once-daily gliclazide MR and glimepiride in type 2 diabetics. *Eur J Clin Inv* 2004;34:535-42.
7. Simonson DC, Kourides IA, Feinglos M, Shamooh H, Fischette CT. Efficacy, safety, and dose-response characteristics of glipizide gastrointestinal therapeutic system on glycemic control and insulin secretion in NIDDM. Results of two multicenter, randomized, placebo-controlled clinical trials. The Glipizide Gastrointestinal Therapeutic System Study Group. *Diabetes Care* 1997;20:597-606.
8. Tsung-Ming Lee and Tsai-Fwu Chou. Impairment of myocardial protection in type 2 diabetic patients. *J Clin Endocrinol and Metab* 2003;88:531-537.
9. Wan Mohamad WB, Tun Fizi A, Ismail RB, Mafauzy M. Efficacy and safety of single versus multiple daily doses of glibenclamide in type 2 diabetes mellitus. *Diabetes Res Clin Pract* 2000;49:93-9.