Gliclazide Modified Release: From Once-Daily Administration to 24-Hour Blood Glucose Control

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Although sulfonylureas have been used for more than 40 years, it is only recently that their molecular mechanisms of action have been elucidated. Gliclazide modified release, whose introduction comes soon after the sequencing and cloning of the sulfonylurea receptor, is the first sulfonylurea for which it is possible to detail its action from the moment of oral administration through to its effects on long-term glycemic control. Piecing together these steps for this new agent underlines the rationality of its development and the important differences from other members of the sulfonylurea class. Employing an innovative pharmaceutical form based on a hydrophilic matrix to deliver this short-acting sulfonylurea, gliclazide modified release is associated with an unsurpassed efficacy:acceptability ratio, with the potential additional advantages inherent in reduced dosage and once-daily administration.

TODAY'S CLINICIANS are encouraged to practice evidence-based medicine, but many day-to-day decisions remain empirical as knowledge of many domains is incomplete. It is often forgotten that the recognition of the glucose-lowering potential of sulfonamide-related compounds was a fortuitous discovery.[1] The choice of an oral antidiabetic agent may be influenced by a large number of factors, but often comes down as much to personal preference or experience as to detailed knowledge of the differential actions of each molecule. Although now prescribed by 3 generations of diabetologists, it is only very recent molecular biologic work, culminating in the sequencing and cloning of the sulfonylurea receptors,[2] that has substantially advanced understanding of the mechanisms of action of the sulfonylureas, including important differences in action between members of the class, which correlate well with previous clinical experience. Gliclazide is among the most extensively investigated sulfonylureas. The large body of research available with this sulfonylurea, and the welcome recent introduction of the new once-daily modified-release preparation, conspire to make this the first sulfonylurea for which it is possible to detail its action step-by-step from administration to elimination. This article describes the pharmacokinetics, pharmacodynamics, and clinical effects of gliclazide modified release, piecing together observations with the old and new formulations. The heterogeneity of the sulfonylurea class is underlined and differences that may influence their clinical use are identified.

PHARMACOKINETICS

Gliclazide modified release is the first oral antidiabetic agent to employ a hydrophilic matrix. This allows once-daily administration with 24-hour efficacy through progressive delivery of short-acting gliclazide. Each tablet is constituted of a matrix of hydrophilic hypromellose fibers, trapping granules composed of gliclazide, calcium hydrogen phosphate dihydrate, and maltodextrin. Once in contact with gastrointestinal fluid, the hypromellose polymer expands to form a gel, through which active ingredient is progressively released. These characteristics are highly reproducible, with predictable consistent release of active ingredient over 24 hours, allowing once-daily administration (unpublished data: Moliner P, November 1998; Thomas RH, November 1998; Wemer J, November 1998). Pharmacokinetics are virtually unaffected by pH, thus the agent can be given before, during, or after breakfast (unpublished data, Moliner P, November 1998). The modified-release preparation demonstrates very high bioavailability (unpublished data, Thomas RH, November 1998), which has allowed reduction in the clinically effective gliclazide dose to 30 to 120 mg/d. In steady-state, morning administration is followed by a progressive increase in plasma gliclazide concentration during the first 6 hours, followed by a plateau, and a progressive reduction over 18 hours (unpublished data, Wemer J, November 1998). As a result, gliclazide levels are therapeutic throughout the 24 hours, but nonetheless relatively reduced during the (fasting) nighttime period. The circadian variations of glycemia in type 2 diabetes[3] support the rational basis for this pharmacokinetic profile.

RECEPTOR DYNAMICS

Like other sulfonylureas, gliclazide is extensively protein-bound (87% to 94%) in the circulation,[4,5] which may account for the minimal hepatic first-pass effect. In the pancreas, gliclazide binds β-cell sulfonylurea receptors (with its sulfonylurea moiety) with high affinity,[6] which is reflected in the effective daily dosing of gliclazide, in the milligram range, compared with the gram level requirements of lower-affinity agents such as tolbutamide. As well as having high affinity, gliclazide's β-cell interaction is rapidly reversible, as studied in cloned receptor models by Gribble and Ashcroft,[6] and in the isolated perfused pancreas.[7] In the latter, insulin release falls to baseline on gliclazide withdrawal, while with glibenclamide there is persisting significant insulin secretion (Fig 1). Glibenclamide and also, for example, glimepiride are thought to have more complex binding to sulfonylurea receptor type 1 (SUR1) with both their sulfonylurea and benzamido groups.[8] The low probability of spontaneous unbinding of the 2 sites (in conjunction with incorporation into the β cell in the case of glibenclamide) is likely to explain the poor reversibility of interaction of these agents, and their long duration of effect. Potential clinical implications of poorly reversible binding have been evoked in the literature; "avid" fixation to the pancreatic receptors is pro-

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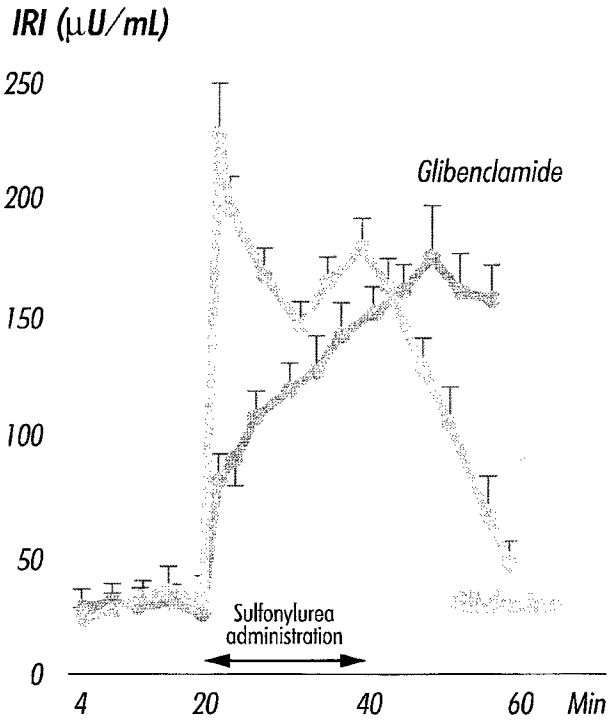

Fig 1. Effect of gliclazide and glibenclamide on insulin release in an isolated perfused pancreas model, showing restoration of the first peak of secretion by gliclazide, and its reversibility of action.[7]

posed by the United Kingdom Prospective Diabetes Study (UKPDS) team as an explanation for secondary failure with glibenclamide,[9] and, indeed, adenosine triphosphate–sensitive potassium (K_{ATP}) channel downregulation has been observed during chronic exposure of the pancreas to this long-acting agent.[10]

SYNERGY WITH GLUCOSE

Sulfonylureas promote insulin secretion by favoring the closure of K_{ATP} channels. Hyperglycemia acts similarly by increasing the adenosine triphosphate:adenosine diphosphate (ATP:ADP) ratio through oxidative glucose metabolism. This results in opening of voltage-dependent calcium channels, leading to insulin release from stocked vesicles.[11] Insulin secretion is therefore promoted synergistically by high glucose levels and sulfonylurea sensitization of the pancreas (Fig 2). This mechanism is well demonstrated in the isolated perfused pancreas, where ambient glucose concentrations strongly influence the amount, but not the kinetics, of sulfonylurea-stimulated insulin secretion, with insulin release decreasing rapidly when glucose levels are reduced despite maintained sulfonylurea concentrations.[7] The synergy with glucose was more marked with gliclazide than with glibenclamide, tolbutamide, or gliquidone, and was hypothesized by the authors to act as a self-regulatory mechanism limiting the risk of hypoglycemic events. Data from Hosker et al[12] confirm the relevance of these results for type 2 diabetic patients, with insulin responses to gliclazide being more marked at higher glycemic clamp levels.

RESTORING BIPHASIC SECRETION

One of the earliest demonstrable abnormalities during the development of type 2 diabetes is the loss of the first peak of insulin secretion.[13,14] Indeed, genetically determined insulin secretion abnormalities, including reduced first-phase responses, predate altered insulin sensitivity in type 2 diabetes pathogenesis.[13] This first-phase secretion normally limits the prandial rise in glycemia and primes insulin target tissues. The inverse relationship between early insulin secretion and 2-hour plasma glucose values after oral glucose tolerance testing stresses that the early peak is important in determining later plasma glucose and insulin concentrations.[15] Data from epidemiologic and intervention studies link postprandial hyperglycemia more closely to cardiovascular risk than fasting glucose levels. In the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study,[16] for example, coronary heart disease mortality was correlated with 2-hour postprandial glucose, but not fasting glucose levels, reflecting a similar pattern seen in the earlier Diabetes Intervention Study.[17] Thus, restoration of the physiologic dynamic of secretion has significant potential benefits for patients, and has recently been re-emphasized as a priority in the design of an efficient treatment for type 2 diabetes.[18] Both in experimental models and in type 2 diabetic patients, gliclazide has been shown to restore a biphasic profile of insulin secretion as opposed to the late monophasic response to glibenclamide.[7,12] It is possible that the incorporation of glibenclamide into the β cells,[19] as well as its poorly reversible receptor binding,[11] and active metabolites,[20] contribute to this difference. Important aspects of gliclazide's efficacy and acceptability profile, notably its weight-neutrality[21-24] and low hypoglycemia risk,[21,25-27] can be associated with restoration of a physiologic insulin secretory response. Clinical support for absence of hyperinsulinism between meals with gliclazide modified release comes from phase III

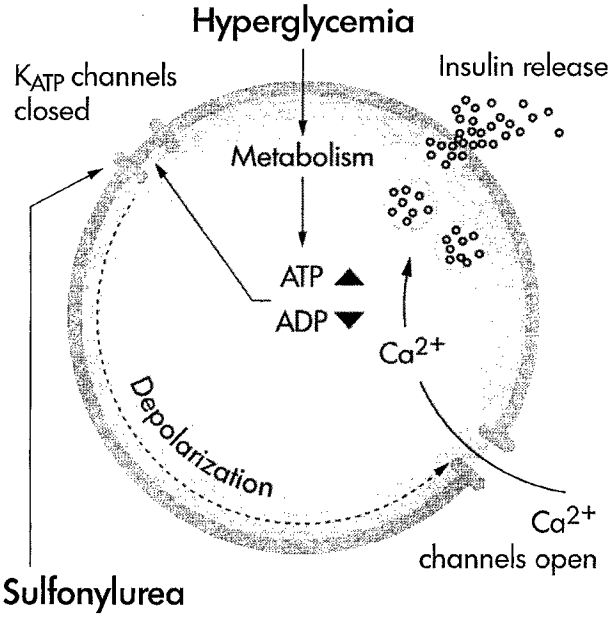

Fig 2. Common mechanism of insulin release in response to hyperglycemia or sulfonylurea administration.

study data, where no increase in fasting insulin was observed after 10 months of treatment of a heterogeneous population of 401 type 2 diabetic patients despite a sustained effect in reducing plasma glucose (Fig 3).[21] This confirms previous data demonstrating significant improvement in postprandial insulin levels without fasting hyperinsulinemia in type 2 diabetic patients treated with gliclazide.[28]

CONTRIBUTION OF INSULIN SENSITIZATION

Extrapancreatic effects of gliclazide on tissue insulin sensitivity have been extensively investigated using a variety of methodologies including clamp techniques, isotope dilution, and tissue biopsy. In type 2 diabetic patients, under insulin-stimulated conditions, gliclazide treatment is associated with increases in the activity of glycogen synthase in skeletal muscle, with concomitant improvement in insulin-mediated glucose disposal.[29] These effects are apparently independent of any reduction in glucotoxicity, and mediated by a postreceptor mechanism, as glycogen synthase activity increases despite unchanged insulin receptor kinase activity. Stabilization of the transporter GLUT1 in the plasma membrane by gliclazide has been described and may contribute to this effect.[30] Gliclazide also suppresses hepatic glucose production during hyperglycemia, an effect thought to be independent of increased portal insulinemia.[29] Thus, there would appear to be direct effects of gliclazide on insulin sensitivity at both hepatic and skeletal muscle levels that may play a role in the control of both fasting and postprandial glycemia in long-term treatment.

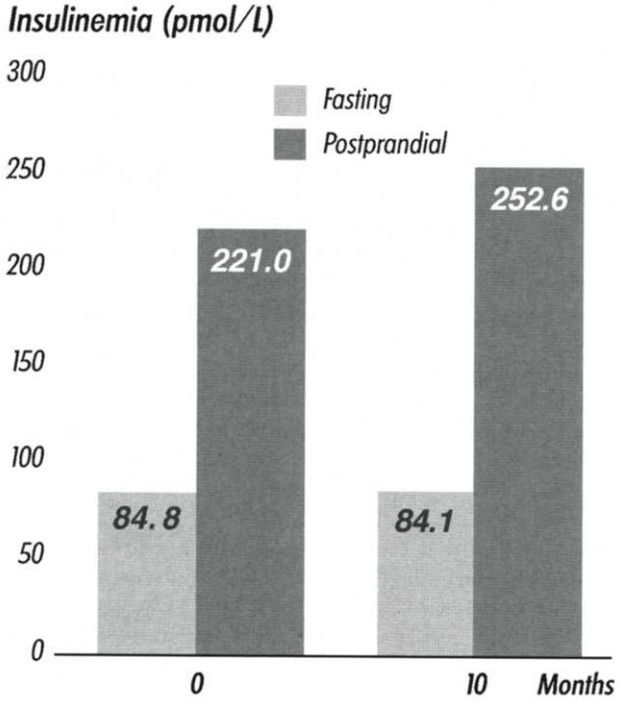

Fig 3. Effect of gliclazide modified release on fasting and postprandial plasma insulin levels in the treatment of 400 type 2 diabetic patients over 10 months (unpublished data, Drouin P, January 1999).

ACHIEVING 24-HOUR CONTROL

The modified-release preparation delivers short-acting gliclazide progressively over 24 hours. It is thus of fundamental importance for this new agent to demonstrate efficacy around the clock. A specific study has been performed for this purpose, which will form the subject of a separate publication. The preliminary data available already allow the conclusion that the glucose-lowering effect of gliclazide modified release is efficient over 24 hours following breakfast-time administration (unpublished data, Greb WH, November 1999). At the same time, larger-scale clinical experience with the new product demonstrates that this control is achieved without an excess of hypoglycemia,[21] notably without any nocturnal episodes. The pharmacokinetic profile of gliclazide modified release offers an attractive explanation for these data, which stress the successful marriage of the new delivery system with the well-tried and -tested gliclazide molecule.

MAINTENANCE OF CONTROL LONG-TERM

The phase III development program of gliclazide modified release included a population of 1,462 type 2 diabetic patients[21] (also unpublished data, Harrower ADB, February 1999). Deliberately minimalist exclusion criteria were applied, leading to inclusion of a study population quite representative of the heterogeneity seen in type 2 diabetes. Results of a preceding prospective, randomized, multicenter dose-ranging study (unpublished data, Unger P, November 1997) led to the selection of 30 mg as the standard starting dose of gliclazide modified release, with the possibility of upward titration to 60, 90, or 120 mg as necessary. The largest phase III study randomized 401 type 2 diabetics to the new agent once daily for 10 months.[21] A 2-week washout period was undertaken; up-titration was allowed at monthly intervals depending on fasting plasma glucose values. Despite previous treatment with up to 2 oral agents, and a washout period of only 2 weeks, the overall population showed a net improvement in control, maintained at the end of the study, on monotherapy with gliclazide modified release given once daily. This was the case for glycated hemoglobin (ΔHbA_{1c}, −0.22%), fasting plasma glucose (ΔFPG, −0.83 mmol/L), and postprandial plasma glucose (ΔPPG, −1.18 mmol/L). One in 5 of the included patients was recently diagnosed (previously diet-treated), thus allowing a more realistic evaluation of the efficacy of the new agent in monotherapy. At the end of the study, these patients maintained a mean improvement in HbA_{1c} of 0.91%, and had acceptable metabolic control (HbA_{1c}, 7.38%, full analysis set). A key finding of this study was that gliclazide modified release was at least as effective as the existing gliclazide formulation in terms of metabolic control over 10 months, whilst associated with excellent tolerance, and particularly a low incidence of hypoglycemia, in all the subpopulations of type 2 diabetic patients.

The results of phase III studies with the new agent are thus entirely consistent with results previously obtained with gliclazide. These have included trials of long-term efficacy, and several efficacy comparisons with other agents. Maintenance of control to normal glycated hemoglobin levels was seen during a

prospective 5-year study of gliclazide therapy.[22] A third of the patients selected were newly diagnosed, the remainder previously treated. The latter had inadequate response to previous treatment, which was stopped, and dietary management alone followed for 2 months. After this run-in period, inadequately controlled patients were prescribed gliclazide and included in the 5-year follow-up. Significantly improved control compared with baseline was maintained at 3, 4, and 5 years of follow-up, as reflected in the mean HbA_1 of 7.3% at 5 years.

COMPARISON WITH OTHER SULFONYLUREAS

Available interagent efficacy comparisons include a randomized 1-year study in 112 type 2 diabetic patients allocated to a standard escalating-dose regimen of gliclazide, chlorpropamide, glipizide, gliquidone, or glibenclamide.[31] Glycemic control on gliclazide was significantly better than on gliquidone or chlorpropamide in this study, and normalization of glycated hemoglobin was achieved in 80% of gliclazide-treated patients versus 74%, 40%, 40%, and 14% for glibenclamide, glipizide, gliquidone, and chlorpropamide, respectively. Furthermore, a secondary failure rate of only 7% on gliclazide therapy, as compared with 17.9% on glibenclamide and 25.6% on glipizide ($P < .05$), was observed over 5 years of follow-up (Fig 4).[32]

These efficacy results correlate well with the differential actions of the sulfonylureas on β cells. Gliclazide's rapidly reversible receptor interaction,[6] lack of active circulating metabolite[33] (unpublished data, Wemer J, November 1998), restoration of the early peak of insulin secretion,[7,12] marked synergy with glucose,[7] and effects on insulin sensitivity[29,30] are all factors contributing to the avoidance of excessive β-cell stimulation in the late postprandial phase. Each is also likely to have its role in the sustained efficacy of gliclazide compared with other sulfonylurea agents with different pharmacodynamic actions and metabolism.

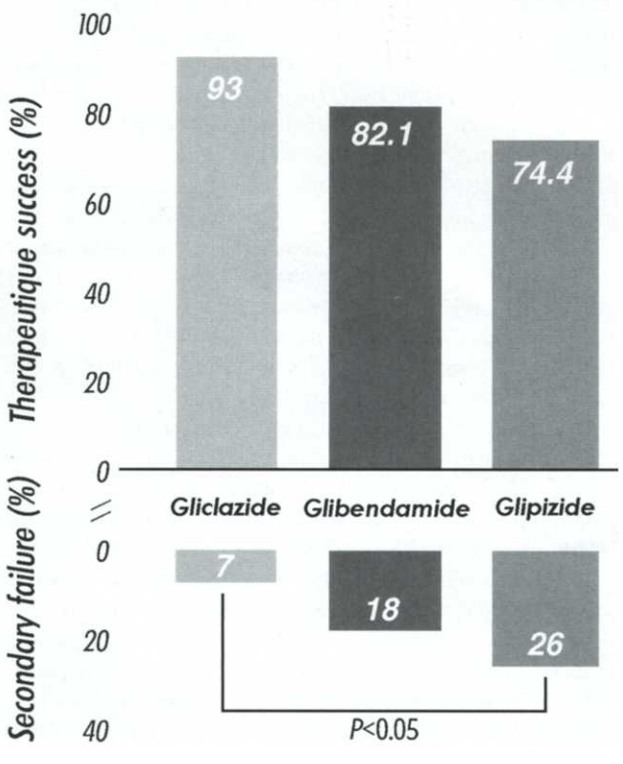

Fig 4. Rates of therapeutic success and secondary failure at 5 years on different sulfonylureas. Secondary failure was defined as postprandial glycemia ≥10 mmol/L or HbA_1 ≥10% during supervised compliance with medication and diet.[32]

METABOLISM/ELIMINATION

Gliclazide is extensively metabolized, mainly in the liver, and principally by hydroxylation.[33] At least 7 metabolites have been identified, with no circulating active metabolite. The major route of elimination of gliclazide and its metabolites is via the urine.[34] Studies with radiolabeled gliclazide indicate 60% to 70% urinary excretion and 10% to 20% fecal excretion. In the urine, hydroxymethyl and carboxymethyl, hydroxyl and 2-O-glucoronide conjugates are found, with only trace quantities of unchanged gliclazide. Elimination parameters are not significantly affected in the elderly,[35] nor in patients with mild-to-moderate renal insufficiency, suggesting that dose adjustments are unnecessary for such patients.[36] Strong support for this suggestion comes from clinical studies showing a very low incidence of hypoglycemia in elderly patients and those with mild-to-moderate renal insufficiency receiving full doses of gliclazide modified release, comparable with that observed in the general study populations of heterogeneous type 2 diabetic patients despite similar glycemic control[21] (unpublished data, Harrower ADB, February 1999).

CONCLUSION

Clinical and preclinical observations with gliclazide underline important differences with other sulfonylureas. Clinical advantages, including reductions in hypoglycemia risk,[21,25-27] weight gain,[22-24] and secondary failure,[32] are of significant interest and have long drawn attention to gliclazide in clinical practice and consensus guidelines.[37,38] Recent investigation into the pharmacodynamics of sulfonylurea action has identified mechanistic explanations for the differential clinical effects of the sulfonylureas. Substantial differences exist between gliclazide and other sulfonylureas (eg, glibenclamide or glimepiride) in terms of their pancreatic receptor interactions,[6,8,11] metabolite activity[20,26] (unpublished data, Wemer J, November 1998), effects on the early peak of insulin secretion,[7,12] incorporation into β cells,[19] synergy of secretagogue effect with glucose,[7] and documented effects on insulin sensitivity.[29,30] Gliclazide modified release combines the desirable properties of short-acting gliclazide with an innovative pharmaceutical form—the hydrophilic matrix permitting progressive delivery of active principle over 24 hours and in a profile adapted to the glycemia pattern of type 2 diabetic patients. Reviewing the relevant data, step-by-step from administration to elimination, underlines the rationality of the new gliclazide modified-release preparation, which has well-demonstrated efficacy and tolerance, and the potential additional advantages inherent in reduced dosage and once-daily administration.

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