Gliclazide Modified Release: Its Place in the Therapeutic Armamentarium

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The constraints of intensive multifactorial management of type 2 diabetes dictate a need for effective, well-tolerated agents with simple administration regimens. Sulfonylureas remain the most frequently used agents, and represent a rational approach when consideration is given to the pathophysiology of this common condition. Trials of gliclazide modified release in varied populations have yielded very acceptable clinical results that support its first-line use in type 2 diabetes, including obese, elderly, and mild-to-moderate renal insufficient patients. The simplicity of its dose regimen and its efficacy and tolerance profile may significantly contribute to improving compliance.

MANY STILL-PRACTICING diabetologists who started their career offering primarily symptomatic treatment for type 2 diabetes are now committed to managing other factors, including hyperlipidemia, hypertension, obesity, and renal disease, in addition to glycemia. The range of therapies available to diabetologists is thus extensive and growing at an exponential rate. Keeping updated and providing management according to current guidelines represents a considerable daily challenge for clinicians. In this context, simple treatment regimens using active, well-tolerated molecules may be one of the keys to success, and are certainly appreciated by patients. The availability of an active agent given once daily would also be extremely useful in improving compliance, since most patients already receive multiple pills every day. This review will discuss the potential contribution of a newly introduced agent—gliclazide modified release.

SECRETAGOGUES IN TYPE 2 DIABETES

The blanket term "type 2 diabetes" covers a variety of patient phenotypes. Even the basics of its pathophysiology remain open to some debate, particularly the relative contributions of reduced insulin sensitivity and impaired insulin secretion. Certainly, both the quantity and quality of insulin secretion are altered in established disease—from the time of diagnosis an increased proinsulin:insulin ratio is seen, which appears to reflect a primary defect in β-cell function.[1] This abnormality correlates with attenuation of the first peak of insulin secretion,[2,3] which has a major impact on postprandial hyperglycemia and its deleterious consequences.[4] Interestingly, β-cell function continues to decline, whereas insulin sensitivity remains unchanged during disease progression[5] and progression from normal glucose tolerance (NGT) to impaired glucose tolerance (IGT) to diabetes. Thus, based on current understanding of the pathophysiology of type 2 diabetes, it is desirable to restore insulin secretion with improvement of the first phase; this provides a solid rational basis for the use of insulin secretagogues in the management of hyperglycemia.

THE ROLE OF SULFONYLUREAS

Diet and exercise are indisputably necessary to reduce blood glucose levels in type 2 diabetic patients, but are rarely sufficient alone. Most clinicians follow the approach of initiating drug therapy with a sulfonylurea or biguanide. The most recent guidelines of the International Diabetes Federation[6] reflect this, giving priority to these drugs as they have the best evidence bases. More recently introduced agents, namely the α-glucosidase inhibitors, novel short-acting secretagogues, and thiazolidinediones are listed, with the proviso that their use may change as experience increases. The long-term efficacy and tolerance profiles of these newer classes remains to be seen, the importance of postmarketing surveillance having been recently underlined by the unfortunate experience with troglitazone. For the foreseeable future, sulfonylureas and biguanides promise to remain rational first-line choices, and useful in combination. According to a recent analysis of the United Kingdom Prospective Diabetes Study (UKPDS), sulfonylureas in monotherapy are more effective in the long term than metformin for achieving glycemic targets in overweight patients (Fig 1),[7] although clearly the natural history of the disease demonstrates a progressive need for combination therapies.

THE MULTIFACTORIAL APPROACH

Hypertension and dyslipidemia, often clustered with diabetes, are definitely implicated as risk factors for diabetic microangiopathy and macroangiopathy, and appear additive in their deleterious impact. Together, they contribute to making vascular disease the overwhelmingly dominant cause of morbidity and mortality in type 2 diabetes. Achieving good glycemic control is effective in primary and secondary prevention of microvascular, and possibly macrovascular complications,[8,9] but is necessarily part of a broader risk reduction approach. Gliclazide was chosen as the sulfonylurea for one of the most rigorous prospective trials of intensive global type 2 diabetes management, which recently definitively confirmed the efficacy of the multifactorial approach.[10]

ACHIEVING EFFECTIVE ONCE-DAILY ADMINISTRATION

In the multifactorial management era, it has been stated that probably the single most important action that health care providers can take to improve compliance is to select medications that allow the lowest daily dose frequency.[11] Improved compliance is demonstrated with once-daily dosing in type 2 diabetes (Fig 2),[12] a finding that may have important implications for glycemic control. For younger, more active patients with complex, variable daily routines, as well as for polymedi-

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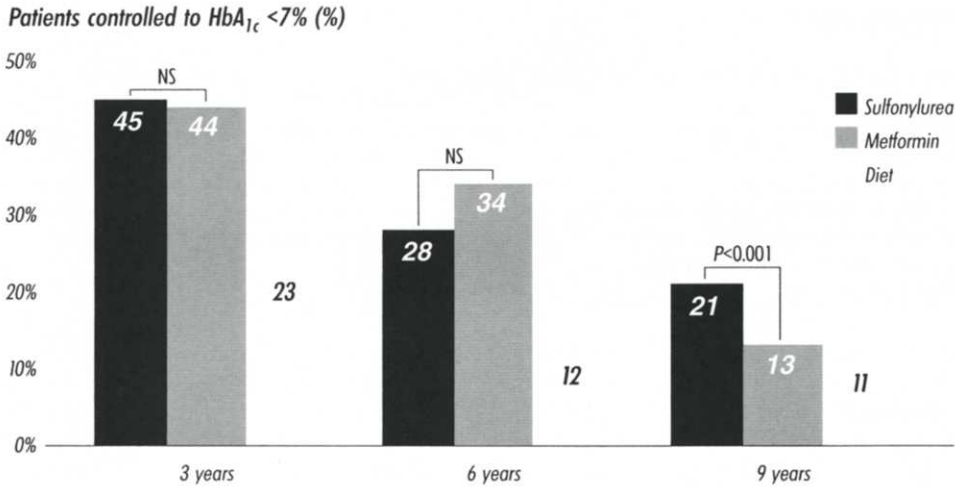

Fig 1. Prevalence rates of control to $HbA_{1c} \leq 7\%$ with different treatment regimens over long-term follow-up of obese newly diagnosed patients in the UKPDS.[7]

cated elderly patients, this may be of particular interest. Approaches to developing an effective and well-tolerated once-daily sulfonylurea have differed in important pharmacokinetic and pharmacodynamic respects. Glimepiride, for example, is a long-acting sulfonylurea delivered by an immediate-release preparation and is more effective in controlling fasting glycemia when given twice daily.[13,14] The once-daily glipizide preparation has been associated with reports of excess hypoglycemia in the elderly, possibly due to unvarying long-acting sulfonylurea blood levels over 24 hours. Gliclazide is a short-acting sulfonylurea, and the new modified-release preparation has been developed with pharmacokinetic characteristics suited to the circadian glycemic profile of type 2 diabetes, this approach having provided favorable results during clinical development.[15]

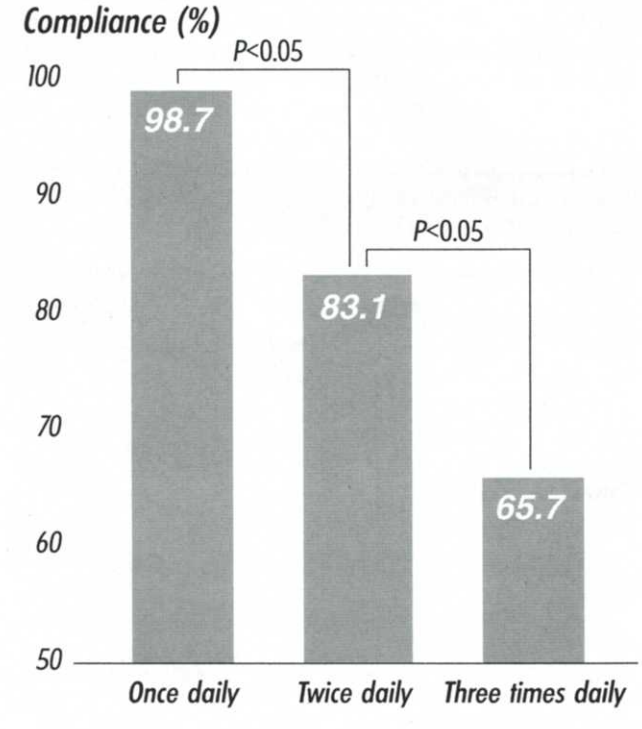

Fig 2. Mean compliance as a function of dosage regimen in type 2 diabetes.[12]

HETEROGENEITY OF THE SULFONYLUREA CLASS

Two commonly used sulfonylureas, glibenclamide and glimepiride, have their effects mainly on the late phase of insulin secretion,[16-18] and have active metabolites.[19] Moreover, poorly reversible interactions of these drugs with the β-cell sulfonylurea receptors have been demonstrated.[20] In contrast, gliclazide has been shown to be able to restore an early peak of insulin secretion,[18,21,22] has no active circulating metabolites[23] (Wemer J, unpublished data, November 1998), and receptor binding is rapidly reversible.[24] These differences may help to explain the observed weight neutrality,[15,25-27] low risk of hypoglycemia,[15,28-30] and low secondary failure rates[31] during gliclazide treatment. In addition, gliclazide, unlike other sulfonylureas, does not interact with cardiovascular adenosine triphosphate–sensitive potassium (K_{ATP}) channels at therapeutic concentrations,[24] and has powerful free radical scavenging effects.[32-34] In view of the role of the cardiovascular channels in protective defense mechanisms during ischemia,[35,36] and the central role of oxidative stress in the pathogenesis of vascular complications,[37-39] these properties appear desirable, and have potential implications for vascular prognosis.

Table 1. Incidence of Recorded Possible Hypoglycemic Episodes for Different Subpopulations of Type 2 Diabetic Patients During Phase III Development of Gliclazide Modified Release

Population	Possible Hypoglycemia (episodes/100 patient-months)
Whole population	3.5
Subpopulations	
Age ≥65 years	2.6
Age ≥75 years	0.9
Renal insufficiency*	4.1

Unpublished data from Drouin P, January 1999; Harrower AJ, February 1999.

*Creatinine clearance 20-80 mL/min.

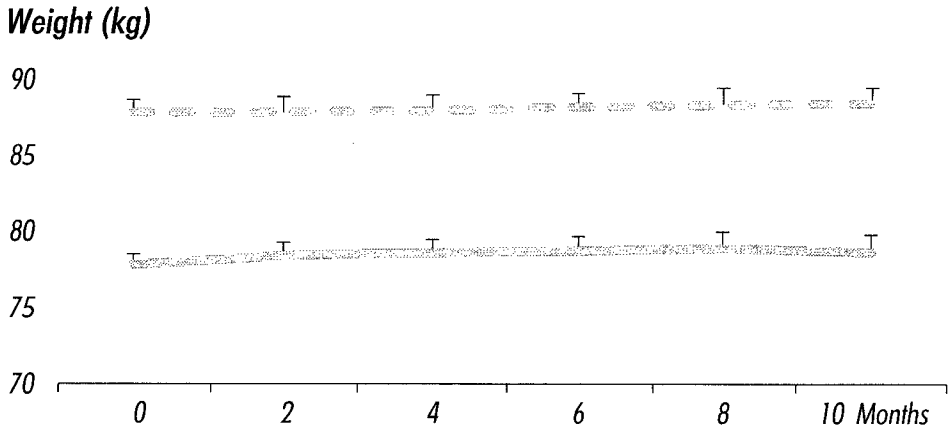

Fig 3. Absence of effect on weight of gliclazide modified release in the general type 2 diabetic population (—) and obese (body mass index ≥ 30 kg/m²) (---) population over 10 months of treatment.[15]

GLICLAZIDE MODIFIED RELEASE AND DIFFERENT PATIENT PROFILES

The once-daily formulation is as effective as the previously available gliclazide at a lower dosage, thanks to the new galenic formulation; indeed, a sustained reduction in glycosylated hemoglobin (HbA_{1c}) was achieved despite patients previously receiving up to 2 oral agents.[15] Importantly, in the context of a once-daily preparation, the new drug is at least as well tolerated as the existing gliclazide, which is associated with fewer hypoglycemic episodes than glibenclamide[28-30] and probably glimepiride.[40] Furthermore, subpopulation analyses suggest the suitability of this once-daily formulation for first-line prescription to type 2 diabetic patients with a variety of special needs.

In Newly Diagnosed Patients

Previously untreated patients may be particularly susceptible to hypoglycemia during the administration of their first oral treatment. Results obtained in this population offer reassurance as to the tolerance of gliclazide modified release in this at-risk group, where reported possible hypoglycemia was no more common than in the global study population. At the same time, the efficacy of the new formulation is well demonstrated in this population, a reduction in HbA_{1c} of about 1% being sustained at the end of 10 months of treatment.[15]

In Fragile Patients

Importantly, in the context of a once-daily preparation, efficacy and tolerance of gliclazide modified release were fully maintained in the substantial subpopulations of elderly patients and patients with mild-to-moderate renal insufficiency (Table 1).[15] A solid body of evidence supports the use of gliclazide in the elderly,[28,29,41,42] and has led to preference for this molecule over other sulfonylureas.[41,43,44] The new data indicate that the modified preparation remains suitable for these fragile patients, without dose adaptation being required in the elderly or in patients with mild-to-moderate renal insufficiency.[15]

In Obese Patients

Obese patients are common among the diabetic population and avoiding further weight gain is a clinical priority. The absence of weight gain during treatment of normal-weight and obese patients with gliclazide modified release[15] (Fig 3) is in keeping with previous studies with this molecule, and may represent a significant advantage over other agents.

In Diabetes Poorly Controlled by a Single Agent

For patients with diabetes that is inadequately controlled by a single agent, extensive experience and a number of clinical studies support the effectiveness and acceptability of gliclazide in combination with metformin[42,45,46] and insulin.[42,47-50] Gliclazide modified release promises to retain these benefits, with a potential additional compliance advantage through once-daily administration.

CONCLUSION

The constraints of intensive multifactorial management of type 2 diabetes dictate a need for effective, well-tolerated agents with straightforward administration regimens. Prescribers and patients may appreciate the efficacy, tolerance profile and simplicity of administration of gliclazide modified release. The new agent is suitable for first-line use in a wide variety of type 2 diabetic patients, from the newly diagnosed through late disease with its complications. Gliclazide modified release is thus a promising new addition to the therapeutic armamentarium.

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