Available online at www.sciencedirect.com

SCIENCE DIRECT

Metabolism Clinical and Experimental 55 (Suppl 1) (2006) S20–S27

Metabolism
Clinical and Experimental

www.elsevier.com/locate/metabol

The place of sulfonylureas in the therapy for type 2 diabetes mellitus

Stefano Del Prato*, Nicolò Pulizzi

Department of Endocrinology and Metabolism, Section of Diabetes and Metabolic Diseases, University of Pisa, Italy

Abstract

Sulfonylureas are still largely used for treatment of type 2 diabetic patients, and they still occupy a central position in many international therapy guidelines. More recently concern has been raised with respect to possible adverse effects associated with the use of these agents. Sulfonylureas are, indeed, believed to favor the development of hypoglycemia, to accelerate beta-cell apoptosis and beta-cell exhaustion, and to impair endothelial function with increased risk for ischemic complications. However, because of the intrinsic pathogenetic heterogeneity of type 2 diabetes, sulfonylureas are likely to remain a therapeutic option. Careful choice of a specific sulfonylurea should be made on the basis of efficacy, safety, convenience, tissue specificity, and neutrality with respect to the beta cell. In this review the advantage:disadvantage ratio of available sulfonylureas is analyzed with the purpose of providing a critical clinical appraisal of the role of sulfonylureas in the modern treatment of type 2 diabetes.

1. Treating type 2 diabetes mellitus: the challenge

The treatment of type 2 diabetes mellitus will be a major challenge in the coming decades for 2 main reasons. The first is the exponential increase in its global prevalence. The second is the complexity of the pathogenetic basis of the disease requiring multiple therapeutic intervention.

Recent epidemiologic evaluation has suggested that the current number of 190 million people with diabetes worldwide is expected to increase to 350 million individuals affected by the disease in the next 15 to 20 years [1]. These figures most likely underestimate the real impact of the problem because up to 50% of the population with diabetes is likely to remain undiagnosed and, therefore, untreated [2]. Such a phenomenal increase in diabetes prevalence is due to a multiplicity of factors including population growth, aging, urbanization, and the concomitant epidemic of obesity.

With the increase in the number of affected individuals, the likelihood of an increase in diabetic complications is also a matter of concern. Patients with diabetes have an increased incidence of both microvascular and macrovascular complications. Moreover, complications can be already present at the time of diagnosis of diabetes. In the United Kingdom Prospective Diabetes Study (UKPDS), at least 40% of patients with newly diagnosed type 2 diabetes mellitus already had some sign or symptom of diabetic complications [3]. In addition to impacting on the quality of life, diabetic complications carry a significant economic burden. For example, in the Cost Of Diabetes in Europe—Type 2 study, oral antidiabetic agents and insulin accounted for no more than 7% of health care expenditure, compared with 55% of total type 2 diabetes mellitus costs due to hospitalizations [4]. The costs of diabetes are inversely related to the degree of glycemic control. Gilmer et al [5] showed that the medical costs of diabetes increase in a significant manner for every 1% increase in HbA_{1c} value of more than 7%.

There is considerable evidence that hyperglycemia increases the risk of diabetes-related complications and that effective blood glucose lowering significantly reduces the development or progression of microangiopathy. Long-term, prospective randomized clinical trials, such as the UKPDS [6], have demonstrated the fundamental role of good glycemic control in reducing the burden of complications. For each 1% reduction in HbA_{1c}, there was a 37% reduction in microvascular disease, 14% reduction in myocardial infarction, 12% reduction in stroke, and 43% reduction in peripheral vascular disease.

The results of intervention trials have led official guidelines to identify stringent therapeutic goals. The most recent International Diabetes Federation (IDF) [7] Global Type 2 Diabetes Guidelines set the glycemic goal at a HbA_{1c} value of 6.5% or less. In spite of evidence and

* Corresponding author. Tel.: +39 050 995 103; fax: +39 050 542 115.
E-mail address: delprato@immr.med.unipi.it (S. Del Prato).

0026-0495/$ – see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2006.02.003

recommendations, current management of glycemia is falling significantly short of such treatment goals. For example, only 37% of diabetic patients participating in the US-based National Health and Nutrition Examination Survey achieved, between 1999 and 2000, an HbA_{1c} goal of less than 7% [8]. Similar results have been reported in Europe, with no more than 31% of diabetic patients achieving HbA_{1c} of 6.5% or less [9].

Although multiple factors are likely to be involved in this partial efficacy of antidiabetic therapy, pathophysiologic complexity is likely to make type 2 diabetes mellitus a heterogeneous disease that renders therapeutic intervention complex.

2. Pathophysiologic basis for treatment

The recent increase in the incidence of type 2 diabetes mellitus is largely dependent on the rise in the prevalence of obesity, which is closely associated with insulin resistance. Improvement in insulin sensitivity is thus considered a primary target for the prevention and treatment of diabetes. However, insulin resistance cannot completely explain the development of diabetes because the pathogenesis of the disease involves impairment of beta-cell function as well [10]. Declining beta-cell function has been identified as a major factor associated with progressively rising plasma glucose levels and disease progression in both the Belfast Diabetes Study [11] and the UKPDS [12]. In both studies, extrapolation of data suggests that initial deterioration in islet function may occur up to 15 years before diagnosis of the disease. Loss of first-phase insulin secretion is indeed commonly found in individuals with fasting plasma glucose of 110 mg/dL or more (6.1 mmol/L) and is a powerful predictor for progression toward overt diabetes [13]. We have recently compared beta-cell function in individuals with normal and impaired glucose regulation (IGR, ie, subjects with impaired fasting glucose and/or impaired glucose tolerance [IGT]) [14]. Homeostasis model assessment insulin resistance index was higher in subjects with IGR compared with healthy subjects ($P < .01$). Assessment of beta-cell function in response to changes in plasma glucose levels was assessed by mathematical modeling of plasma C-peptide response to show a progressive decline across categories of glucose tolerance ($P < .05$ vs normals). These differences were not influenced by age, sex, and body mass index, suggesting that IGR is associated with defects of both insulin secretion and action. Early-phase insulin secretion was also an independent predictor of the progression from normal glucose tolerance to IGT in the San Antonio Heart Study [15]. In a longitudinal study performed in Pima Indians [16], progression from IGT to diabetes was associated with a modest worsening in insulin sensitivity, but a much greater decline in acute insulin response to glucose. Thus, in Pima Indians, low insulin sensitivity and low acute insulin response (ie, early-phase insulin response to glucose) are independent and additive predictors of the progression from normal glucose tolerance to IGT and from IGT to overt diabetes [17].

In the light of the early contribution of defective beta-cell function in the pathogenesis of the disturbances of glucose homeostasis, the use of therapeutic agents that may improve glucose-mediated insulin secretion appears not only legitimate but also a rational approach.

3. Sulfonylureas: a long-standing history

Stimulation of glucose-mediated insulin secretion was the first pharmacologic approach for the treatment of type 2 diabetes mellitus as heralded by the introduction of sulfonylureas into the antidiabetic pharmacopoeia more than 50 years ago. Initially synthesized by Rhône-Poulenc, the first sulfonylurea VK 57 (or 2254 RP) was tested at the Section of Infectious Diseases, Montpellier Hospital, in 1942 by Marcel Janbon. A couple of years later, Auguste Loubatières demonstrated the neoformation of insulin granules in rat beta cells after treatment with the compound. After these pioneering experiments, treatment with sulfonylureas remained the main pharmacologic approach for the treatment of type 2 diabetes mellitus for many decades because of their reliable efficacy in many newly diagnosed diabetic patients, limited side effects (mainly associated with hypoglycemia), and low cost. More recently, their ease of administration has been improved with once-daily formulations.

Their special position has been maintained over the years in many official guidelines. The 1999 IDF [18], the 2002 National Institute of Clinical Excellence [19], and the 2004 American Diabetes Association [20] guidelines all indicate sulfonylureas as potential first-line monotherapy as well as in combination with other oral antidiabetic agents. A main indication for use of sulfonylureas is still found even in the most recent 2005 IDF Global Guidelines for Type 2 Diabetes [7].

In spite of the extensive use of these drugs, recommendations in guidelines, and pathophysiologic plausibility, concern has grown over the past decade with respect to sulfonylurea therapy. This concern has its roots in the risk of hypoglycemia, body weight gain, beta-cell exhaustion, and limited specificity for beta-cell K_{ATP} channels of sulfonylurea agents.

4. Hypoglycemia

Sulfonylureas are the most widely used antihyperglycemic drugs for treatment of type 2 diabetic patients. In this case, hypoglycemia represents a major clinical concern. Jennings et al [21] reported that up to 20% of patients treated with sulfonylureas had symptoms suggestive of hypoglycemia, although episodes were not always corroborated by plasma glucose determinations. During the first year of the UKPDS, hypoglycemia occurred in at least 30% of the glibenclamide-treated patients, a figure similar to that

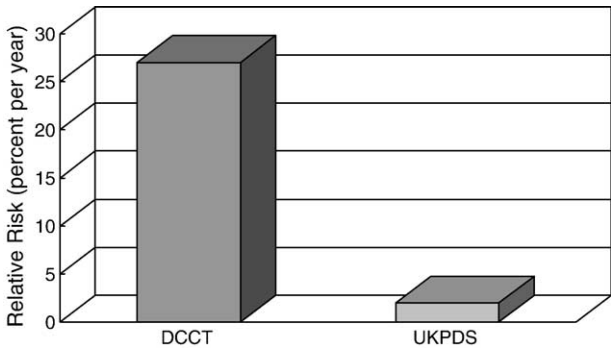

Fig. 1. Relative risk of hypoglycemia in type 1 diabetic patients in the Diabetes Control and Complications Trial compared with type 2 diabetic patients in the UKPDS.

observed in insulin-treated individuals [6]. Over the 10-year follow-up period, the annual incidence of patients experiencing at least one hypoglycemic event was 11.0%, 17.7%, and 36.5% with chlorpropamide, glibenclamide, and insulin, respectively. When the incidence of major events is considered, the corresponding figures decreased to 1.0%, 1.4%, and 1.8%. The relative risk of severe hypoglycemia in the UKPDS is much lower than the 27% observed in intensively treated type 1 diabetic patients reported by the Diabetes Control and Complications Trial (DCCT) [22] despite similar glycemic control (Fig. 1). Nonetheless, severe hypoglycemic episodes are likely to be more protracted and associated with greater mortality when induced by sulfonylureas than with insulin [23]. Sulfonylurea-induced hypoglycemia seems to be of particular concern in older diabetic patients. In the survey of Shorr et al [24], the rate of serious hypoglycemia was 1.23/100 person-years in sulfonylurea-treated patients compared with 2.76/100 patient-years among individuals treated with a sulfonylurea and insulin.

Hypoglycemia in type 2 diabetes mellitus tends to be more common among specific groups of patients, namely, older individuals [25,26] and patients treated with polypharmacy. In the survey of Asplund et al [25], more than 90% of the 57 type 2 diabetic patients experiencing glibenclamide-associated hypoglycemia were older than 60 years and more than 70% were older than 70 years. Concomitant use of insulin and sulfonylurea-potentiating or sulfonylurea-antagonizing drugs was also associated with an increased risk of hypoglycemia [26].

Long-acting sulfonylureas such as chlorpropamide and glyburide are more likely to cause hypoglycemia [23,24,27]. In a United Kingdom survey [27], the rate of diagnosis of hypoglycemia was higher for glibenclamide than for other sulfonylurea drugs. In the analysis performed by Shorr et al [24], the rate of serious hypoglycemic events was highest in glibenclamide users and lowest among patients on tolbutamide. Compared with chlorpropamide, the adjusted relative risk was 0.2 for tolbutamide, 0.6 for glipizide and tolazamide, and 1.0 for glibenclamide [24]. The variation in hypoglycemic risk is the likely consequence of differences in duration, timing, dose equivalence, and potency of hypoglycemic action of the individual agents.

Although a long duration of action also characterizes glimepiride, a newer sulfonylurea, fewer hypoglycemic reactions compared with glibenclamide (105 vs 150 episodes) were recorded during a 1-year study performed in a total of 1044 type 2 diabetic patients [28], possibly because of a better modulation of insulin release, as a function of prevalent plasma glucose concentrations.

More recently, a head-to-head comparison of 2 sulfonylureas designed for once-daily administration was performed under conditions of everyday clinical practice [29]. Eight hundred forty-five type 2 diabetic patients were randomized to either gliclazide modified release (MR) 30 to 120 mg daily or glimepiride 1 to 6 mg daily as monotherapy or in combination with their current treatment (metformin or an α-glucosidase inhibitor) according to a double-blind, 27-week, parallel-group design. HbA_{1c} decreased similarly in both groups from 8.4% to 7.2% on gliclazide MR and from 8.2% to 7.2% on glimepiride. With both treatments, no hypoglycemia requiring external assistance occurred. Nonetheless, hypoglycemia with a blood glucose level of less than 3 mmol/L occurred significantly less frequently with gliclazide MR (3.7% of patients) compared with glimepiride (8.9% of patients; $P = .003$). Of interest, the same results were obtained when individuals younger or older than 65 years were considered (Fig. 2).

The latter findings outline the need for careful phenotyping of the patient, a search for all conditions that may precipitate sulfonylurea-mediated hypoglycemia, and accurate selection of the agent to be used. If all these procedures are followed the risk-benefit ratio for the use of a sulfonylurea is not any worse than that of other oral hypoglycemic agents.

5. Body weight gain

Improvement in glycemic control is often associated with some degree of body weight gain [6,30], a collateral effect that is common to many antidiabetic treatments including

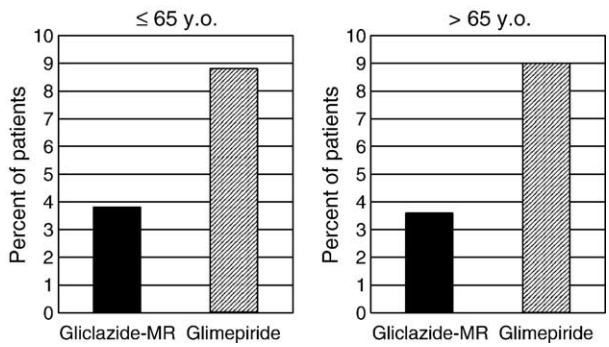

Fig. 2. Percentage of patients with hypoglycemia (defined according to the European Agency for the Evaluation of Medicinal Products) in type 2 diabetic patients younger or older than 65 years treated with glimepiride (cross-hatched columns) and gliclazide MR (closed columns).

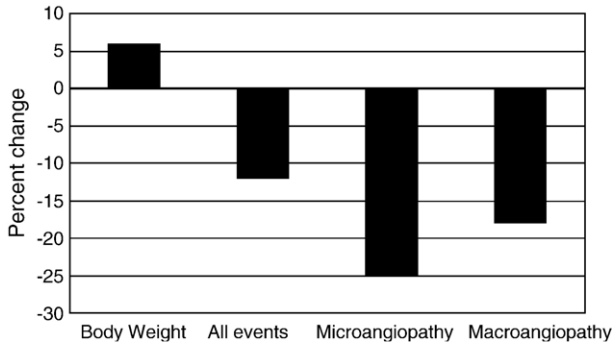

Fig. 3. Percentage of changes in body weight and the main outcomes in the UKPDS.

insulin, thiazolidinediones, and sulfonylureas. Of the 3 options, sulfonylureas seem to be associated with much less increase in body weight. In the UKPDS, after 10 years of follow-up, the mean body weight change ranged from a minimum of 1.7 kg for glibenclamide to a maximum of 2.6 kg for chlorpropamide [6]. In spite of the fact that body weight gain may be seen as an undesirable effect, the change in body weight should nevertheless be considered in a more comprehensive risk-to-benefit ratio. Thus, the increase in body weight during the UKPDS [6] occurred together with the achievement and maintenance of good glycemic control and significant reduction in all diabetes-related events, microangiopathy, and, to some extent, macroangiopathy (Fig. 3).

Other studies also report moderate changes in body weight even in insulin-resistant type 2 diabetic patients. In a group of Mexican Americans, a 14-week period of treatment with glimepiride was associated with a 2.3 kg gain in body weight and was no different from the 2.1 kg increase in those treated with glibenclamide [31]. Glimepiride has been claimed to be at least neutral with respect to body weight and weight reduction has been observed by some authors [32,33]. Body weight neutrality has been reported with other sulfonylureas, particularly with once-a-day preparations such as extended-release glipizide [34] and gliclazide MR [29]. In the GlUcose control In type 2 diabetes: Diamicron MR versus glimEperide study, over the 27-week period of follow-up, body weight was stable with mean changes from 83.1 to 83.6 and 83.7 to 84.3 kg on gliclazide MR and glimepiride, respectively [29].

Altogether, these findings may suggest that body weight gain in response to sulfonylurea therapy may have been overemphasized and that more accurate choice of the agent may allow an easier control of body weight, even in overweight type 2 diabetic patients.

6. Beta-cell exhaustion

Sulfonylureas represented one of main therapeutic approaches in the UKPDS. The use of glibenclamide and chlorpropamide was shown to be associated with an improvement in glycemic control and a significant impact on the development of events and complications associated with diabetes [6]. The improvement in glycemic control was associated with an initial increase in the homeostasis model assessment beta-cell function index that was followed by a progressive and linear reduction [12]. Interestingly, the decline in beta-cell function paralleled the progressive deterioration of glycemic control, prompting the hypothesis that it is the loss of beta-cell function that influences the natural history of the disease and, therefore, treatments capable of protecting the beta cell should be sought. Loss of beta-cell mass and function has raised concern regarding the use of sulfonylureas for the treatment of type 2 diabetes mellitus because studies have shown that these agents may induce apoptosis in beta-cell lines and rodent islets [35]. More recent studies have been conducted in isolated human islets assessing the effect of glibenclamide as well as the nonsulfonylurea secretagogues repaglinide and nateglinide on beta-cell apoptosis [36]. Glibenclamide induced a 2.09- and 2.46-fold increase in beta-cell apoptosis, respectively, whereas repaglinide did not change the number of apoptotic beta cells. At low concentration, nateglinide did not induce beta-cell apoptosis, although a 1.49-fold increase in the number of apoptotic beta cells was observed at high concentrations. On 4-day exposure of the islets to secretagogues, beta-cell apoptosis was apparent for all secretagogues.

In our laboratories, we have assessed insulin content, glucose-stimulated insulin release, islet cell apoptosis, and messenger RNA expression of insulin and glucose transporter-1 in isolated human islets cultured in the presence of therapeutic concentrations of glimepiride (10 μmol/L), glibenclamide (10 μmol/L), or chlorpropamide (600 μmol/L) [37]. Insulin content decreased significantly after culture with all 3 sulfonylureas. Insulin responsiveness to glucose was preserved in islets incubated with glimepiride, but not when islets were preincubated with glibenclamide or chlorpropamide. These alterations were reverted by an additional 48-hour incubation in drug-free conditions. Quantitative reverse transcriptase–polymerase chain reaction studies showed that, compared with the control islets, cells preincubated with glibenclamide or chlorpropamide had an increased expression of insulin messenger RNA, with no change in the expression of glucose transporter 1.

These observations indicate that differences may exist among sulfonylureas with respect to function and survival of cultured human islets. To what extent this translates into in vivo conditions is difficult to establish. In the UKPDS, for instance, the loss of beta-cell function was not unique for sulfonylureas, but occurred at the same rate of decline in type 2 diabetic patients on metformin or on conventional (mainly diet) treatment, suggesting that other factors had to be at work. The most apparent factor is hyperglycemia per se, as it concomitantly increased. The toxic effect of hyperglycemia on the beta cell is now well documented [38].

In initial studies performed in our laboratories [39], we have observed that incubation of human islets in the

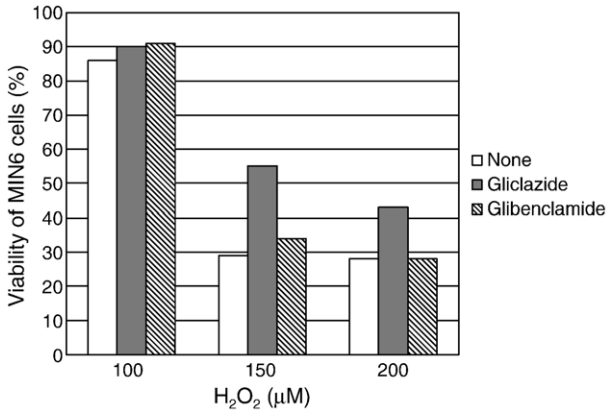

Fig. 4. Viability of MIN6 beta cell exposed to H_2O_2 in the presence of gliclazide (5 μmol/L) or glibenclamide (5 μmol/L). Similar results were obtained with 1 μmol/L gliclazide or glibenclamide. Adapted from *Biochem Biophys Res Commun* 2003;303:112-9.

presence of 22.2 mmol/L glucose is associated with significant oxidative stress and marked impairment of glucose-stimulated insulin release. These alterations can be almost completely prevented by concomitant incubation with an antioxidant compound such as glutathione. Thus, agents that may exert a similar antioxidant effect may have a beneficial action in preventing loss of beta-cell function and, as such, they may turn out to maintain more persistent glycemic control.

Gliclazide is known to be a general free radical scavenger [40]. A recent study investigated whether gliclazide could protect pancreatic beta cells from oxidative damage [41]. One hundred fifty micromoles per liter of hydrogen peroxide reduced the viability of mouse MIN6 beta cells to 29%. Addition of 2 μmol/L gliclazide protected MIN6 cells from the cell death induced by H_2O_2 to 56%. On the contrary, glibenclamide had no significant effect (Fig. 4). Nuclear chromatin staining analysis revealed that the preserved viability by gliclazide was due to inhibition of apoptosis. Hydrogen peroxide–induced expression of an antioxidative gene *heme oxygenase 1* and stress genes *A20* and *p21(CIP1/WAF1)* was suppressed by gliclazide. A similar experiment has been replicated by ourselves in isolated human islets [42]. Incubation of human islets in the presence of therapeutic concentrations of gliclazide was associated, compared with glibenclamide, with significant reduction in nitrotyrosine content, a marker of peroxynitrite generation, as well as apoptosis.

7. Selectivity

Sulfonylureas stimulate insulin release by binding to the sulfonylurea receptor, a subunit of the K_{ATP} channel complex. This binding leads to closure of the channel, resulting in voltage change in the beta-cell membrane and, in turn, influx of Ca^{2+} ions causing exocytosis of insulin granules [43,44]. Different sulfonylureas have different cross-reactivity with cardiovascular K_{ATP} channels [45]. Pharmacologic agents closing these channels oppose ischemic preconditioning, and this effect has raised concern because of a possible deleterious effect of sulfonylurea treatment with respect to cardiovascular mortality. In addition to animal experiments [46-48], recent human studies also support interference of some sulfonylureas on cardiac function under ischemic challenge. Thus, in response to dipyridamole stress, type 2 diabetic patients treated with glibenclamide compared with insulin had much worse myocardial function when assessed by echocardiography [49]. More recently, Lee and Chou [50] showed that protection by preconditioning occurred in type 2 patients treated with glimepiride, but not when glibenclamide was used. This different selectivity confirms previous experimental findings [46,47,51].

The effects of short- and long-term treatment with glibenclamide and gliclazide on forearm postischemic reactive hyperemia (RH) have been recently investigated in type 2 diabetic patients [52]. For this, a double-blind, randomized, crossover study with gliclazide (80 mg, BID) and glibenclamide (5 mg, BID) was performed in 15 type 2 diabetic patients. Forearm vascular reactivity was measured after 5 minutes of ischemia by plethysmography before and after 4 weeks of treatment. After short-term administration of gliclazide (80 mg) or glibenclamide (5 mg), RH was not influenced. However, after 4 weeks of treatment, glibenclamide induced a significant ($P = .004$) reduction in RH from 26.4 ± 6.9 to 21.9 ± 7.6 mL · min^{-1} · 100 mL^{-1} (Fig. 5). Gliclazide, conversely, did not induce a reduction in RH (23.9 ± 6.0 to 23.3 ± 6.6 mL · min^{-1} · 100 mL^{-1}).

Although this difference is most probably based on different sulfonylurea receptor binding, other mechanisms may contribute to this protective effect. Several studies have shown that gliclazide not only lowers blood glucose,

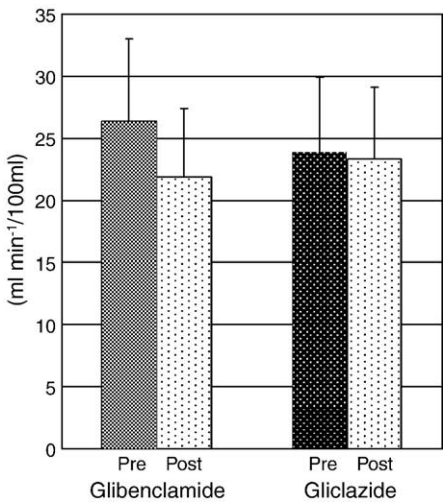

Fig. 5. Postischemic reactive hyperemia in type 2 diabetic patients treated with gliclazide or glibenclamide. See text for details. Adapted from *Clin Physiol Funct Imaging* 2005;25:40-6.

but also possesses hemorrheologic properties [53,54]. Clinically, gliclazide reduces platelet reactivity, stimulates endothelial prostacyclin synthesis, and increases fibrinolysis. In clinical studies, the beneficial effects of gliclazide on platelets have been related to a reduction in oxidative stress. Oxidative parameters have been assessed in 44 type 2 diabetic patients during 10 months of sulfonylurea treatment [55]. Administration of either MR or standard gliclazide to type 2 diabetic patients resulted in a fall in 8-isoprostanes, a marker of lipid oxidation, and an increase in the antioxidant parameters total plasma antioxidant capacity, superoxide dismutase, and thiols. Most likely, this property is due to gliclazide's free radical-scavenging ability that relates to the unique aminoazabicyclo-octane ring grafted onto the sulfonylurea.

8. Translating experimental medicine into clinical practice

Accurate analysis of the overwhelming bulk of literature on sulfonylureas suggests we should operate a better choice in deciding which sulfonylurea agent we are to use in our type 2 diabetic patients. In doing so, there are data to suggest that some of these drugs may provide persistent glycemic control, while limiting the risk of hypoglycemia and the increase in body weight. Once-daily sulfonylureas such as glimepiride and gliclazide MR may have much less interference with vasculature ensuring neutrality on the endothelial function and the protecting effect of ischemic preconditioning. On top of that, the latter has been shown to exert hemorrheologic effects that together with an antioxidant action might provide an antiatherogenic advantage. Even more intriguingly, the antioxidant properties of gliclazide may reduce the burden that long-term stimulation of defective beta cells has to face over the years of diabetes duration. However, most of the available data are experimental in nature and the use of any therapeutic approach should be based as much as possible on clinical evidence. The good pointers given so far by experimental investigation have to be challenged in the daily clinical life of our diabetic patients. We have not yet such evidence, but studies are ongoing that might provide us with such evidence. The Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation study is a large-scale, 2 × 2 factorial, randomized controlled trial that has been designed specifically to assess, among other issues, whether intensive glucose control therapy reduces the risk of major macrovascular disease and whether it may confer greater protection against microvascular complications [56]. The glucose control regimen chosen is based on gliclazide MR (30-120 mg). Nonpharmacologic therapy, other oral agents, and then insulin will be added as required to achieve the target level of HbA_{1c} (6.5% or less). More than 11 000 type 2 diabetic patients aged 55 years or older have been enrolled in the study, the results of which are expected in 2008.

9. What is the place of sulfonylureas in the treatment of type 2 diabetes mellitus?

As mentioned earlier on, sulfonylureas still occupy a central position in the recommendations of many guidelines for treatment of type 2 diabetes mellitus. Nevertheless, as discussed, concerns have been raised with respect to possible adverse effects that the use of these drugs might cause. However, in the light of the intrinsic pathogenetic heterogeneity of type 2 diabetes mellitus, sulfonylureas are likely to continue to be a reliable and effective treatment, particularly as combination therapy. Given the fact that insulin resistance and defective insulin secretion contribute, although in variable proportions, to the development and progression of hyperglycemia, agents tackling these main pathogenetic mechanisms represent a rational therapeutic approach. In individuals with a prevalent defect in insulin secretion, the use of a sulfonylurea may sound a better choice as a front-line treatment. The use of once-daily administration and the choice of sulfonylurea agents that may not exert further stress on the beta cell and are associated with beneficial properties other than a glucose-lowering effect may then confer specific advantages. These advantages are likely to exert a favorable effect even when used in combination with other antidiabetic agents. In many type 2 diabetic patients, combination therapy dealing with both pathogenetic defects is likely to ensure and maintain better glycemic control at lower doses and with fewer adverse events [57]. Thus, early combination of metformin and sulfonylureas in the UKPDS was associated with a significant reduction in both fasting plasma glucose and FPG and HbA_{1c} (7.5% vs 8.1%; $P = .006$) compared with sulfonylurea alone [58].

The appreciation of the prominent role of beta-cell defects in the development and progression of hyperglycemia in type 2 diabetes mellitus has highlighted the need for treatments that may stimulate insulin secretion and preserve the beta-cell mass. The recent introduction of exenatide, an incretin mimetic, and the dipeptidyl peptidase 4 inhibitors might provide such an opportunity, enlarging the therapeutic opportunities for the treatment of type 2 diabetes mellitus [59,60]. Of interest, the concomitant use of exenatide and sulfonylureas has resulted in significant improvement in glycemic control, which was associated with body weight reduction [13]. In these individuals, the proinsulin-to-insulin ratio improved, suggesting an amelioration in beta-cell function.

In conclusion, advancement in the formulation and established non–glucose-lowering properties of specific sulfonylurea agents still provide an opportunity for effective treatment of type 2 diabetes mellitus. Besides this classic form of therapy, many others are available and much more are under development, so that our armamentarium will grow. With increased therapeutic options it will be the diabetologist's duty to take as much advantage in ensuring glycemic control and in reducing the risk of diabetic

complications by full comprehension of the mechanisms of action and features of antidiabetic agents. It is mandatory now, at the time when we are experiencing unpreceded diabetes epidemics, that we put to work all our expertise and effort to ensure more patients achieve target values [13].

References

[1] International Diabetes Federation. Facts and figures. Available at: http://www.idf.org/home/ [Accessed December 20, 2005].

[2] Gonzalez-Clemente JM, Galdon G, Mitjavila J, Minarro A, Gimenez-Perez G, Mauricio D. Translation of the recommendations for the diagnosis of diabetes mellitus into daily clinical practice in a primary health care setting. Diabetes Res Clin Pract 2003;62:123-9.

[3] Turner RC, Holman RR. Lessons from UK Prospective Diabetes Study. Diabetes Res Clin Pract 1995;28:S151-7.

[4] Jonsson B. Revealing the cost of type II diabetes in Europe. Diabetologia 2002;45:S5-S12.

[5] Gilmer TP, O'Connor PJ, Manning WG, Rush WA. The cost to health plans of poor glycemic control. Diabetes Care 1997;20:1847-53.

[6] UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837-53.

[7] International Diabetes Federation. Global guidelines for type 2 diabetes. Available at http://www.idf.org/home/ [Accessed December 20, 2005].

[8] Saydah SH, Fradkin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. JAMA 2004;291:335-42.

[9] Liebl A, Mata M, Eschwege E. Evaluation of risk factors for development of complications in type II diabetes in Europe. Diabetologia 2002;45:S23-8.

[10] DeFronzo RA. Pathogenesis of type 2 diabetes mellitus. Med Clin North Am 2004;88:787-835.

[11] Bagust A, Beale S. Deteriorating beta-cell function in type 2 diabetes: a long-term model. Q J Med 2003;96:281-8.

[12] UKPDS Study Group. Overview of six years' therapy of type 2 diabetes—a progressive disease. Diabetes 1995;44:1249-58.

[13] Del Prato S, Felton AM, Munro N, Nesto R, Zimmet P, Zinman B. Global Partnership for Effective Diabetes Management. Improving glucose management: ten steps to get more patients with type 2 diabetes to glycaemic goal. Int J Clin Pract 2005;59:1345-55.

[14] Del Prato S, Marchetti P, Bonadonna RC. Phasic insulin release and metabolic regulation in type 2 diabetes. Diabetes 2002; 51(Suppl 1):S109-16.

[15] Gastaldelli A, Ferrannini E, Miyazaki Y, Matsuda M, DeFronzo RA. San Antonio metabolism study. Beta-cell dysfunction and glucose intolerance: results from the San Antonio metabolism (SAM) study. Diabetologia 2004;47:31-9.

[16] Weyer C, Bogardus C, Mott DM, Pratley RE. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. J Clin Invest 1999;104: 787-94.

[17] Weyer C, Tataranni PA, Bogardus C, Pratley RE. Insulin resistance and insulin secretory dysfunction are independent predictors of worsening of glucose tolerance during each stage of type 2 diabetes development. Diabetes Care 2001;24:89-94.

[18] European Diabetes Policy Group. A desktop guide to type 2 diabetes. Diabet Med 1999;16:716-30.

[19] Management of type 2 diabetes—management of blood glucose—NICE summary. Available at http://www.nelh.nhs.uk/guidelinesdb/html/fulltext-guidelines/Bloodglucose.html.

[20] American Diabetes Association. Standards of medical care in diabetes. Diabetes Care 2004;27(Suppl 1):S15-S34.

[21] Jennings AM, Wilson RM, Ward JD. Symptomatic hypoglycaemia in NIDDM patients treated with oral hypoglycaemiac agents. Diabetes Care 1989;12:203-8.

[22] The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin dependent diabetes mellitus. N Engl J Med 1993;329:977-86.

[23] Ferner RE, Neil HA. Sulphonylureas and hypoglycemia. BMJ 1988;296:949-50.

[24] Shorr RI, Ray WA, Daugherty JR, Griffin MR. Individual sulfonylureas and serious hypoglycemia in older people. J Am Geriatr Soc 1996;44:751-5.

[25] Asplund K, Wiholm B-E, Lithner F. Glibenclamide-associated hypoglycemia: a report on 57 cases. Diabetologia 1983;24:412-7.

[26] Van Staa T, Abenhaim L, Monette J. Rates of hypoglycemia in users of sulfonylureas. J Clin Epidemiol 1997;50:735-41.

[27] Ben-Ami H, Nagachandran P, Mendelson A, Edoute Y. Drug-induced hypoglycemic coma in 102 diabetic patients. Arch Intern Med 1999;159:281-4.

[28] Draeger KE, Wernicke-Panten T, Lomp HJ, Schuler E, Rosskamp R. Long-term treatment of type 2 diabetic patients with the new oral antidiabetic agent glimepiride (Amaryl): a double-blind comparison with glibenclamide. Horm Metab Res 1996;28:419-25.

[29] Schernthaner G, Grimaldi A, Di Mario U, Drzewoski J, Kempler P, Kvapil M, et al. GUIDE study: double-blind comparison of once-daily gliclazide MR and glimepiride in type 2 diabetic patients. Eur J Clin Invest 2004;34:535-42.

[30] United Kingdom Prospective Diabetes Study Group. United Kingdom Prospective Diabetes Study 24: a 6-year, randomized, controlled trial comparing sulfonylurea, insulin, and metformin therapy in patients with newly diagnosed type 2 diabetes that could not be controlled with diet therapy. Ann Intern Med 1998;128:165-75.

[31] Luis Bautista J, Bugos C, Dimberger G, Atherton T. Efficacy and safety profile of glimepiride in Mexican American patients with type 2 diabetes mellitus: a randomized, placebo-controlled study. Clin Ther 2003;25:194-209.

[32] Martin S, Kolb H, Beuth J, van Leendert R, Schneider B, Scherbaum WA. Change in patients' body weight after 12 months of treatment with glimepiride or glibenclamide in type 2 diabetes: a multicentre retrospective cohort study. Diabetologia 2003;46:1611-7.

[33] Bugos C, Austin M, Atherton T, Viereck C. Long-term treatment of type 2 diabetes mellitus with glimepiride is weight neutral: a meta-analysis. Diabetes Res Clin Pract 2000;50(Suppl 1):S47 [Abstract P251].

[34] Simonson DC, Kourides IA, Feinglos M, Shamoon H, Fischette CT, Glipizide Gastrointestinal Therapeutic System Study Group. Efficacy, safety, and dose-response characteristics of glipizide gastrointestinal therapeutic system on glycemic control and insulin secretion in NIDDM. Results of two multicentre, randomized, placebo-controlled clinical trials. Diabetes Care 1997;20:597-606.

[35] Efanova IB, Zaitsev SV, Zhivotovsky B, Kohler M, Efendic S, Orrenius S, et al. Glucose and tolbutamide induce apoptosis in pancreatic beta-cells. A process dependent on intracellular Ca^{2+} concentration. J Biol Chem 1998;273:33501-7.

[36] Maedler K, Carr RD, Bosco D, Zuellig RA, Berney T, Donath MY. Sulfonylurea induced beta-cell apoptosis in cultured human islets. J Clin Endocrinol Metab 2005;90:501-6.

[37] Del Guerra S, Marselli L, Lupi R, Boggi U, Mosca F, Benzi L, et al. Effects of prolonged in vitro exposure to sulphonylureas on the function and survival of human islets. J Diabetes Complications 2005;19:60-4.

[38] Poitout V, Robertson RP. Minireview: secondary beta-cell failure in type 2 diabetes—a convergence of glucotoxicity and lipotoxicity. Endocrinology 2002;143:339-42.

[39] Del Prato S, Lupi R, Bugliani M, Del Guerra S, Torri S, Sbrana S, et al. Glucotoxicity in human pancreatic islets is mediated by oxidative stress: evidence for limited defense capacity. Diabetologia 2004; 47(Suppl 1):A39.

[40] McGavin JK, Perry CM, Goa KL. Gliclazide modified release. Drugs 2002;62:1357-64.
[41] Kimoto K, Suzuki K, Kizaki T, Hitomi Y, Ishida H, Kastuta H, et al. Gliclazide protects pancreatic beta-cells from damage by hydrogen peroxide. Biochem Biophys Res Commun 2003;303:112-9.
[42] Grupillo M, Del Guerra S, Masini M, Lupi R, Bugliani M, Torri S, et al. Gliclazide protects isolated human islets from apoptosis induced by intermittent high glucose: the role of oxidative stress. Diabetologia 2005;48(Suppl 1):A45.
[43] Lebovitz HE, Melander A. Sulfonylureas: basic aspects and clinical uses. In: Alberti KGMM, Zimmet P, DeFronzo RA, Keen H, editors. International textbook of diabetes mellitus. 2nd ed. London: Wiley & Sons Ltd; 1997. p. 817-40.
[44] Edwards G, Weston A. The pharmacology of ATP-sensitive K^+-channels. Annu Rev Pharmacol Toxicol 1993;33:597-637.
[45] Lazdunski M. Ion channel effects of antidiabetic sulfonylureas. Horm Metab Res 1996;28:488-95.
[46] Geisen K, Vegh A, Krause E, Papp JG. Cardiovascular effects of conventional sulfonylureas and glimepiride. Horm Metab Res 1996;28: 496-507.
[47] Mocanu MM, Maddock HL, Baxter GF, Lawrence CL, Standen NB, Yellon DM. Glimepiride, a novel sulfonylurea, does not abolish myocardial protection afforded by either ischemic preconditioning or diazoxide. Circulation 2001;103:3111-6.
[48] Maddock HL, Siedlecka SM, Yellon DM. Myocardial protection from either ischaemic preconditioning or nicorandil is not blocked by gliclazide. Cardiovasc Drugs Ther 2004;18:113-9.
[49] Scognamiglio R, Avogaro A, Vigili de Kreutzenberg S, Negut C, Palisi M, Bagolin E, et al. Effects of treatment with sulfonylurea drugs or insulin on ischemia-induced myocardial dysfunction in type 2 diabetes. Diabetes 2002;51:808-12.
[50] Lee TM, Chou TF. Impairment of myocardial protection in type 2 diabetic patients. J Clin Endocrinol Metab 2003;88:531-7.
[51] Klepzig H, Kober G, Matter C, Luus H, Schneider H, Boedeker KH, et al. Sulfonylureas and ischaemic preconditioning; a double-blind, placebo-controlled evaluation of glimepiride and glibenclamide. Eur Heart J 1999;20:439-46.
[52] Wascher TC, Boes U. Forearm vascular reactivity is differentially influenced by gliclazide and glibenclamide in chronically treated type 2 diabetic patients. Clin Physiol Funct Imaging 2005;25:40-6.
[53] Renier G, Mamputu JC, Serri O. Benefits of gliclazide in the atherosclerotic process: decrease in monocyte adhesion to endothelial cells. Metabolism 2003;52(8 Suppl 1):13-8.
[54] Jennings PE. Vascular benefits of gliclazide beyond glycemic control. Metabolism 2000;49(Suppl 2):17-20.
[55] O'Brien RC, Luo M, Balazs N, Mercuri J. In vitro and in vivo antioxidant properties of gliclazide. J Diabetes Complications 2000;14:201-6.
[56] ADVANCE Management Committee. Study rationale and design of ADVANCE: action in diabetes and vascular disease—pretarax and Diamicron MR controlled evaluation. Diabetologia 2001;9: 1118-20.
[57] DeFronzo RA, Goodman AM. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. N Engl J Med 1995;333:541-9.
[58] UKPDS Study Group. A randomised trial of efficacy of early addition of metformin in sulphonylurea-treated non-insulin dependent diabetes. Diabetes Care 1998;21:87-92.
[59] Ahren B, Schmitz O. GLP-1 receptor agonists and DPP-4 inhibitors in the treatment of type 2 diabetes. Horm Metab Res 2004;36: 867-76.
[60] Buse JB, Henry RR, Han J, Kim DD, Fineman MS, Baron AD, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. Diabetes Care 2004;27:2628-35.