Repaglinide and Prandial Glucose Regulation: The Rational Approach to Therapy in Type 2 Diabetes?

revisão

Kirstine Brown Frandsen
Marcos A. Tambascia

ABSTRACT

This article reviews the clinical evidence and pharmacological rationale for repaglinide, a prandial glucose regulator. Repaglinide has a rapid onset and short duration of action – a pharmacokinetic profile that allows administration in a flexible schedule at mealtimes to limit the postprandial blood glucose excursions typical of type 2 diabetes mellitus. Placebo-controlled and comparative studies of repaglinide have demonstrated that prandial repaglinide also achieves overall glycaemic control, indicated by essential blood glucose parameters such as fasting blood glucose and hemoglobin A1c (HbA1c) levels. Regulation of postprandial glucose is of clinical importance, as this is an important independent risk factor for diabetic complications. Glycaemic control has been further improved in patients with drug-resistant type 2 diabetes when repaglinide is incorporated into combination therapy regimens with insulin-sensitizing agents such as metformin or troglitazone. There are also data to suggest that a mealtime regimen of repaglinide can reduce the likelihood of hypoglycemia compared with traditional sulphonylurea-based regimens. This benefit may be particularly marked when the patient is free to adopt a varying meal pattern. While sulphonylureas can effectively improve overall glycaemic control, their prolonged action may result in inappropriate stimulation of beta-cells during periods of relatively low blood glucose, thereby incurring the risk of hypoglycemia. Although this risk can be reduced if meals are consumed at regular intervals, such an approach places restrictions on the patient's routine and freedom to implement lifestyle measures such as caloric restriction. Repaglinide is metabolized in the liver to inactive metabolites and excreted in bile, a potential advantage for patients with renal dysfunction. In conclusion, compelling reasons for considering a prandial approach to glycaemic management include risk reductions for diabetic complications and hypoglycemia, and greater flexibility for the patient. Available data concerning repaglinide suggest that many theoretical benefits of the prandial approach to glucose regulation may be achievable in clinical practice. **(Arq Bras Endocrinol Metab 1999;**43/5: 325-335**)**

Keywords: Type 2 diabetes; Prandial glucose regulation; Repaglinide; Hypoglycemia

Department of Clinical Development, Novo Nordisk A/S, Bagsvaerd, Denmark and Disciplina de Endocrinologia, Hospital de Clínicas - Universidade de Campinas, UNICAMP, Campinas, SP.

RESUMO

Este artigo revisa as evidências clínicas e farmacológicas para o uso da repaglinida, um regulador da glicose prandial. Repaglinida tem um início rápido de ação e curta duração – um perfil farmacocinético que permite sua administração em esquemas flexíveis no horário das alimentações limitando as flutuações pós-prandiais da glicemia, típicas do diabetes mellitus do tipo 2 (DM2). Estudos comparativos com repaglinida controlados por placebo demonstram que seu uso também controla os níveis médios da glicemia, conforme indicado por parâmetros essenciais de glicemia, como a glicemia de jejum e os níveis de hemoglobina A1c (HbA1c). O controle da glicemia pós-prandial é de grande importância clínica, uma vez que ela é um importante fator de risco

Recebido em 10/08/99
Revisado em 29/09/99
Aceito em 01/10/99

independente para as complicações do DM. O controle glicêmico melhorou ainda mais em pacientes com DM2 resistente a drogas quando a repaglinida foi incorporada ao esquema terapêutico combinado com agentes sensibilizadores de insulina, como a metformina ou o troglitazone. Existem, também, dados sugerindo que o esquema de repaglinida durante as alimentações pode reduzir a possibilidade de hipoglicemia quando comparado com esquemas tradicionais baseados nas sulfoniluréias. Isto pode ser particularmente benéfico para deixar o paciente livre para adotar padrões alimentares variados. Enquanto as sulfoniluréias podem efetivamente melhorar o controle glicêmico global, sua ação prolongada pode resultar em estimulação inapropriada das células beta durante períodos de glicemia relativamente baixa, incorrendo em risco aumentado para hipogicemia. Embora este risco possa ser reduzido se as alimentações forem consumidas em espaços regulares, este esquema impõe restrições à rotina dos pacientes e à liberdade para implementar melhorias no estilo de vida, como a restrição calórica. A repaglinida é metabolizada no fígado produzindo metabólitos inativos e excretada na bile, uma vantagem potencial para pacientes com comprometimento da função renal. Em conclusão, razões óbvias para se considerar um esquema prandial para controle da glicemia incluem a redução dos riscos de complicações diabéticas e de hipoglicemia, e uma maior flexibilidade por o paciente. Dados já disponíveis sobre a repaglinida sugerem que muitos benefícios teóricos deste esquema prandial para regulação da glicemia pode ser obtido na prática clínica. **(Arq Bras Endocrinol Metab 1999;**43/5: 325-335**)**

Unitermos: Diabetes mellitus do tipo 2; Regulação prandial da glicemia; Repaglinida; Hipoglicemia

REPAGLINIDE IS A CARBAMOYLMETHYL BENZOIC acid (CMBA) derivative that has been exclusively developed and recently introduced for use as a prandial glucose regulator – that is, the drug is taken at mealtimes to stimulate insulin secretion at the most appropriate times. This approach limits postprandial rises in blood glucose concentration as well as providing good overall glycaemic control. Repaglinide increases the output of endogenous insulin from pancreatic beta-cells by blocking ATP-gated potassium channels (1). This action has a depolarizing effect on the beta-cell membrane, thereby increasing calcium influx through voltage-gated calcium channels; the cell is thus primed for the exocytosis of stored insulin granules. Repaglinide binds with markedly different affinities compared to glibenclamide to two receptor sites identified in the pancreatic beta-cell membrane (2). In contrast to SUs, repaglinide does not stimulate insulin release independently of its effects on beta-cell potassium channels (2,3), and does not inhibit insulin biosynthesis (4, 5). Furthermore, while repaglinide augments insulin release from pancreatic islets in vitro in the presence of glucose, in contrast to SUs, it does not stimulate insulin release when glucose is absent (2,6). This pharmacodynamic characteristic infers that repaglinide enhances glucose-mediated insulin release, and hence may be especially suited for prandial glucose regulation.

There are also important pharmacokinetic characteristics that make repaglinide suitable for prandial dosing, most notably its extremely rapid onset and short duration of action (1,2). Repaglinide reaches maximum plasma concentrations 50 minutes after oral dosing and is eliminated with a terminal half-life of just 32 minutes (7). In contrast, other antidiabetic agents have much more prolonged kinetics. For example, the insulin-sensitizing agents metformin and troglitazone have elimination half-lives of 2.6–8 hours (8) and approximately 24 hours (9,10), respectively, while the SUs glipizide and glibenclamide have respective half-lives of 1–5 and 10–16 hours (11). While a relatively lengthy half-life may be appropriate for an insulin-sensitizing agent, it may be disadvantageous in the case of an insulin secretagogue, as discussed below.

The elimination profile of repaglinide is also attractive when the needs of patients with diabetes are considered. It is extensively metabolized in the liver by the cytochrome P-450 system, principally the CYP3A4 enzyme, to inactive metabolites that are primarily excreted in bile (1). Thus, repaglinide may be suitable for the many patients with type 2 diabetes who have concomitant mild to moderate renal dysfunction. Interactions with medications that inhibit or induce CYP3A4 could be anticipated, however unpublished interaction studies involving ketoconazole and rifampicin have not suggested clinically significant interactions. Indeed, repaglinide appears to have a large therapeutic window, as animal toxicology studies have shown doses up to 100-fold greater than the maximum therapeutic dose recommended for humans to have little or no toxic, carcinogenic or teratogenic effects (1). In vivo interaction studies of repaglinide have been performed with warfarin, digoxin, theophylline and cimetidine (1). These studies showed repaglinide to have no clinically relevant effect on the pharmacokinetics of digoxin, warfarin or theophylline, while co-administration of cimetidine did not affect the kinetics of repaglinide (1). Interaction studies involving cardiovascular drugs commonly employed in patients with diabetes have yet to be published, but preliminary data suggest that no clinically relevant

interactions occur with nifedipine or simvastatin, despite these agents being CYP3A4 substrates.

The rationale behind a strategy of prandial glucose regulation in Type 2 diabetes, and hence the development of repaglinide, is based on a number of key concepts:

Glucose regulation in Type 2 diabetes is most compromised during the prandial phase. It is therefore 'physiological' to limit blood glucose excursions at these times.

Postprandial glucose excursions contribute directly to adverse diabetic outcomes as well as to the impairment of overall glucose control. Effective prandial glucose regulation will therefore improve overall glycaemic control and may be of utmost clinical importance when the patient's long-term outcome is considered.

Traditional oral hypoglycemic agents stimulate insulin release at inappropriate times, incurring the risk of hypoglycemia. By selectively augmenting insulin release with a rapid and short acting prandial glucose regulator during times of elevated blood glucose, the risk of hypoglycemia can be reduced.

By reducing risks of hypoglycemia, patients are afforded more freedom in their eating patterns and caloric intake. The patient's treatment is thus dictated by their mealtime choices, not vice versa, and yet glycaemic control is maintained.

The remainder of this article considers the evidence in support of these arguments and reviews clinical experience to date with repaglinide.

THE PRANDIAL GLUCOSE RESPONSE IN TYPE 2 DIABETES.

In nondiabetic individuals, homeostatic mechanisms regulate blood glucose levels within narrow limits. Even after ingestion of a high-sugar meal there is only a modest rise in blood glucose. This is ensured by a rapid increase in insulin secretion from pancreatic beta-cells in response to various stimuli such as rising blood glucose levels and the release of incretins from the gut wall (12). In health, the insulin response to a meal is biphasic. An initial early rise in insulin secretion precedes the prandial rise in blood glucose. This is thought to be an adaptation aimed at limiting endogenous glucose production in 'anticipation' of the increased absorption of exogenous glucose. Hepatic gluconeogenesis and glycogenolysis are reduced, and splanchnic glucose sequestration increased in response to this early rise in insulin release (8,13,14). A subsequent, more sustained rise in insulin output increases peripheral glucose disposal until absorption of glucose from the gut declines. The early phase of insulin release has been shown to be of vital importance in the regulation of prandial blood glucose levels (15).

In the individual with Type 2 diabetes, blood glucose control is progressively compromised. Although fasting blood glucose levels are elevated, it is at mealtimes that the greatest imbalances between insulin supply and metabolic demands are detected (16-18). At these times, blood glucose peaks may be elevated by as much as 2.5–3-fold compared with healthy controls (16). A similar situation is also present in the absence of fasting hyperglycemia in individuals with impaired glucose tolerance, a condition that can be viewed as a precursor to Type 2 diabetes (19).

There has been much debate about whether this situation first arises as a result of insulin resistance or impaired beta-cell function. Certainly, both pathological conditions occur in Type 2 diabetes, and different pathologies in glucose monitoring/signaling mechanisms, beta-cell function and the hepatic or peripheral response to insulin may contribute to greater or lesser extents in individual patients (20). Nevertheless, patients with Type 2 diabetes can be regarded as being relatively insulin-deficient whether or not peripheral or hepatic insulin resistance is present (8,18,21).

Importantly, a consistent finding in individuals with Type 2 diabetes is that the first-phase prandial insulin response is lost (Figure 1), and that postprandial blood glucose levels become greatly elevated (13,15-18). Attempts at restoring the first-phase insulin response (with exogenous insulin given intravenously over 30 minutes from commencing a meal) have significantly attenuated abnormalities in the prandial and postprandi-

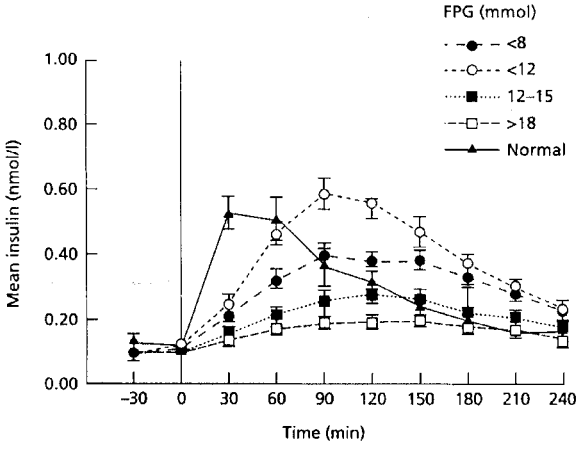


Figure 1. Mean prandial blood glucose and insulin response in healthy individuals and patients with newly-diagnosed Type 2 diabetes stratified by fasting blood glucose level. The loss of the early rise in insulin in Type 2 diabetes is evident. Reproduced from Coates et al. (ref 17).

al glycaemic and endocrine responses of such patients (15). This finding highlights the importance of the first-phase insulin response in glycaemic control, and implicates its absence as a key secretory defect in Type 2 diabetes. Furthermore, as the loss of a first-phase insulin response is also found in patients with impaired glucose tolerance, this defect may be a pivotal early event in the natural history of Type 2 diabetes (8,19). Support for this hypothesis is also provided by the observation that the physiological prandial insulin response cannot be restored in patients with Type 2 diabetes even when insulin sensitivity is improved through weight loss (22).

THE CLINICAL CONSEQUENCES OF POSTPRANDIAL HYPERGLYCEMIA

Loss of the early rise in insulin secretion in response to a meal and the resulting postprandial hyperglycemia are of great clinical importance. The risk of both microvascular and macrovascular complications is now known to correlate independently with postprandial hyperglycemia (as well as with HbA1c and fasting blood glucose level), and this correlation appears to begin in the prediabetic state (23). That postprandial as well as fasting hyperglycemia is a cardiovascular risk factor has been a consistent finding of epidemiological studies, which have been comprehensively reviewed by other authors (23-27). Indeed, there is a growing body of opinion that many of the vascular consequences of diabetes may arise during acute periods of prandial hyperglycemia (23-25,28,29). Suggested mechanisms by which vascular damage may occur in the postprandial phase include acutely increased labile glycation of proteins involved in cardiovascular regulation, and oxidative stress via generation of free radicals (23-25,28,29). The latter process may contribute to vasoconstriction, activation of coagulation, increased expression of vascular endothelial adhesion molecules and increased collagen formation in the vascular wall. In addition, acutely elevated levels of glucose may lead to enduring activation of protein kinase C in vascular cells (23,24,28,29). This enzyme is important in signaling transduction pathways and its over activity may contribute to various atherosclerotic processes, including increased endothelial permeability (24,28).

Indeed, recent clinical data suggest that postprandial rather than fasting hyperglycemia is associated with the greater increase in risk for atherosclerosis. A cross-sectional B-mode ultrasound study of subjects with impaired fasting blood glucose levels showed that the carotid artery intima media thickness was significantly increased in subjects with both fasting and postprandial hyperglycemia compared to those with elevated fasting glucose but normal glucose tolerance (30). Furthermore, in the Diabetes Intervention Study (DIS), multivariate analysis showed poorly controlled postprandial, but not fasting, hyperglycemia to be a risk factor for myocardial infarction in nearly 1000 subjects with Type 2 diabetes, followed up over 11 years (Figure 2) (31). A recently published epidemiological survey from Japan has also suggested impaired glucose tolerance, but not fasting hyperglycemia, to be a risk factor for cardiovascular disease (32).

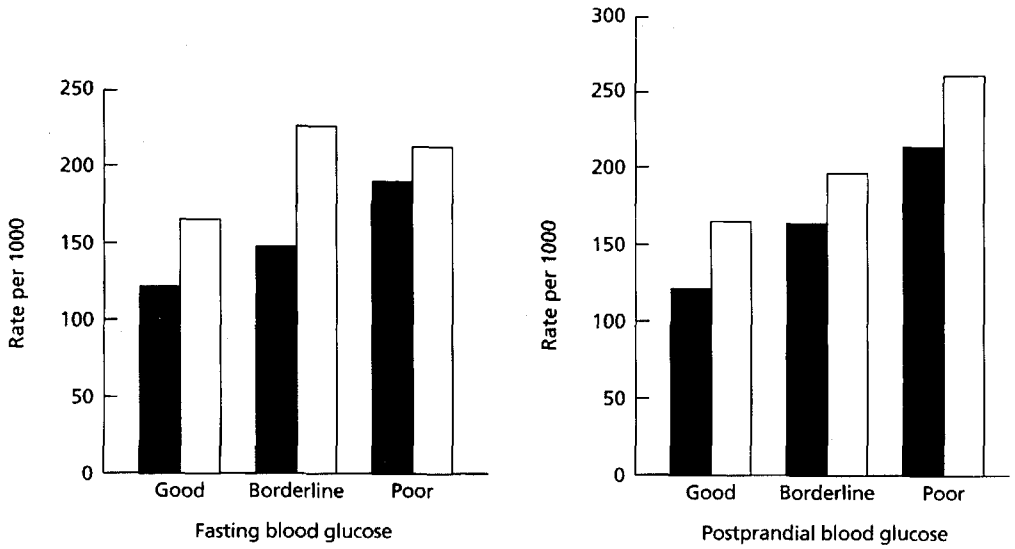


Figure 2. Incidence of myocardial infarction (■) and mortality rate (□) in relation to the quality of control of fasting glucose and postprandial glucose; data from 11-year follow-up of the Diabetes Intervention Study. A correlation between these outcomes and postprandial blood glucose is seen. Reproduced from Hanefeld et al. (ref 31).

Importantly, the risks associated with hyperglycemia are modifiable, and positive outcome benefits have been demonstrated with intensive pharmacological interventions aimed at improving glycaemic control. A 6-year study involving 110 patients in Japan with Type 2 diabetes showed that strict glycaemic control, achieved with an intensive insulin-based treatment strategy, delayed the onset and progression of retinopathy, nephropathy and neuropathy compared with conventional insulin regimens (33). In this study, a postprandial blood glucose concentration of 10 mmol was identified as a threshold above which risk increased. The UKPD study, in which over 5000 patients with Type 2 diabetes were enrolled, also showed improved glycaemic control to be associated with dramatic reductions in diabetic retinopathy, nephropathy, stroke and diabetes-related mortality (34). These benefits were achieved with intensive treatment based on SUs, metformin and exogenous insulin, often in combination regimens, but at the cost of higher incidences of hypoglycemia. Nevertheless, this study also concluded that there is no threshold value, at least for HbA1c, below which further risk reductions cannot be achieved with greater control. Furthermore, the UKPDS dispelled concerns that increased levels of blood insulin caused by treatment with secretagogues might adversely affect patients' outcomes. In conclusion, then, it appears that effective glycaemic control, especially during the postprandial phase, is important for the long-term well-being of the patient.

INSULIN SECRETAGOGUES, HYPOGLYCEMIA AND MEALTIME FLEXIBILITY

After failure of diet and exercise, insulin secretagogues such as SUs are established among the first-line therapies for improving glycaemic control in Type 2 diabetes. Many SUs can be given as a once-daily oral dose to increase and enhance endogenous insulin production throughout the day. However, the profile of pancreatic beta-cell stimulation developed by SU treatment is not physiological. The prolonged action of these drugs means that stimulation of insulin release extends well beyond mealtimes, and may therefore be inappropriately high when glucose levels are not elevated. Under these circumstances, hypoglycemia is an ever-present risk, and the patient treated with a SU must ensure an adequate carbohydrate intake throughout the day to counter this threat; a missed meal is particularly likely to result in a hypoglycemic episode (35,36). Indeed, symptomatic hypoglycemia is the most common side effect associated with SU therapy, particularly in elderly patients, and irregular meals have been identified as a contributing factor in this high incidence (35). Accumulation of SUs that are partially excreted by the renal route may be another reason for an increased risk of hypoglycemia in elderly patients (35). The American Diabetes Association and European NIDDM Policy Group have recommended short-acting insulin secretagogues to reduce this risk (37,38). In the UKPDS, 30% of patients treated with glibenclamide experienced hypoglycemia during the first year of therapy – the same incidence as was seen in insulin-treated patients (34).

Such considerations mean that the sulphonylurea-treated patient's medication must, by necessity, determine their eating pattern. Patients are likely to be prescribed a strict mealtime regimen by their caring physician, and may be asked to consume regular snacks between meals. However, not only does such a situation place restraints on the patient's routine, it may also compromise their ability to reduce caloric intake. Weight loss will inevitably be difficult to achieve when the patient's therapy dictates such eating behavior. Ironically, the patient's treatment may deny them the opportunity to improve insulin sensitivity and glycaemic control through truly physiological mechanisms by the natural process of weight loss.

While hypoglycemia may be of particular concern to the patient, prandial hyperglycemia may also be inadequately controlled by SU therapy. The presence of SU may enhance the patient's residual prandial insulin response when the drug is present at high concentration, but prandial insulin peaks may become progressively diminished with later meals if plasma drug levels decline between dosing intervals.

A NEW STRATEGY: THE PRANDIAL APPROACH TO GLUCOSE REGULATION

In Type 1 diabetes, the use of basal-bolus insulin therapy is now acknowledged as the method of choice for precise glycaemic control. By supplementing one or two daily injections of long-acting insulin with mealtime injections of short-acting insulins, this approach seeks to recreate, on a day by day basis, a physiological blood insulin profile that reflects the patient's meal consumption and closely resembles that of the nondiabetic individual. However, the use in Type 2 diabetes of rapid-, short-acting secretagogues to recreate flexible, physiological profiles of endogenous insulin secretion is a relatively new phenomenon. This strategy of prandial glucose regulation (PGR) may overcome some of the limitations of conventional oral hypo-

glycemic agents, but drugs with the necessary properties were not available until the development of repaglinide. As part of an overall management plan involving lifestyle, diet and exercise, PGR seeks to correct a fundamental metabolic defect in Type 2 diabetes, and may be the closest method available to recreate physiological patterns of endogenous insulin secretion. It can be expected that postprandial hyperglycemia will be effectively reduced by PGR. Fasting hyperglycemia will also be reduced if disposal of prandial glucose is more complete, as is the case in normal individuals. In addition, it can be expected that the risk of hypoglycemia will decrease when a short- and rapid-acting prandial glucose regulator is utilized.

From the patient's point of view, PGR offers the opportunity for greater flexibility in eating patterns. Meals can be delayed to more convenient times or missed altogether without undue fear of hypoglycemia. Thus, PGR as a strategy is not restrictive; it is patient-driven rather than treatment-driven. It is recognized that many patients with Type 2 diabetes are confused about the reasons for taking meals according to a regular and rigid schedule, and would welcome greater flexibility. Furthermore, patients wishing to reduce caloric intake will be less restricted by a PGR strategy, so weight loss may be easier to achieve; glycaemic control and quality of life could be anticipated to improve accordingly. By linking medication to food consumption it can also be anticipated that PGR will provide a therapy regimen that facilitates compliance.

REPAGLINIDE IN CLINICAL PRACTICE: GLYCAEMIC CONTROL

Early clinical studies of repaglinide, used according to the PGR strategy, have provided encouraging results. In a 16-week, placebo-controlled trial involving 408 patients with Type 2 diabetes, naïve to antidiabetic pharmacotherapy and poorly controlled by diet, the introduction of repaglinide was associated with a significant improvement in HbA1c from 7.8% at baseline to 6.6% at endpoint ($p < 0.001$) (39). In contrast, there was no significant change in HbA1c in patients randomized to placebo (7.6% and 7.4% at baseline and endpoint, respectively). Importantly, the reduction in HbA1c associated with repaglinide occurred regardless of whether patients chose to have two, three or four meals (with preprandial dosing) per day, thus demonstrating the validity of the PGR strategy. HbA1c was lowered by repaglinide in all patient categories independent of age or body mass index. Furthermore, repaglinide was not associated with weight gain in this study.

Similar findings were made in another placebo-controlled study of repaglinide involving 99 patients over 18 weeks of treatment (40). Patients who had already been receiving antidiabetic medications were given a 2-week washout to establish baseline data. In this study, repaglinide was associated with a decrease in HbA1c from 8.5% at baseline to 7.8%, while in the placebo group HbA1c increased from 8.1 to 9.3%. This between-group difference was highly significant ($p < 0.0001$). There were also statistically significant advantages for patients receiving repaglinide versus placebo in terms of the fasting and postprandial changes in glucose, insulin and C-peptide levels.

Studies comparing repaglinide with other agents have also been encouraging, showing that repaglinide provides overall glycaemic control that is at least equivalent to that obtained with SU therapy or metformin and superior to troglitazone. Two comparative, 1-year studies of repaglinide involving nearly 900 patients with Type 2 diabetes showed similar levels of glycaemic control to glibenclamide (41,42). One of these studies also suggested that pharmacotherapy-naïve patients treated with repaglinide were likely to gain less weight than those receiving the SU (Figure 3) (42). In this study, both repaglinide and glibenclamide rapidly lowered HbA1c levels over the initial 3 months in patients naïve to pharmacotherapy (from 9.4% to 7.6%, and from 9.6% to 8.0%, respectively). Over the 12-month period, there was a more pronounced increase in fasting insulin and C-peptide levels in patients treated with glibenclamide than in those receiving repaglinide, while at 3 months, only repaglinide-treated patients had a reduction from

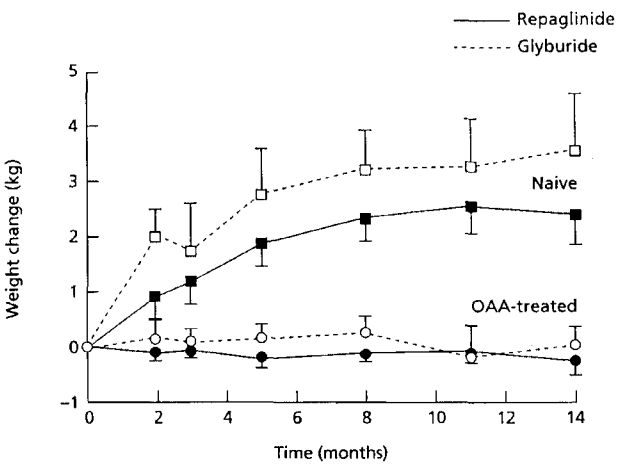


Figure 3. Change in body weight (mean ± SEM) in pharmacotherapy-naïve and previously treated patients with Type 2 diabetes, randomized to receive repaglinide or glyburide. Reproduced from Marbury et al. (ref 42).

baseline in these parameters. These findings imply that repaglinide was associated with a superior preservation of insulin sensitivity than the SU, and are consistent with its shorter duration of beta cell stimulation.

A recently published study in which 195 patients with Type 2 diabetes were randomized to receive preprandial repaglinide or once or twice daily glibenclamide for 14 weeks, also showed equivalent levels of glycaemic control in terms of HbA1c, fasting glucose, C-peptide, insulin and proinsulin (43). However, this study demonstrated a difference in 2-hour postprandial blood glucose level between repaglinide and glibenclamide that approached statistical significance (8.1 mmol/l versus 9.1 mmol/l, p = 0.07).

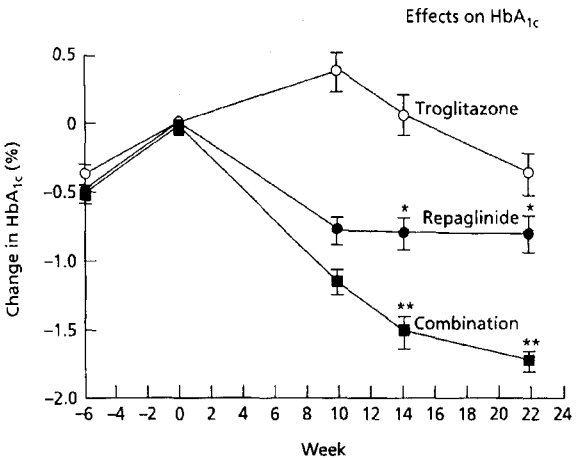
REPAGLINIDE IN COMBINATION REGIMENS

The efficacy of repaglinide in combination regimens has also been demonstrated. This is important, as Type 2 diabetes tends to be a progressive disease, and effective control with antidiabetic monotherapy is often a temporary situation. Secondary failure is common and it is often necessary to combine hypoglycemic agents with insulin sensitizing drugs or exogenous insulin to maintain glycaemic control. For example, in the UKPDS, over 40% of patients given SU therapy required additional antidiabetic drug therapy or insulin therapy within 6 years of their diagnosis of Type 2 diabetes (44).

Repaglinide appears to provide glycaemic control at least equivalent to that with metformin, and further improvement in glycaemic control can be achieved by combining repaglinide with metformin, compared with either agent alone. These findings were demonstrated in a study of 83 patients with Type 2 diabetes, who were no longer adequately controlled by metformin after a period of about 4 years (45). While continuation of metformin as monotherapy did not result in significant changes in HbA1c or fasting blood glucose over the 3-month study period, patients given additional preprandial repaglinide had significant decreases in these parameters. HbA1c and fasting plasma glucose decreased, respectively, from 8.3% to 6.9% (p = 0.0016) and from 10.22 mmol/l to 8.04 mmol/l (p = 0.0003) with combination therapy, and 59% of these patients achieved optimal glycaemic control (HbA1c < 7.1%). In patients for whom repaglinide was substituted for metformin there was no deterioration in parameters of glycaemic control. This may be of clinical significance as primarily the renal route excretes metformin. Repaglinide may thus be a suitable alternative to metformin for patients with declining renal function (45).

Metformin has traditionally been regarded as particularly suitable for use in obese patients as, in contrast to SU therapy, it is not associated with weight gain. The relative lack of weight gain reported in some studies of repaglinide (39,42) can also be seen as a good reason for considering repaglinide as an alternative to metformin. Thus, the repaglinide–metformin combination provides a particularly attractive option for obese patients with Type 2 diabetes who begin to lose glycaemic control with metformin monotherapy, and may be seen as preferable to a metformin–SU combination (45). Furthermore, this apparently synergistic combination may allow dose reductions of metformin to be made in patients experiencing gastrointestinal side effects with this agent (45).

A three-way comparison of monotherapy and combination therapy has also been made in a study of repaglinide and troglitazone in 256 patients with Type 2 diabetes (46). After a washout period to establish baseline characteristics, HbA1c decreased over the 22-week study period from 8.8% to 8.0% in repaglinide-treated patients, from 8.5% to 8.1 % in troglitazone-treated patients, and from 8.7% to 7.0% in the repaglinide–troglitazone combination group (Figure 4). ANOVA showed repaglinide to be significantly more effective than troglitazone in this respect (p< 0.05), while combination therapy was significantly more effective than monotherapy (p< 0.05).



*p < 0.05 combination therapy vs. either troglitazone or repaglinide
**p < 0.05 repaglinide vs. troglitazone therapy

Figure 4. Change in HbA1c over time in patients with Type 2 diabetes treated with repaglinide, troglitazone or the combination of these two drugs. Greater control was achieved with repaglinide than troglitazone, and combination therapy resulted in greater metabolic control than monotherapy. Reproduced from Raskin et al. (ref 46).

The combination of insulin secretagogues with exogenous insulin is increasingly used for patients experiencing secondary failure to SU-based therapy, as glycaemic control can often be restored without undue weight gain using this approach (47). Potentially, a prandial glucose regulator such as repaglinide could also be utilized in combination with an intermediate-acting insulin for drug-resistant patients (a basal bolus approach), and further reductions in weight gain or hypoglycemia in comparison to SU–insulin combinations might be expected. Ongoing studies will determine the clinical profile of repaglinide–insulin combinations.

HYPOGLYCEMIA

An important predicted advantage of the PGR strategy is a reduction in the incidence and severity of hypoglycemia, relative to treatment regimens involving long-acting insulin secretagogues. The potential of this strategy to minimize the risk of hypoglycemia in everyday life was clearly demonstrated in a randomized study in which 43 patients with well-controlled Type 2 diabetes received either repaglinide with meals or glibenclamide given according to label recommendations (36). These patients were subsequently assessed with and without omission of their midday meal; those receiving repaglinide also omitted their midday dose when lunch was withheld, according to the dosing recommendations for the drug. The two treatments were found to be equivalent in terms of postprandial blood glucose excursions. However, significant between-treatment differences were found in terms of the influence that omitting the midday meal had upon glycaemia ($p = 0.014$). The mean minimum blood glucose level remained unchanged at 4.3 mmol/l in repaglinide-treated patients, whereas omission of lunch in glibenclamide-treated patients led to a fall from 4.3 to 3.4 mmol/l. Six episodes of hypoglycemia (four requiring treatment) occurred, all in glibenclamide-treated patients and all in association with omission of lunch. No hypoglycemic episodes occurred in the repaglinide-treated patients when lunch was omitted.

This study demonstrates the value of the PGR strategy for reducing the risk of hypoglycemia in everyday life, when flexible meal patterns may be followed. However, other data suggest that repaglinide may be associated with a reduced risk of hypoglycemia in comparison to SU therapy per se – even when dosing and food consumption are tightly controlled by strict study protocols in line with the requirements of SU therapy. Pooled data from comparative studies involving glibenclamide, gliclazide and glipizide show repaglinide to be associated with lower incidences of hypoglycemia than these comparators, suggesting a relative risk of major hypoglycemia of 2.8 for SU-treated patients compared with repaglinide-treated patients (48). This difference was manifest despite identical levels of metabolic control (determined by HbA1c) with all treatments. Objective evidence from those patients for whom blood glucose measurements were available show the relative risk of hypoglycemia (defined as blood glucose < 2.5 mmol/l) to be two-fold higher with glibenclamide and glipizide, and four-fold higher with gliclazide, in comparison to repaglinide (1).

Individual comparative studies designed to assess glycaemic control have not identified significant differences between repaglinide and comparator SUs in terms of patient-reported incidences of hypoglycemia (41-43). However, this parameter does not provide information about the relative extents of the blood glucose nadirs. In a randomized study of 576 patients with Type 2 diabetes, 15% of patients receiving repaglinide and 19% receiving glibenclamide reported symptoms of hypoglycemia (42). While this difference was not significant, blood glucose meter readings made by patients at the time of their hypoglycemic symptoms revealed that the blood glucose levels were significantly lower ($p = 0.004$) at these times in patients receiving glibenclamide than in those receiving repaglinide (Figure 5).

In another comparative study of repaglinide and glibenclamide, a study cohort of 424 patients reported low incidences of hypoglycemia; 9% in each group (41). Again, however, data from self-measured assessments of

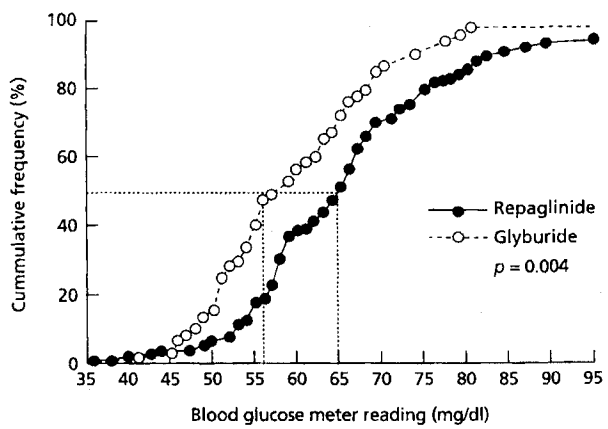


Figure 5. Blood glucose meter readings at the time of clinical symptoms of hypoglycemia in patients with Type 2 diabetes randomized to receive either repaglinide or glibenclamide. Glibenclamide-treated patients recorded significantly lower blood glucose nadirs. Reproduced from Marbury et al. (ref 42).

blood glucose levels according to the protocol schedule suggested an advantage for repaglinide-treated patients. Blood glucose readings < 4.4 mmol/l were recorded by 9% of repaglinide-treated and 21% of glibenclamide-treated patients in the pre-lunch measurement.

Placebo-controlled studies indicate that the incidence of symptomatic hypoglycemia is elevated in repaglinide-treated patients compared to those receiving placebo, but this is to be expected as a consequence of improving glycaemic control through increased insulin secretion. In the study by Goldberg et al (40), the incidence of reported hypoglycemia among repaglinide-treated patients was 36% (versus 6% with placebo), but only one event was associated with a blood glucose level < 2.5 mmol/l. Half of these incidents occurred during a dose-adjustment phase of the study. Another placebo-controlled study of repaglinide in which patients took repaglinide at mealtimes but chose to have either two, three or four meals per day showed the risk of hypoglycemia to be independent of the meal pattern (39).

In conclusion, it appears that while repaglinide does increase the incidence of hypoglycemia relative to placebo, in comparison to treatment with SUs, the frequency and intensity of hypoglycemic events are reduced, even in the situation of well-disciplined drug dosing and food consumption. This is an advantage that may be enhanced in every day clinical usage when the PGR principle is applied.

CONCLUSION

Given the association between postprandial glucose excursions and adverse diabetic complications, and given the risks of hypoglycemia inherent in traditional methods of increasing blood insulin levels, a treatment strategy based upon prandial blood glucose regulation is both logical and appealing. The greater flexibility that PGR can offer the patient may also be seen as a major advantage of this strategy, although PGR is by no means a license to abandon good dietary habits. Modern treatment regimens for Type 1 diabetes with exogenous insulins are aimed at recreating flexible, physiological blood insulin profiles. Now, with the concept of PGR and the advent of the first prandial glucose regulators, it is logical that treatment regimens be developed for Type 2 diabetes that take this same approach. There is still no therapy available that can recreate a perfectly physiological insulin response on a minute by minute (or even hour by hour) basis in patients with diabetes; the risk of hypoglycemia remains the price to be paid for improved glycaemic control with all interventions that increase blood insulin levels. However, the first prandial glucose regulator, repaglinide, does go some way towards this goal. Repaglinide has been shown to achieve good metabolic control, at least equivalent to that provided by treatment with SUs, but to afford the patient a reduced risk of hypoglycemia as well as greater mealtime flexibility.

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Address for correspondence:

Marcos A. Tambascia
Disciplina de Endocrinologia, HC - UNICAMP
Rua Frei Manoel da Ressurreição 965
13073-020 Campinas, SP.