Repaglinide – Prandial Glucose Regulator: A New Class of Oral Antidiabetic Drugs

David R. Owens*

Diabetes Research Unit, Llandough Hospital, University of Wales College of Medicine, Cardiff, UK

The highest demand on insulin secretion occurs in connection with meals. In normal people, following a meal, the insulin secretion increases rapidly, reaching peak concentration in the blood within an hour. The mealtime insulin response in patients with Type 2 diabetes is blunted and delayed, whereas basal levels often remain within the normal range (albeit at elevated fasting glucose levels). Restoration of the insulin secretion pattern at mealtimes (prandial phase)—without stimulating insulin secretion in the 'postabsorptive' phase—is the rationale for the development of 'prandial glucose regulators', drugs that are characterized by a very rapid onset and short duration of action in stimulating insulin secretion. Repaglinide, a carbamoylmethyl benzoic acid (CMBA) derivative is the first such compound, which recently has become available for clinical use. Repaglinide is very rapidly absorbed (t_{max} less than 1 hour) with a $t_{\frac{1}{2}}$ of less than one hour. Furthermore, repaglinide is inactivated in the liver and more than 90 % excreted via the bile. The implications of tailoring repaglinide treatment to meals were examined in a study where repaglinide was dosed either morning and evening, or with each main meal (i.e. breakfast, lunch, dinner), with the total daily dose of repaglinide being identical. The mealtime dosing caused a significant improvement in both fasting and 24-hour glucose profiles, as well as a significant decrease in HbA_{1c}. In other studies, repaglinide caused a decrease of 5.8 $mmol \cdot l^{-1}$ in peak postprandial glucose levels, and a decrease of 3.1 $mmol \cdot l^{-1}$ in fasting levels with a reduction in HbA_{1c} of 1.8 % compared with placebo. In comparative studies with either sulphonylurea or metformin, repaglinide caused similar or improved control (i.e. HbA_{1c}, mean glucose levels) and the drug was well tolerated (e.g. reported gastrointestinal side-effects were more than halved when patients were switched from metformin to repaglinide). A hallmark of repaglinide treatment is that this medication follows the eating pattern, and not vice versa. Hence the risk of developing severe hypoglycaemia (BG $\leq$ 2.5 $mmol \cdot l^{-1}$) in connection with flexible lifestyles should be reduced. This concept was examined in a study in which patients well controlled on repaglinide skipped their lunch on one occasion. When a meal (i.e. lunch) was skipped—so was the repaglinide dose, whereas in the comparative group on glibenclamide the recommended morning and evening doses were taken. Twenty-four per cent of the patients in the glibenclamide group developed severe hypoglycaemia, whereas no hypoglycaemic events occurred in the group receiving repaglinide. However, in long-term studies the overall prevalence of hypoglycaemia was similar to that found with other insulin secretagogues. In summary, current evidence shows that the concept of prandial glucose regulation offers good long-term glycaemic control combined with a low risk of severe hypoglycaemia with missed meals. The concept should meet the needs of Type 2 diabetic patients, allowing flexibility in their lifestyle.

***Diabet. Med.* 15 (Suppl. 4): S28–S36 (1998)**

KEY WORDS **repaglinide; prandial; Type 2 diabetes mellitus; first-line monotherapy; glycaemic control; clinical pharmacology**

Received 3 September 1998; accepted 7 September 1998

Introduction

Repaglinide is the active antihyperglycaemic enantiomer of 2-ethoxy-4-[2-[[3-methyl-1-[2-(1-piperidinyl) phenyl]-butyl] amino]-2-oxoethyl] benzoic acid, a member of the carbamoylmethyl benzoic acid (CMBA) family (Figure 1), with a structure different from that of the sulphonylureas.[1]

The insulinotropic action of repaglinide is mediated via the inhibition of ATP-dependent potassium ion channels in the pancreatic β-cell membrane, which results in the depolarization of the cell membrane and an influx of calcium ions through voltage-gated calcium channels. Intracellular calcium concentration is therefore increased and insulin secretion is stimulated.[2] Repaglinide binds to the sulphonylurea receptor and to its own distinct site on the pancreatic β-cell. This has been demonstrated in mouse β-cells during co-incubation with

* Correspondence to: D. Owens, Diabetes Research Unit, Llandough Hospital, University of Wales College of Medicine, Cardiff, UK

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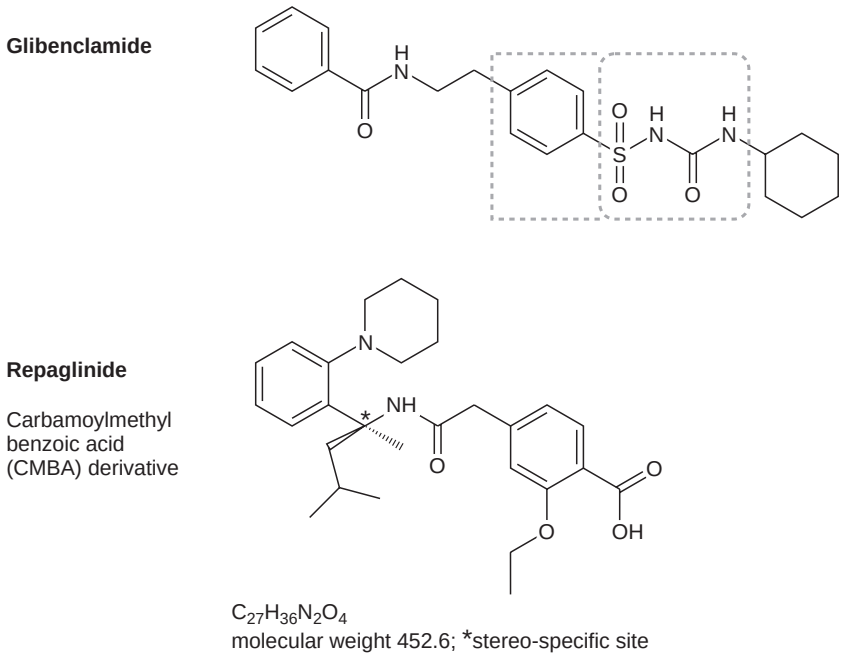

Figure 1. Chemical structure of repaglinide and the sulphonylurea glibenclamide

PPP (3-(3-hydroxyphenyl)-N-(1-propyl)-piperidine), a drug selected as a pharmacological tool to differentiate between the two different binding sites.[3] In contrast to the sulphonylureas, repaglinide does not stimulate exocytosis independently of its effect on ATP-sensitive potassium channels, insulin biosynthesis is not impaired and the insulinotropic effect is not inhibited by 2,4-dinitrophenol.[3,4]

Preclinical Pharmacology

Results from *in-vitro* studies with isolated intact mouse pancreatic islets show that in the absence of glucose, repaglinide has no effect on basal insulin secretion in contrast to glibenclamide, which stimulates insulin secretion significantly at 0 mmol·l^{-1} glucose.[3,5] However, in the presence of either 5 or 10 mmol·l^{-1} of glucose, repaglinide is up to five times more potent than glibenclamide in stimulating insulin secretion.[3] *In-vivo* studies have been carried out in fasted (rats) and fed (rats, dogs) non-diabetic animals. A dose-dependent reduction in blood glucose was seen following oral administration of repaglinide to fasted Wistar rats.[6] Compared with glibenclamide and glimepiride in fed and fasted normal rats, repaglinide brought about a greater and more rapid increase in plasma insulin concentration preceding an earlier decrease in blood glucose concentration.[7] *In-vivo* results support the findings of a glucose-dependent insulinotropic effect of repaglinide on normal pancreatic β-cells.

Toxicology

Results from toxicology studies have demonstrated that repaglinide has little or no toxicological effects at doses of up to 100-fold greater than the maximum therapeutic dose in humans (2 mg·kg^{-1}·day^{-1}). Increased electrolyte loss was seen in rats at 30 mg·kg^{-1}·day^{-1}, cardiovascular events in rabbits at 20 mg·kg^{-1}·day^{-1}, mild hepatotoxicity in dogs at 50 mg·kg^{-1}·day^{-1} and weight loss observed in rats at doses as high as 120 mg·kg^{-1}·day^{-1}. No carcinogenic effect has been seen at doses below 60 mg·kg^{-1}·day^{-1}and no teratogenic effects below 30 mg·kg^{-1}·day^{-1}. Repaglinide does not appear to represent a carcinogenic or teratogenic risk in humans. LD50 values in rats and dogs were >2500 mg·kg^{-1}·day^{-1} and approximately 300 mg·kg^{-1}·day^{-1}, respectively. Taken together, the results from the toxicological studies indicate that repaglinide has a large therapeutic window.

Metabolism

Repaglinide is metabolized predominantly in the liver by the cytochrome P450 enzymes, the principal isoform involved being CYP3A4. In humans, approximately 98 % of repaglinide is metabolized within 96 h of dosing, with 90 % recovered in faeces and 8 % in urine. The two main biotransformation products of repaglinide occur through the oxidative opening of the piperidine ring and glucuronidation of the aromatic carboxylic acid group (Figure 2). The dicarboxylic acid metabolite (M_2) is the major transformation product, i.e. 66 % of the administered dose and the main metabolite recovered in faeces (72 %), with less than 2 % of repaglinide excreted unchanged. None of the metabolites contribute to the hypoglycaemic actions of repaglinide. *In-vitro* data indicate that drugs that inhibit cytochrome P450 activity, such as the antifungal agent ketoconazole, antibacterial agents, steroids and cyclosporin, can inhibit the metabolism of repaglinide. Drugs, such as rifampicin,

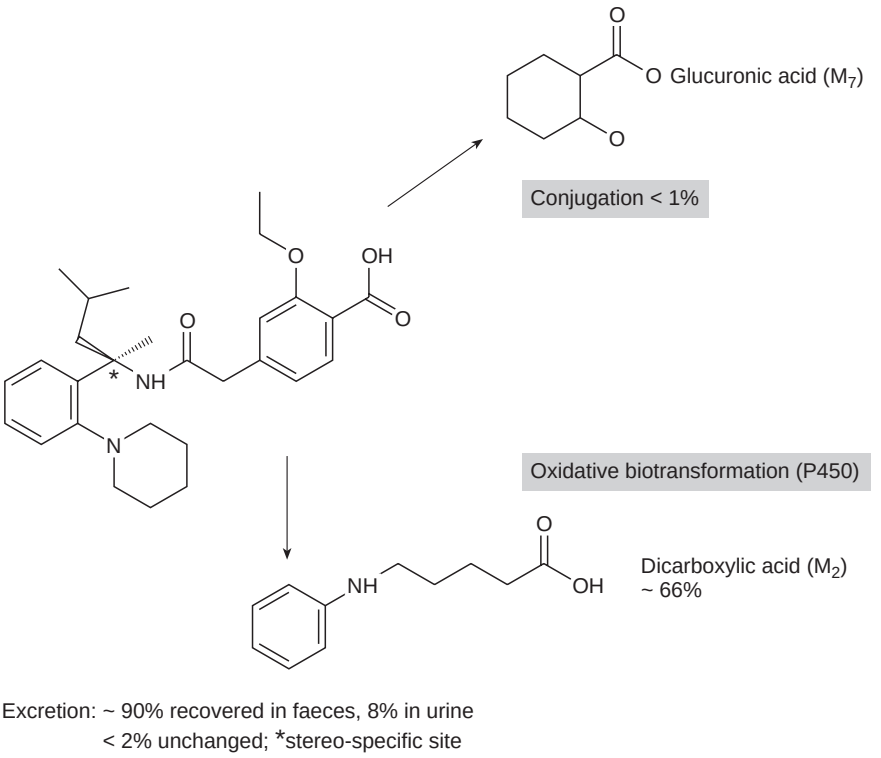

Figure 2. Metabolism of repaglinide

barbiturates and carbamazepine, which induce the P450 3A4 isoenzyme system, increase repaglinide metabolism. Additional interaction studies with other therapeutic agents, such as fibric acid derivatives, statins and angiotensin-converting enzyme (ACE) inhibitors, all of which are used frequently in Type 2 diabetic patients, also need to be carried out.

Repaglinide is bound to human serum albumin and α_1-acid glycoprotein. *In vitro*, protein binding was approximately 98.5 %, with binding studies showing displacement of repaglinide by warfarin, furosemide and tolbutamide; however, no effect was seen with the addition of diazepam, glibenclamide or nicardipine.

Pharmacokinetics

After a 15 min intravenous infusion of repaglinide in normal individuals, the elimination half-life ($t_{\frac{1}{2}}$) was 0.6 (0.5–1.4) h, with a plasma clearance rate of 33 (15–57) $l \cdot h^{-1}$, an apparent volume of distribution of 28.9 l with the total blood clearance calculated at 876 $ml \cdot min^{-1}$, which is approximately 58 % of total liver blood flow per min. There was rapid absorption following oral administration in the fasting state, with a time to maximum concentration (t_{max}) of 0.6 h, independent of dose. Bioavailability was calculated at 63 % (95 % confidence interval [CI]; 49–79 %), with an intra-individual variation of 17 % and inter-individual variation of 45–62 % for area under curve ($AUC_{(0-24\ h)}$) measurement after oral administration. This may reflect the variation in the activity of the P450 3A4 isoenzyme activity between individuals. Single- and multiple-dose response studies in both normal people and Type 2 diabetic patients demonstrated a dose-dependent increase in the maximum plasma concentration (C_{max}) for doses of 0.5, 1.0, 2.0 and 4.0 mg. The pharmacokinetics of repaglinide in Type 2 diabetic patients in both single- and multiple-dose studies were similar to those seen in normal individuals.[8]

Following preprandial dosing (–15 min) of 0.125–4.0 mg repaglinide, the t_{max} ranged between 0.5 and 1.4 h (independent of dose), but with a linear C_{max} dose-response relationship and no accumulation in repeated dosing studies. The $t_{\frac{1}{2}}$ of repaglinide in Type 2 diabetic patients was 1.0–1.4 h for doses ranging from 0.25 to 4.0 mg, with no difference evident between single and multiple dosing. Administration of repaglinide in Type 2 diabetic patients showed a slightly faster rate of absorption when given immediately before a meal compared with administration 15 or 30 min before the meal. In normal individuals who had a high-fat meal, the C_{max} was reduced by 20 %, with no change seen in t_{max}.

Pharmacokinetic studies were also carried out in specific population groups. No differences existed between certain races (African-American and Caucasian). Increased C_{max} and AUC measurements in elderly individuals were seen in repeat-dose studies only, and considerable inter-individual variation was observed. A difference between the sexes in respect to AUC was seen, with a higher value in female Type 2 diabetic patients on multiple dosing, but no difference in the pharmacodynamic response was seen (8-point blood glucose profile).

Patients with moderate to severe impairment of liver function had higher plasma repaglinide concentrations than healthy individuals in response to a single 4.0 mg oral dose. Surprisingly, in patients with severe renal impairment, after chronic dosing (7 days) the C_{max} and AUC for repaglinide was elevated compared with healthy individuals, with a trend to increasing $t_{\frac{1}{2}}$; however, this difference in $t_{\frac{1}{2}}$ was not significant. Further studies will be required in both elderly and renally compromised patients.

In-vivo drug interaction studies have been carried out with warfarin, digoxin, theophylline and cimetidine. Repaglinide had no significant effect on warfarin pharmacokinetics or prothrombin measurements during steady state warfarin dosing, and pharmacokinetic properties of digoxin were not altered by co-administration of repaglinide. Theophylline and cimetidine are, in part, both metabolized by the cytochrome P450 system and more reliant on isoenzymes other than CYP 3A4 for biotransformation. The metabolism and excretion of theophylline (300 mg twice daily) was unaffected by the co-administration of repaglinide and the pharmacokinetics of repaglinide (2 mg twice daily) was unaffected during multiple dosing influenced by concurrent cimetidine administration (400 mg twice daily).

Pharmacodynamics

Dose-tolerance studies for single and multiple dosing have been carried out to determine short-term safety in patients with Type 2 diabetes in the 0.25–20 mg dose range, two or four times daily over 2–6 weeks. No clinically relevant changes in electrocardiogram patterns, liver enzyme or serum electrolyte concentrations were recorded, except for isolated abnormal results. The majority of reported adverse events were mild or moderate in severity, the most frequent being hypoglycaemia and headache.

Dose-response studies after single dosing with repaglinide 0.5–4.0 mg were carried out in healthy individuals using either a euglycaemic clamp method or parallel-group, double-blind, placebo-controlled studies. A dose-dependent pharmacodynamic effect (glucose infusion rate) was observed in the euglycaemic clamp study and a linear dose-response was seen in mean blood glucose concentration during a 24-h profile in a double-blind, placebo-controlled study during 4 weeks of chronic dosing at 0.25–4.0 mg preprandially. The blood glucose concentration stabilized between 1 and 3 weeks of treatment and no simple dose-response relationship was seen with the insulin response, presumably because of the interaction between the prevailing glucose and the β-cell secretory response; the lowered glucose profile masking the insulinotropic effect of repaglinide.

A single-dose, placebo-controlled, double-blind, dose-response (0.5, 1.0, 2.0 and 4.0 mg) study was conducted in 17 previously untreated patients with Type 2 diabetes involving pre-breakfast administration (–15 min) followed by a second meal after 4 h with 8 h of metabolic profiling (Figure 3).[9] A log-linear insulinotropic response was observed with a comparable reduction in the glucose profile during the first meal only (Figure 4). No additional pharmacodynamic effects were observed during the second meal at any dose, which indicates that the rapid and short action of repaglinide limits its effect to the prandial period ('prandial glucose regulator') in patients with Type 2 diabetes, as described in this pivotal study.

The concept that the optimal regimen for repaglinide is preprandial dosing before main meals was examined in a double-blind study of 18 diet-treated Type 2 diabetic patients. Patients were randomized to receive either repaglinide in the morning and evening or before each main meal, at the same total daily dose over a 4-week treatment period.[10] The overall glycaemic control was better with dosing before main meals and the blood glucose $AUC_{(0-24\ h)}$ was significantly lower ($p < 0.05$) as reflected in a significant change in the HbA_{1c} in only this treatment group. The plasma insulin levels returned to pretreatment levels before the next meal during daytime and overnight periods.

Another double-blind study compared the consequences of omitting a midday meal in well-controlled (fasting glucose 5.0–7.8 $mmol \cdot l^{-1}$) Type 2 diabetic patients randomized to treatment with glibenclamide or repaglinide.[11] Hypoglycaemia (blood glucose <3.3 $mmol \cdot l^{-1}$) occurred in six of 25 patients (24 %) on glibenclamide between 12.00–15.00 h, with four patients requiring oral administration of glucose; none of the patients experienced hypoglycaemia on repaglinide (Figure 5). This study demonstrated a smaller risk of developing hypoglycaemia at midday with repaglinide in contrast to glibenclamide in well controlled Type 2 diabetic patients when lunch was omitted.

Finally, in a study with flexible meal patterns of between 2 to 4 meals per day with corresponding preprandial dosing with repaglinide, no difference was observed in glycaemic control between all the groups over a 2–3 week period of treatment (Figure 6). This supports the concept of a flexible meal-related dosing regimen with repaglinide without additional risk of hypoglycaemia or change in glycaemic control.

Clinical Efficacy Studies

Evidence of efficacy has been collected from two placebo-controlled, two active-controlled medium-term and five long-term double-blind, randomized clinical studies involving 2313 Type 2 diabetic patients, carried out according to Good Clinical Practice guidelines, following ethical local approval and using central laboratory services.

In the placebo-controlled study, 99 Type 2 diabetic patients were enrolled. A 2-week washout period was followed by 6-week titration and a 12-week maintenance treatment period. At the end of the study period, the repaglinide-treated patients had reduced the mean fasting

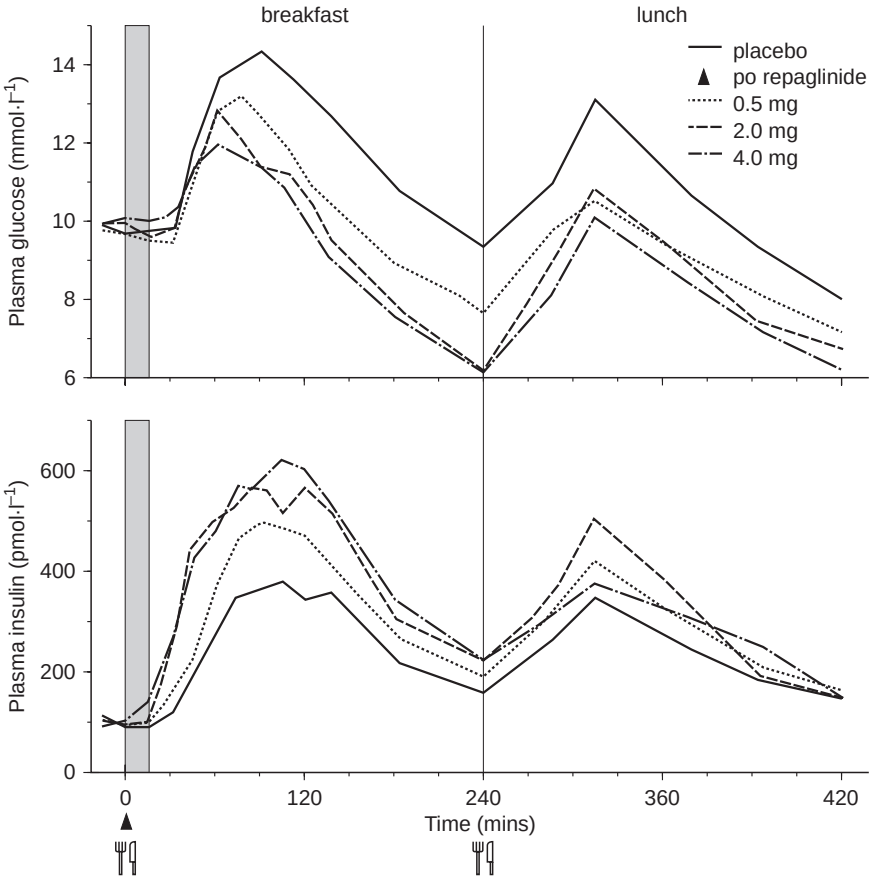

Figure 3. Plasma glucose and insulin concentrations in patients with Type 2 diabetes randomly allocated to placebo, repaglinide 0.5, 2.0 and 4.0 mg doses in a double-blind study.[9] Test preparations were given 15 min before the first of two standard meals (500 kcals), eaten 4 h apart

glucose concentration by 3.0 mmol·l^{-1} ($p < 0.05$), 2 h postprandial glucose by 5.8 mmol·l^{-1} ($p < 0.05$) and HbA_{1c} by 1.9 % points ($p < 0.05$), at a dose ranging between 0.25 and 8.0 mg before each main meal, compared with the placebo-treated group. In a similar patient group (the comparison of repaglinide taken before the three main meals and glibenclamide administered once or twice daily in a multicentre, double-blind study comprising a washout, titration and maintenance period), repaglinide achieved significantly better mean and 2 h postprandial (breakfast) values than glibenclamide, with no difference in frequency of hypoglycaemia or weight gain between the two groups.[12] In a study involving a twice daily regimen[13] in 44 patients treated previously with sulphonylurea preparations (tolbutamide, glibenclamide or gliclazide), after a titration period of 4 weeks and maintenance for 8 weeks on repaglinide 0.5–2.0 mg twice daily or glibenclamide 5.0–7.5 mg twice daily, both regimens reduced the fasting glucose significantly ($p < 0.05$ and $p = 0.01$, respectively) with the 2 h postprandial concentration reduced only with repaglinide ($p < 0.05$). The HbA_{1c} and frequency of hypoglycaemic events remained unchanged on both treatments. The fasting C-peptide concentration, however, was significantly raised in the glibenclamide-treated group ($p < 0.05$).

In a further study involving obese Type 2 diabetic patients unacceptably controlled ($HbA_{1c} > 7.1$ %) on metformin, patients were randomized after a 1-month run-in period to continue on metformin (1–3 g·day^{-1}), change to repaglinide (0.5–4.0 mg with each of the three main meals) monotherapy or receive a combination of repaglinide and metformin in a large multicentre, double-blind study.[14]

At the end of a 3-month maintenance treatment period, the change from baseline in HbA_{1c} was −0.33 % point with metformin, −0.38 % point with repaglinide and −1.41 % point with combination therapy ($p < 0.005$ for combined therapy vs. the two monotherapies). Similarly, the changes in concentrations of fasting glucose changes were −0.25, −0.49 and −2.18 mmol·l^{-1} for metformin, repaglinide and combination therapy, respectively ($p < 0.005$ for combined therapy vs. the two monotherapies). Only approximately 20 % of patients in the two monotherapy arms of the study achieved good glycaemic control (HbA_{1c} <7 %) by the end of the study, with the percentage of patients having poor control (HbA_{1c} >9 %) remaining unchanged at approximately 20 %. In the combination group, however, 60 % of the patients achieved good metabolic control, with none remaining in the poorly controlled category. No severe hypoglycaemic events were recorded in any of the three

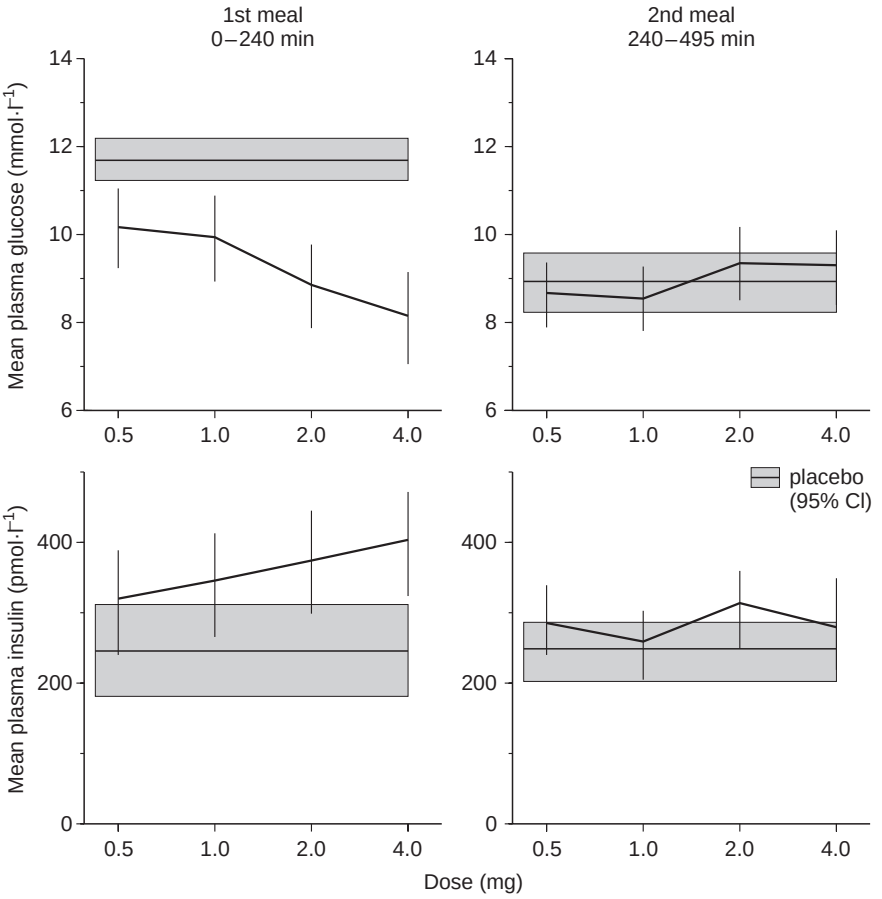

Figure 4. Dose-response analysis of study by Robling *et al.*,[9] based on the estimated means and 95 % confidence intervals for plasma glucose and insulin concentration responses (AUC/time for each meal period) to a single dose of placebo, or repaglinide 0.5, 1.0, 2.0 and 4.0 mg in patients with Type 2 diabetes

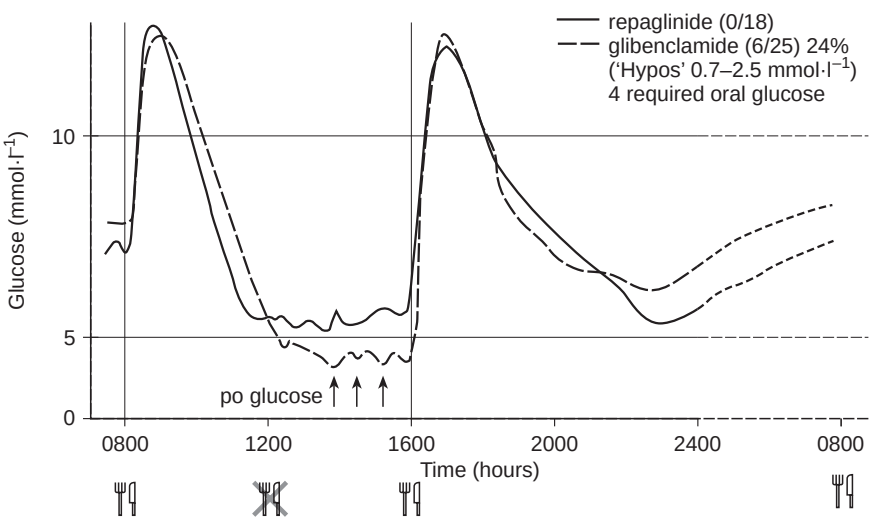

Figure 5. 'Skip-a-meal' study in well controlled Type 2 diabetic patients[11]

treatment groups. A 50 % lower rate of gastrointestinal side-effects was observed in the repaglinide group compared with the metformin monotherapy group.

Five long-term, active-controlled, parallel-group, double-blind studies were carried out, all with an 8-week titration period, omitting a washout period and followed by a 12-month maintenance period. The treatments compared were repaglinide (n = 1228), glibenclamide (n = 417), gliclazide (n = 98) and glipizide (n = 80), with efficacy endpoints being the change from baseline of HbA_{1c} and fasting glucose concentration. In relationship to efficacy, repaglinide was equally as

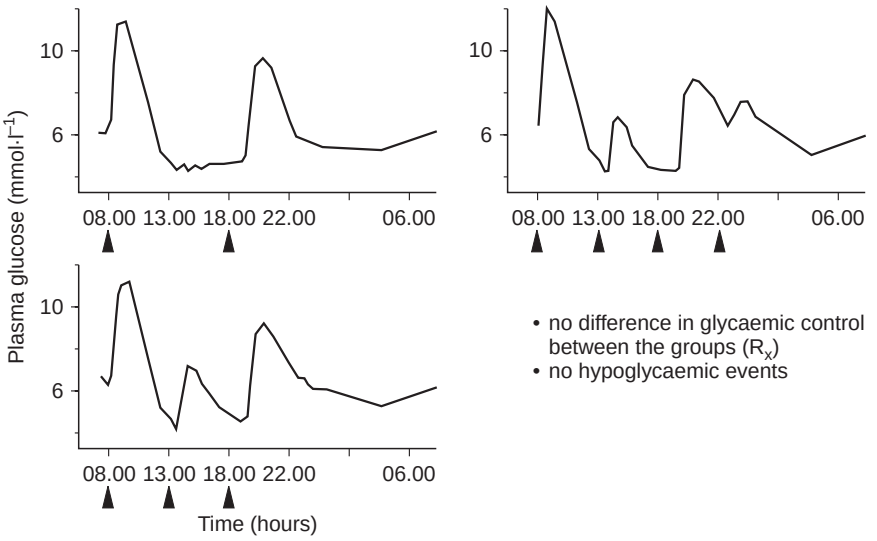

Figure 6. Meal-related dosing study (Marbury, 1993, personal communication.)

effective as glibenclamide and gliclazide, and superior to glipizide after 12 months of treatment. Subset analysis of all five studies showed a greater effect of repaglinide in patients previously on diet treatment only, with a 73 % response rate and a mean reduction in HbA_{1c} of 1.5 % point. In patients previously on sulphonylurea therapy, apart from a small early reduction in HbA_{1c}, glycaemic control remained essentially unchanged over the study duration. Patients previously on combination therapy who converted to repaglinide monotherapy experienced an increase in HbA_{1c} of approximately 1 % point over the 12-month study period. No differences in lipid parameters were seen between active treatments.

Safety and Tolerability

Safety and tolerability data of repaglinide and comparator preparations derive from all the clinical and pharmacological studies and represent approximate patient years of exposure to repaglinide of 1205, glibenclamide 412, gliclazide 89, glipizide 74, metformin 18 and placebo 14. Deaths in the four active treatment groups were similar at 1.2–1.4 % with treatment emergent adverse events and mortality from the long-term clinical studies estimated at 0.7–1.4 %. In long-term, active-controlled clinical studies, serious adverse events were recorded in 9–10 % of patients on repaglinide, glibenclamide or gliclazide, and 16 % in the gliclazide-treated group, which were categorized as possibly drug-related in ≤1 % of cases in the first two treatment categories (Table 1). Hypoglycaemic events were recorded in 20 % of patients on glibenclamide, 19 % on glipizide, 16 % on repaglinide and 15 % in the gliclazide-treated group. In a small group of patients, where objective evidence in the form of blood glucose measurements (blood glucose <2.5 $mmol \cdot l^{-1}$) were available, the relative risk of hypoglycaemia compared with repaglinide was two-fold higher with glibenclamide and glipizide and four-fold higher with gliclazide (Table 1). From the cardiovascular perspective, serious events occurred in 4 %, 2 % and 6 % of patients in the repaglinide, glibenclamide and glipizide-treated groups, respectively, with documented ischaemic events occurring in 2 %, 1 % and 5 %, respectively (Table 2). The frequency of ischaemic heart disease (angina pectoris, myocardial infarction, coronary artery disease, angina aggravation and myocardial ischaemia) was comparable for repaglinide and the sulphonylurea-treated patients grouped together. The incidence of neoplasm was similar (1–2 %) for all the treatment groups in long-term studies.

Conclusions

Repaglinide represents the first in a new class of oral antidiabetic agents: the carbamoylmethyl benzoic acid (CMBA) group. Repaglinide is a potent insulin secretagogue that acts on the ATP-sensitive potassium channels on the β-cell membrane through a distinct binding site. Preclinical studies demonstrated a 10–20-fold greater potency in the hypoglycaemic action of repaglinide compared with glibenclamide. Repaglinide is absorbed quickly after oral administration and has a rapid, short-lived insulinotropic action suitable for prandial glucose control and thus suitable for meal-related dosing. The excretion of repaglinide is non-renal, metabolized by the liver and repaglinide is highly protein bound. Further studies are needed to examine the pharmacokinetics of repaglinide both in elderly and renally compromised patients, and to examine potential drug interactions with certain hypolipidaemic and hypotensive agents used frequently in patients with Type 2 diabetes.

Repaglinide is suitable as first-line monotherapy in the management of Type 2 diabetic patients who have failed to respond adequately to diet alone. It works synergistically with metformin in poorly controlled obese patients with Type 2 diabetes, and can be substituted for metformin in patients with gastrointestinal side-effects

Table 1. Summary of safety profile of repaglinide and the sulphonylurea preparations glibenclamide, gliclazide and glipizide based on five double-blind, randomized, controlled clinical trials over a 1-year treatment period

	Treatment group			
	Repaglinide	Glibenclamide	Gliclazide	Glipizide
Number of individuals exposed	1228	417	99	81
Adverse events, *n* (%)	961 (78)	341 (82)	66 (67)	66 (81)
Serious adverse events, *n* (%)	128 (10)	41 (10)	9 (9)	13 (16)
Possible drug-related adverse events, *n* (%)	5 (<1)	6 (1)	–	–
Proportion of hypoglycaemic individuals (%)	16	20	15	19
Relative risk of blood glucose <2.5 mmol·l^{-1}	1	2	4	2

Table 2. Cardiovascular events in the 1-year safety and efficacy trials for repaglinide, glibenclamide and glipizide

	Cardiovascular events		
	Repaglinide (*n* = 1228)	Glibenclamide (*n* = 417)	Glipizide (*n* = 81)
Serious events, *n* (%)	51 (4)	8 (2)	5 (6)
Ischaemic events, *n* (%)	29 (2)	5 (1)	4 (5)
Deaths, *n* (%)	6 (0.1)	2 (0.1)	0 (0)

	Ischaemic heart disease (%)				
	Angina	Myocardial infarction	Coronary artery disease	Angina aggravation	Myocardial ischaemia
Repaglinide (*n* = 1228)	1.8	1.1	0.3	0.24	0.16
Sulphonylureas (*n* = 597)	1.5	1.3	0.3	0.34	0.08

without jeopardizing glycaemic control. Repaglinide is superior to glibenclamide in reducing postprandial glycaemic excursions and has been shown to maintain better glycaemic control than glipizide in long-term studies. Repaglinide has an excellent safety profile, with a similar cardiovascular outcome to sulphonylurea preparations. The flexible meal-related dosing and reduced risk of hypoglycaemia from repaglinide, and its short-lived ('prandial') effect on insulin secretion should improve the patient's lifestyle without compromising glycaemic control. Continued monitoring will be required during the early years of the introduction of repaglinide, as for all new drugs introduced into clinical practice. These are all essential elements in the long-term management of the ever increasing population of patients with Type 2 diabetes.

The recently published United Kingdom Prospective Diabetes Study (UKPDS) has shown that intensive blood glucose control with either sulphonylureas or insulin decreases the risk of diabetes-specific microvascular disease without incurring any adverse effect on the cardiovascular system.[15] The concurrent use of sulphonylureas and metformin does not increase the risk of diabetes-related deaths.[16] The insulin secretagogue repaglinide offers the opportunity to intensify blood glucose control, especially through prandial glycaemic control, because of its rapid absorption and short duration of action combining potency with safety. The flexibility of repaglinide as a meal-related insulinotropic agent should also improve compliance, which is necessary in an attempt to achieve a favourable long-term outcome.

Acknowledgements

I wish to convey my gratitude to Drs Peter Damsbo, Jørgen Smedegaard Kristensen and Kirstine Brown Frandsen, Novo Nordisk, Copenhagen, Denmark, for allowing me to read internal reports as a basis of this review, and be prepared to discuss openly the current state of knowledge on repaglinide. My thanks also to my secretary, Catherine Murray and Adrian Shaw for the artwork.

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