

Effect of Repaglinide Addition to Metformin Monotherapy on Glycemic Control in Patients with Type 2 Diabetes

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OBJECTIVE — To compare the effect of repaglinide in combination with metformin with monotherapy of each drug on glycemic control in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — A total of 83 patients with type 2 diabetes who had inadequate glycemic control ($HbA_{1c} > 7.1\%$) when receiving the antidiabetic agent metformin were enrolled in this multicenter, double-blind trial. Subjects were randomized to continue with their prestudy dose of metformin ($n = 27$), to continue with their prestudy dose of metformin with the addition of repaglinide ($n = 27$), or to receive repaglinide alone ($n = 29$). For patients receiving repaglinide, the optimal dose was determined during a 4- to 8-week titration and continued for a 3-month maintenance period.

RESULTS — In subjects receiving combined therapy, HbA_{1c} was reduced by $1.4 \pm 0.2\%$, from 8.3 to 6.9% ($P = 0.0016$) and fasting plasma glucose by 2.2 mmol/l ($P = 0.0003$). No significant changes were observed in subjects treated with either repaglinide or metformin monotherapy in HbA_{1c} (0.4 and 0.3% decrease, respectively) or fasting plasma glucose (0.5 mmol/l increase and 0.3 mmol/l decrease, respectively). Subjects receiving repaglinide, either alone or in combination with metformin, had an increase in fasting levels of insulin between baseline and the end of the trial of 4.04 ± 1.56 and $4.23 \pm 1.50 \text{ mU/l}$, respectively ($P < 0.02$). Gastrointestinal adverse events were common in the metformin group. An increase in body weight occurred in the repaglinide and combined therapy groups (2.4 ± 0.5 and $3.0 \pm 0.5 \text{ kg}$, respectively; $P < 0.05$).

CONCLUSIONS — Combined metformin and repaglinide therapy resulted in superior glycemic control compared with repaglinide or metformin monotherapy in patients with type 2 diabetes whose glycemia had not been well controlled on metformin alone. Repaglinide monotherapy was as effective as metformin monotherapy.

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In the U.S., there are 7 million people with diagnosed type 2 diabetes (1). Within the first 10 years of diagnosis, more than half of all those with type 2 diabetes take oral hypoglycemic agents (2).

Between 1970 and 1995, sulfonylureas were the only oral antidiabetic agents available in the U.S. Approval of the biguanide metformin in 1995 has resulted in this agent being used increasingly,

either alone or in combination with sulfonylurea drugs.

Metformin is the second most commonly prescribed oral antidiabetic agent in Europe, where it is taken as monotherapy in 40% of patients (3). Because metformin increases sensitivity to insulin, it may be considered the preferred medication for obese or hyperlipidemic patients with type 2 diabetes, who are often very insulin resistant (4). Various studies have shown the advantages of giving metformin to patients inadequately controlled by sulfonylurea monotherapy (5–7).

Repaglinide is a new type of oral hypoglycemic agent. It is a prandial glucose regulator and the first in a new chemical class of insulin secretagogues. Its rapid absorption, short metabolic half-life (~1 h) (8), and novel insulin release profile (9) are all characteristics desired for treating people with type 2 diabetes. The use of repaglinide with each main meal of the day acts to augment insulin release, covering the glucose load associated with meals. Although repaglinide, like the sulfonylurea drugs, stimulates insulin secretion by pancreatic β -cells, it acts via a different binding site on the ATP-sensitive potassium channel (10). While repaglinide has been shown to improve glycemic control when used as monotherapy (11), its effect in facilitating insulin release at meal times may be complementary to the effect of antidiabetic agents that decrease insulin resistance.

The aim of this study was to investigate the efficacy and safety of repaglinide as a substitute for or in combination with metformin in subjects with type 2 diabetes not under optimal glycemic control with metformin alone.

RESEARCH DESIGN AND METHODS

Study Design

This study was a randomized, double-blind, parallel-group trial performed at nine centers in Australia. Included were patients with type 2 diabetes treated with metformin alone (1–3 g per day) for more than 6 months who had not achieved optimal glycemic control

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Abbreviations: ADA, American Diabetes Association; FFA, free fatty acid; FPG, fasting plasma glucose; ITT, intention-to-treat; UKPDS, U.K. Prospective Diabetes Study.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

(HbA_{1c} >7.1%). Additional inclusion criteria were age 40 to 75 years and BMI ≥21 kg/m². The American Diabetes Association (ADA) standards of medical care (12) have as a goal for glycemic control a HbA_{1c} <1% above the upper reference range for a non-diabetic population. For the purposes of this study, a HbA_{1c} >7.1% conformed to the ADA standard of unsatisfactory control. All subjects were required to be able to comply with the protocol and carry out home blood glucose monitoring.

The major initial exclusion criteria included any clinically significant elevation in either serum creatinine or liver transaminases, vitamin B₁₂ <150 pmol/l (associated with hemoglobin <130 g/l in men or 119 g/l in women), anemia, previous insulin treatment, unawareness of hypoglycemia, cardiac problems, uncontrolled hypertension, alcohol or drug abuse, a history of lactic acidosis, known contraindications to metformin, and an intention to become pregnant.

All subjects gave written informed consent to participate in the trial. The study received ethics committee approval for each of the participating centers and was conducted in accordance with the 1964 Declaration of Helsinki and the Guidelines for Good Clinical Research Practice in Australia.

After recruitment, the prestudy dose of metformin for each subject was maintained during a 4- to 5-week baseline period. Subjects who were still not under optimal control after that period were maintained on their prestudy dose of metformin and randomized to enter a 4- to 5-month treatment period, which consisted of 4 to 8 weeks of titration to optimize the dose of repaglinide followed by a 3-month maintenance period.

Subjects were randomized to one of three treatment regimens: maintenance of the usual (prestudy) dose of metformin plus placebo; maintenance of the usual dose of metformin plus repaglinide (combined therapy); and repaglinide plus placebo. A dual-placebo arm was considered inappropriate since all subjects were defined as being inadequately controlled on metformin monotherapy.

Repaglinide was initiated at a dose of 0.5 mg taken before each of the three main meals and increased stepwise to 1.0, 2.0, and 4.0 mg before the three meals depending on the response of the subject to titration. Each of the four titration steps occupied 4 to 7 days. At each visit, subjects with a fasting blood glucose >7.8 mmol/l and without any clinically significant symp-

Table 1—Baseline characteristics after randomization

Characteristic	Metformin	Metformin + repaglinide	Repaglinide
n	27	27	28
Age (years)	57.8 ± 9.5	57.2 ± 8.3	60.3 ± 7.7
Sex (M/F)	17/10	18/9	15/13
Race			
Caucasian	23	26	26
Asian	2	0	2
Other	2	1	0
BMI (kg/m ²)	31.8 ± 6.0	33.2 ± 5.6	31.3 ± 7.2
Duration of diagnosed diabetes (years)	8.0 ± 6.2	5.9 ± 2.9	7.0 ± 5.2
Duration of metformin therapy (years)	4.1 ± 3.7	3.9 ± 2.5	3.3 ± 3.3
Current daily dose of metformin (g)	1.8 ± 0.7	1.8 ± 0.8	1.7 ± 0.7
HbA _{1c} (%)	8.6 ± 1.1	8.3 ± 0.9	8.6 ± 1.3
FPG (mmol/l)	10.80 ± 3.03	10.22 ± 2.28	9.67 ± 2.80
Fasting insulin (mU/l)	18.1 ± 11.8	13.3 ± 6.6	16.7 ± 13.6
C-peptide (nmol/l)	1.4 ± 0.7	1.1 ± 0.3	1.2 ± 0.7
Triglycerides (mmol/l)	2.91 ± 1.64	2.77 ± 2.13	2.45 ± 1.32
Total cholesterol (mmol/l)	5.89 ± 1.11	5.97 ± 1.49	5.65 ± 0.98
HDL cholesterol (mmol/l)	1.07 ± 0.16	1.07 ± 0.20	1.09 ± 0.26
LDL cholesterol (mmol/l)	3.48 ± 0.84	3.36 ± 0.85	3.33 ± 0.79
FFA (μmol/l)	616 ± 175	605 ± 186	646 ± 268

Data are means ± SD.

toms of hypoglycemia had their dose of repaglinide increased to the next step. Subjects with a fasting blood glucose <4.4 mmol/l or with clinically significant hypoglycemic episodes had their dose of repaglinide reduced by one step (or were withdrawn from the study if they were already taking only 0.5 mg with each meal). The usual (prestudy) dose of metformin for each subject was continued unchanged throughout the study.

Each patient was supplied with a home glucose meter and a diary for the duration of the study. The nature of hypoglycemic symptoms were explained before the first dose of trial medication was given. The investigator at each center was responsible for evaluating the significance of hypoglycemic symptoms at each clinic visit.

Efficacy and safety evaluations

Efficacy and safety parameters and exclusion criteria were assessed at the screening visit, the titration visits, and the three maintenance visits. The occurrence of adverse events, which were rated by the investigator as mild, moderate, or severe, were identified at every visit. The relationship of the adverse events to repaglinide or metformin was rated by the investigator as probable, possible, unlikely, or unknown. Sympto-

matic hypoglycemic episodes were rated as mild, moderate (self-treated), or severe (requiring the assistance of another person). Adverse events were monitored by a Safety Surveillance Committee.

The primary endpoints of the efficacy evaluation were HbA_{1c} and fasting plasma glucose (FPG). Secondary endpoints were fasting insulin and C-peptide levels, lipid profile (fasting triglyceride levels, total cholesterol, HDL cholesterol, LDL cholesterol, and free fatty acids [FFAs]), and any change in body weight.

HbA_{1c} was measured using high-performance liquid chromatography with a reference range of 4.3–6.1%. Plasma glucose was measured using a hexokinase method, insulin using an enzyme immunoassay, and C-peptide using a radioimmunoassay.

Statistical analysis

All efficacy data were summarized for the intention-to-treat (ITT) population (all subjects who were randomized, received at least one dose of trial medication, and returned for at least one visit after the start of treatment). All patients who took at least one dose of the study medication were included in the safety analysis.

All statistical analyses were carried out with SAS software, version 6.11. For the

Table 2—Changes in HbA_{1c} and FPG from baseline to end of treatment

Treatment group	Change in HbA _{1c} (%)	Change in FPG (mmol/l)
Metformin	-0.33 ± 0.24 (-0.80 to 0.15)	-0.25 ± 0.47 (-1.18 to 0.68)
Metformin + repaglinide	-1.41 ± 0.23 (-1.87 to -0.95)*	-2.18 ± 0.45 (-3.07 to -1.28)*
Repaglinide	-0.38 ± 0.23 (-0.84 to 0.08)	0.49 ± 0.47 (-0.44 to 1.42)
Metformin + repaglinide vs. metformin	-1.08 ± 0.33 (-1.84 to -0.33)*	-1.92 ± 0.65 (-3.40 to -0.44)*
Metformin + repaglinide vs. repaglinide	-1.03 ± 0.32 (-1.78 to -0.29)*	-2.66 ± 0.65 (-4.14 to -1.18)*

Data are means ± SEM (95% CI). **P* < 0.05.

primary efficacy endpoints (HbA_{1c} and FPG), the change from baseline to the last visit of the maintenance period was evaluated by analysis of variance (ANOVA) with treatment as a fixed effect. In addition, associations were adjusted for center and treatment-by-center effects. Metformin + repaglinide versus metformin and metformin + repaglinide versus repaglinide were compared and 95% CIs calculated. Bonferroni's method was used to adjust for multiple comparisons.

Changes from baseline in lipid profiles, fasting insulin, and C-peptide were analyzed by ANOVA with treatment group as the only factor. The incidence of hypoglycemia was analyzed by a generalized linear model adjusting for exposure time. Changes from baseline in the laboratory tests and body weight were analyzed by ANOVA. Two-sided *P* values < 0.05 were considered statistically significant.

RESULTS — After screening 108 subjects, 83 were randomized: 29 in the repaglinide group, 27 in the metformin group, and 27 in the metformin + repaglinide group. One subject randomized to receive repaglinide withdrew after the first titration visit, so only 82 subjects received study medication and were included in the ITT analysis. Eight subjects withdrew during the course of the study (six in the metformin group and two in the repaglinide group) with no apparent trends concerning the reason. Seventy-four subjects completed the trial: 26 in the repaglinide group, 21 in the metformin group, and 27 in the combined therapy group. Seventeen patients (63%) in the repaglinide monotherapy group were titrated to the highest dose level of repaglinide (12 mg/day) compared with 9 (33%) in the combined therapy group.

Demographic and baseline characteristics of the subjects are given in Table 1. No significant differences were apparent between the three groups for any of the

parameters presented, nor were there any clinically significant differences between the three groups with respect to diabetic history or physical examination.

Glycemic control and metabolic indices

Changes in the primary efficacy endpoints of HbA_{1c} and FPG are shown in Table 2, and progressive changes are shown in Figs. 1 and 2.

For subjects in the metformin + repaglinide group, HbA_{1c} decreased significantly by 1.4%, from 8.3 to 6.9% (*P* = 0.0016), and FPG decreased significantly by 2.2 mmol/l, from 10.2 to 8.0 mmol/l (*P* = 0.0003), between baseline and the final visit. No significant changes were observed in HbA_{1c} or FPG for the monotherapy groups. Adjustment for center and treatment-by-center effects did not change the significance of the results. The observed

changes were similar for men and women and for younger (≤65 years) and older (>65 years) subjects. The reductions in primary efficacy endpoints remained significant for the combined therapy group after adjustment for the relevant changes in the monotherapy groups.

None of the subjects was in optimal glycemic control at entry, and approximately one-quarter were in poor control, with an HbA_{1c} >9%. By the end of the study, nearly 60% of subjects receiving combined therapy were in optimal control (HbA_{1c} <7.1%), compared with about 20% each in the metformin and repaglinide groups. No combined therapy subject remained in poor control, compared with 20 and 26% in the monotherapy groups (Table 3).

Changes in the secondary efficacy endpoints are shown in Table 4. Fasting insulin and C-peptide levels increased significantly during treatment in both the repaglinide-

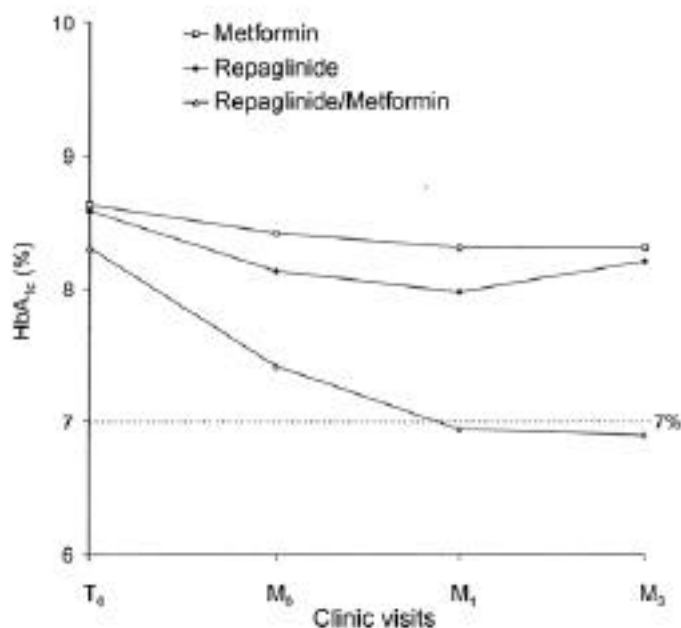


Figure 1—HbA_{1c} at baseline (first titration visit, T₀) and at the clinic visits during the maintenance period at 0 (M₀), 1 (M₁), and 3 (M₃) months in the groups treated with metformin, repaglinide, or a combination of repaglinide and metformin.

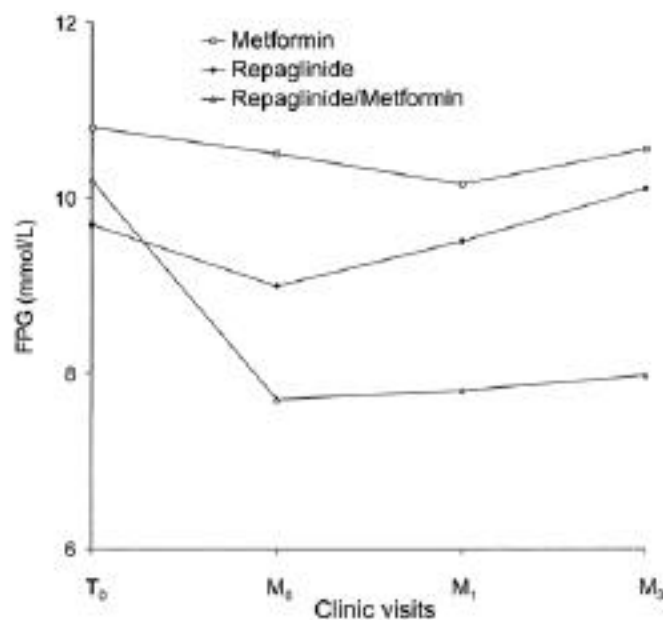


Figure 2—FPG from baseline (first titration visit, T₀) and at the clinic visits during the maintenance period at 0 (M₀), 1 (M₁), and 3 (M₃) months in the groups treated with metformin, repaglinide, or combination of repaglinide and metformin.

treated groups. Lipid levels in the metformin + repaglinide group did not change significantly during the study. No statistically significant differences were found between the metformin + repaglinide group and the monotherapy groups.

Safety evaluation

No serious adverse events occurred that were considered related to the study drugs. The majority of nonserious adverse events were mild or moderate. Only five severe events were reported; four resolved spontaneously (accidental injury, menorrhagia, hemorrhagic gastric ulcer, and back pain) and the other (back pain) was judged to be unrelated to the study medication. Only 68 of the 339 adverse events reported were considered possibly or probably related to the study agents. Three subjects were withdrawn from the study because of hyperglycemia (increase in HbA_{1c} of >2% from baseline), two receiving metformin and one receiving repaglinide. The most common adverse events were hypoglycemia, diarrhea, and headache (Table 5); none was severe.

During the course of the study, 12 patients reported 39 symptomatic hypoglycemic events. The majority were mild, and none was severe. Most hypoglycemic events occurred during the afternoon, and none were recorded during the night. One-third of the patients who experienced hypoglycemia reported all events during titration; 17 of the 39 events (44%)

occurred during titration. For 34 of 39 events (87%), capillary blood glucose results were available and ranged from 2.4 to 4.5 mmol/l. Half the blood glucose results were >3.5 mmol/l, and only four were ≤2.8 mmol/l (50 mg/dl). The incidence of symptomatic hypoglycemia in the combined therapy group was 3.20 events per patient-year compared with 0.97 events per patient-year in the repaglinide group (P < 0.05). Nine patients (33.3%) in the combined therapy group reported a total of 30 hypoglycemic events compared with three patients (10.7%) in the repaglinide group who reported a total of nine events. Hypoglycemia was not experienced by patients on metformin alone. One patient in the

combined therapy group accounted for 12 of the 30 hypoglycemic events recorded, and in only one of those events was blood glucose ≤2.8 mmol/l.

No statistically significant or clinically relevant changes in laboratory tests were observed for any of the three groups. No significant effects on vital signs were reported during the study, except for a small decrease in pulse rate in the repaglinide group. Body weight remained stable in the group on metformin alone but increased in the repaglinide and combined therapy groups (2.4 ± 0.5 and 3.0 ± 0.5 kg, respectively; P < 0.05).

CONCLUSIONS — Because metformin improves sensitivity to insulin but does not increase circulating insulin levels, it may be regarded as an antihyperglycemic agent rather than as a hypoglycemic agent (4). Furthermore, in subjects for whom sulfonylureas provide inadequate glycemic control, studies have demonstrated an improvement when metformin is added (13).

The subjects selected for this study could be considered representative of subjects with type 2 diabetes who, having been started on metformin alone, came to require alternative or additional therapy to control hyperglycemia. As a group, they were nearly 60 years of age and obese and had been taking metformin monotherapy for about 4 years. In the U.K. Prospective Diabetes Study (UKPDS), the HbA_{1c} of obese subjects started on metformin monotherapy took 4 years to return to the pretreatment value (14). For inclusion in the current study, subjects needed HbA_{1c} >1.0% above the reference range (control defined by the ADA as inadequate [12]). The mean HbA_{1c} for the group was 8.5% (within the range in which

Table 3—Changes in glycemic control from baseline to end of treatment with metformin, repaglinide, or a combination of metformin and repaglinide

Treatment group	Glycemic control (% of patients)		
	Optimal (HbA _{1c} <7.1%)	Fair (HbA _{1c} 7.1–9%)	Poor (HbA _{1c} >9%)
Metformin			
Baseline	0	72	28
Final	20	60	20
Repaglinide			
Baseline	0	75	25
Final	22	52	26
Metformin + repaglinide			
Baseline	0	74	26
Final	59	41	0

Table 4—Changes in insulin, lipids, and body weight from baseline to end of treatment

	Metformin	Metformin + repaglinide	Repaglinide
Fasting insulin (mU/l)	1.05 ± 1.60	4.23 ± 1.50*	4.04 ± 1.56*
C-peptide (nmol/l)	0.02 ± 0.07	0.17 ± 0.07*	0.18 ± 0.07*
Cholesterol (mmol/l)	0.13 ± 0.13	0.13 ± 0.12	0.38 ± 0.12*
HDL cholesterol (mmol/l)	0.07 ± 0.03*	0.05 ± 0.03	0.09 ± 0.03*
LDL cholesterol (mmol/l)	0.10 ± 0.12	0.11 ± 0.11	0.41 ± 0.12*
Triglycerides (mmol/l)	−0.20 ± 0.17	−0.10 ± 0.16	0.09 ± 0.16
FFA (μmol/l)	72 ± 53	−74 ± 46	22 ± 50
Body weight (kg)	−0.86 ± 0.51	2.41 ± 0.50*	2.98 ± 0.49*

Data are means ± SEM. * $P < 0.05$.

action to improve glycemic control has been recommended).

Repaglinide is a new oral hypoglycemic agent with a mechanism of action different from that of other insulin secretagogues. A comparative study has shown repaglinide to be better than glyburide at lowering postprandial blood glucose, and its low renal clearance and short half-life make it suitable for use in older patients and subjects with impaired renal function (8).

The dose of metformin used during the study was the same as that each subject was taking at the time they were enrolled. That dose had been determined during the course of their normal clinical management by their usual medical practitioner. It is possible that some improvement in glycemic control could have been obtained by adjusting the dose of metformin; however, the present study was designed to assess the efficacy and safety of repaglinide used instead of, or in combination with, metformin.

The subjects who stayed on their usual dose of metformin showed no significant changes in the major parameters during the course of the study. In particular, there were no changes in glycemic control as measured by the primary endpoints of HbA_{1c} and FPG, no changes in body weight, and no reported episodes of hypoglycemia.

The subjects who were randomized to receive repaglinide in place of metformin showed no deterioration in glycemic control as measured by the primary endpoints of HbA_{1c} and FPG. The ability of repaglinide to maintain glycemic control when used in place of metformin is clinically relevant: while metformin is primarily excreted via the kidneys (15), repaglinide is excreted almost totally in the bile, with only a very small fraction (<8%) excreted in the urine (P. Clauson, unpublished observations). Repaglinide could therefore be substituted for metformin in subjects experiencing a decline in renal function (such as the

elderly). Because it is not associated with a high degree of gastrointestinal problems, repaglinide can also be an alternative for those subjects who experience substantial gastrointestinal side effects with metformin.

The subjects who took the combination of metformin and repaglinide showed significant improvements in glycemic control: HbA_{1c} decreased from 8.3 to 6.9%, and FPG decreased from 10.2 to 8.0 mmol/l. Those improvements remained significant when considered in relation to the changes resulting from treatment with repaglinide or metformin alone. Overall, 59% of subjects in the combined therapy group achieved optimal glycemic control, with HbA_{1c} <7.1%.

The addition of other hypoglycemic agents to the treatment of subjects inadequately controlled on metformin has been the subject of incidental observation but has not been specifically examined. In the UKPDS, 14% of obese subjects allocated to receive metformin needed the addition of glyburide (glibenclamide) by the time of the 6-year review (14). In a study by Hermann et al. (7), it was found that 34% of subjects allocated to metformin monotherapy required addition of glyburide because of failure to achieve glycemic goals.

The gradual deterioration in glycemic control commonly seen in subjects receiving metformin monotherapy has been related to progressive postprandial hyperglycemia (14). Because insulin secretagogues and metformin act in different

ways, it has been reasoned that in combination, they may complement each other (6). The specific mechanisms of action, different from sulfonylureas, and the postprandial glucose regulatory effects of repaglinide would appear to offer advantages in combination with metformin in subjects whose glycemic control has deteriorated with metformin monotherapy.

This study is the first prospective evaluation specifically examining the efficacy and safety of giving an oral hypoglycemic agent to patients with inadequate glycemic control on metformin monotherapy. The improvement in glycemic control demonstrated by the combined therapy group was significantly better than that of the monotherapy results combined, suggesting that the two agents may act synergistically. The clinical significance of this possible synergism is that where there may be unacceptable side effects from metformin, repaglinide could be added and the dose of metformin reduced without any deterioration in glycemic control.

There were no serious side effects reported during the study. Gastrointestinal disorders occurred frequently among those taking metformin. Tight glycemic control is often accompanied by a risk of hypoglycemia, so it was not surprising that hypoglycemia was more common in the combined therapy group, and most episodes were reported either during the titration phase or by one particular subject. Blood glucose results ≤2.8 mmol/l were uncommon. Moreover, all of the hypoglycemic episodes in the combined therapy group were classified as mild or moderate (none was severe). This finding was not unexpected, because repaglinide's short duration of action is unlikely to cause sustained hyperinsulinemia.

A small increase in body weight was observed in the repaglinide-treated groups. The increase in weight may be related to the increase in fasting insulin levels but does not appear to be related to a change in glycemic control. No specific dietary instruction was given to the subjects in the study. The changes in the fasting insulin

Table 5—Summary of the most common adverse events

Adverse event	% of patients		
	Metformin	Metformin + repaglinide	Repaglinide
Hypoglycemia	0	33.3	10.7
Diarrhea	29.6	18.5	7.1
Headache	14.8	22.2	10.7

levels in both repaglinide-treated groups may indicate an overall improvement in β -cell function. The increase in insulin does not appear to be related to any improvement in glycemic control, as it was observed in both groups receiving repaglinide. These findings require further clinical research.

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