



Dose titration of repaglinide in patients with inadequately controlled type 2 diabetes

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Abstract

A total of 385 drug-therapy naïve patients, with inadequately controlled type 2 diabetes, were randomised into a multinational, parallel-group study to compare two strategies for dose titration of the oral hypoglycaemic agent repaglinide. Patients were allocated to either a fasting blood glucose (FBG) monitoring group with titration target 4.4–6.1 mmol/l or to a post-prandial blood glucose (PPBG) monitoring group with titration target 4.4–8.0 mmol/l. An initial titration period of up to 8 weeks was followed by a 12-week treatment period. Glycaemic control and hypoglycaemic outcomes were compared for the respective groups. HbA_{1c} decreased significantly more in the FBG monitoring group by a mean of 1.38% compared to the PPBG group by a mean of 1.22% ($P = 0.03$). The glycaemic control targets were met by fewer patients in the FBG group than in the PPBG group (57% versus 86% ($P < 0.001$)) despite a higher mean dose of repaglinide in the FBG group. The within-patient blood glucose variability was significantly lower in the FBG group than in the PPBG group ($P < 0.001$). In conclusion, repaglinide lowered the HbA_{1c} effectively and safely in both groups and self-monitored FBG is a suitable parameter for titration of repaglinide. Whether a lower PPBG target might be as good a guide as FBG for titration of repaglinide should be addressed in a future study. © 2003 Elsevier Ireland Ltd. All rights reserved.

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1. Introduction

Type 2 diabetes is characterised by insulin resistance and beta-cell failure [1]. In non-diabetic individuals, the beta-cell response to prandial stimuli is

biphasic, with an early ‘burst’ phase of insulin secretion, followed by a sustained increase in insulin release above basal levels, which may last for several hours. A characteristic defect seen in type 2 diabetes is the loss of the early phase of insulin secretion, which may contribute to both fasting and post-prandial hyperglycemia [2,3]. Initially, type 2 diabetes can be treated with diet and exercise alone, but as the disease progresses the patient requires oral treatment(s) and may eventually

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need insulin treatment. To avoid late diabetic complications (microvascular as well as macrovascular) near-normal glycaemic control is needed [4].

Repaglinide is a short-acting insulin secretagogue, used as a prandial glucose regulator agent. It is absorbed rapidly, has a fast elimination profile [5] and is taken immediately before meals to augment early glucose-stimulated insulin release [6,7]. Clinical studies have shown that repaglinide causes significant reductions in HbA_{1c}, fasting blood glucose (FBG) and post-prandial blood glucose (PPBG) levels [8–12]. In other comparative trials, repaglinide has shown blood glucose lowering efficacy similar to or better than that of classical sulphonylureas, with a reduced risk of hypoglycaemia [13,14]. Repaglinide is administered as a mealtime dose of 0.5–4.0 mg [15].

Generally, adjustments to oral therapy doses are based on self-monitored fasting blood glucose levels and on treatment tolerability. However, sometimes patients forget to measure FBG and therefore, to facilitate flexible treatment optimisation, it would be interesting to evaluate if the 2 h PPBG provides as good guidance for the dose adjustment as the FBG for patients on repaglinide. Theoretically, this should be possible due to the pharmacokinetic profile of repaglinide [5]. The objective of this study was to compare FBG and PPBG measurements as guidance for dose titration of repaglinide to obtain glycaemic control.

2. Materials and methods

2.1. Patients and design

This was a controlled, randomised, open-labelled, and parallel-group study, which was performed at 42 centres in the Nordic countries (Denmark, Finland, Iceland, Norway and Sweden). Drug-therapy naïve men and women aged at least 40 years, with type 2 diabetes were enrolled. Despite the fact that patients had received dietary and exercise instructions for 2 months, the investigator had deemed their glycaemic control unsatisfactory. Exclusion criteria were: intolerance to repaglinide, severe hepatic or renal insufficiency, use of medications likely to interact with repaglinide or affect glycaemic control,

pregnancy or likelihood of becoming pregnant during the study period. All patients gave their written, informed consent to participate in the study, which was conducted in accordance with the Declaration of Helsinki.

After the screening period patients were seen by the investigator at baseline, where eligibility was checked and patients were randomised. At the end of each titration period (after 2, 4 and 6 weeks of titration) the patients had telephone contact with the investigator. Patients visited the clinic after completion of titration (start of the 12-week treatment period), 6 weeks later and 12 weeks later (end of study). During the week up to the telephone contact or the visit, patients measured blood glucose twice (once a day on two different days). Each patient was given a home glucose meter and a diary for the duration of the study, and the nature of hypoglycaemic episodes was explained before study medication was given.

Patients were randomly allocated to one of two groups: one group monitored FBG levels and the other group monitored 2 h PPBG levels (2 h after dinner) as guidance for dose adjustment. Target FBG levels were set to 4.4–6.1 mmol/l and the 2 h PPBG levels to 4.4–8.0 mmol/l.

2.2. Dose regimens and titration

Treatment started with a titration period of up to 8 weeks, where the dose of repaglinide was optimised, followed by a 12-week treatment period. At the start of the study all patients were given 0.5 mg repaglinide before each main meal. The dose was increased stepwise to 1, 2, and 4 mg per meal until either target level for glycaemic control were achieved, a maximum dose of 4 mg per meal was reached, or adverse events, including hypoglycaemia, stopped further titration. Each of the four titration steps took 14 days. The patients consulted the investigator by telephone to report the two blood glucose measurements, hypoglycaemic episodes and adverse events, and to have their dose adjusted accordingly. The investigator made further dose adjustments during the 12-week treatment period, but only if self-monitoring indicated deterioration in glycaemic control or the patient reported an unacceptable number of hypoglycaemic episodes. It was not specified whether the target was fulfilled if; both values were within the target; just the last value

was or if it was sufficient that the mean value was within target.

Repaglinide was dispensed as blister packages containing 0.5, 1 and 2 mg tablets, manufactured by Novo Nordisk A/S.

2.3. Biochemical analysis

The analysis of HbA_{1c} was performed centrally by Medi-Lab AS, Copenhagen, DK [16] (normal range 4.5–5.7%). Home monitored blood glucose was measured by patients using OneTouch II meters (LifeScan, Milpitas, CA, USA) after training.

2.4. Efficacy evaluation

HbA_{1c} was assessed twice, once at baseline (at randomisation visit just before repaglinide was initiated) and again at the end of the study (at the end of the treatment period or at discontinuation). The primary endpoint was change in HbA_{1c} (Δ HbA_{1c}) from baseline to the end of study. In addition the following endpoints were described as part of the design outcome: mean blood glucose levels during the 12-week treatment period, the within-patient blood glucose variability in the two readings before each contact to investigator and the number of patients who did not meet the target levels for glycaemic control. Both blood glucose endpoints are derived from the two self-monitored blood glucose values, taken the week before a visit or telephone contact, and recorded in the patient diary. The blood glucose mean and within-patient variability were calculated using the fasting blood glucose values in the FBG group and the 2 h post-dinner values in the PPBG group.

2.5. Safety evaluation

Safety endpoints were the frequency and severity of hypoglycaemic episodes, adverse events, and the change in weight from baseline to the end of the study. Hypoglycaemic episodes were rated as mild (self-treated) or severe (requiring third party assistance, and a blood glucose value <3 mmol/l or prompt recovery after oral glucose). Hypoglycaemic episodes and adverse events were reported continuously during the study and weight was assessed at baseline and at the end of the study.

2.6. Statistical methods

All efficacy analyses were based on the intention-to-treat (ITT) population, defined as all patients exposed to study medication and with available data for that respective analysis. The safety analysis includes all patients who received at least one dose of study medication.

Central randomisation lists were generated, stratified within each country in blocks of 4. Balance within a centre was achieved by distributing randomisation envelopes to a centre in multiples of 4.

Δ HbA_{1c} was compared between groups by analysis of variance (ANOVA), with group and centre as fixed factors, and baseline HbA_{1c} as co-variate. The impact of the different dose distributions was assessed by also including the logged dose as a co-variate in the model. A mixed effect model was used to analyse mean blood glucose values; with patients as random effect, group, time, group by time interaction, and centre as fixed factors, and baseline HbA_{1c} as a co-variate. The within-patient blood glucose variability for each group was estimated by separate analysis of variance, with patient, visit, and the patient by visit interaction as fixed factors. The two variances were compared using the maximum likelihood ratio test. The ratio of the two independent chi-squared distributions, each divided by its number of degrees of freedom, was calculated and compared to the *F*-distribution. The coefficient of variation (CV) for the two groups was calculated by expressing the square root of the within-patient blood glucose variability as a percentage of the overall mean from the same model [$CV = 100 \times \sqrt{(\text{within-patient blood glucose variability}/\text{mean blood glucose})} = 100 \times \text{within-patient blood glucose standard deviation}/\text{mean blood glucose}$]. Cox regression on time to the first hypoglycaemic episode was used to compare the frequency of hypoglycaemic episodes between the groups. Weight was compared between groups by analysis of variance (ANOVA), with group and centre as fixed factors, and baseline weight as co-variate. The proportion of patients who did not meet target levels for glycaemic control and final dose were both compared between the groups using the Mantel–Haenszel test.

Exploratory analyses were made to address the relationship between the two blood glucose measurements and HbA_{1c} to see if one was better than the

other, to predict HbA_{1c}. This was investigated by comparing the correlation between mean FBG and HbA_{1c} to the correlation between mean PPBG and HbA_{1c}. Two different comparisons were made; one where all BG-values were used and a second where only the values in the 12 weeks treatment period were used. The between group comparison was made by first transforming the sample correlation coefficients using the Fisher r-to-Z transformation and then comparing the difference between the two (after standardisation) to the standard normal distribution.

Statistical analyses were carried out with SAS software, version 6.12.

3. Results

3.1. Demographics and dose

Three hundred and eighty-five patients were randomised. Three of these patients did not start treatment and two were lost to follow-up; thus, 190 patients in each group started the titration period (Table 1). Of the patients randomised, 92 and 94% completed the study in the FBG and PPBG monitoring groups, respectively. The number of patients who had data for the primary efficacy variable was not equal to the number of patients who completed the study. The reason was that some of the patients who completed the study had a missing value for HbA_{1c} ($n = 12$) and some

Table 1
Patient flow

	FBG	PPBG	Total
Randomised patients	192	193	385
Did not start treatment	2	3	5
Started treatment	190	190	380
Total withdrawn	13	8	21
Reason			
Adverse event	4	4	
Hypoglycaemic episodes	2	1	
Ineffective treatment	2	1	
Non-compliant	1	1	
Other	4	1	
Completed	177	182	359

FBG: patients randomized to dose titration by fasting blood glucose; PPBG: patients randomized to dose titration by post-prandial blood glucose. All values are numbers of patients.

Table 2

Demographic characteristics (based on the safety population)

	FBG	PPBG	Total
No. of patients	190	190	380
Sex (% women/men)	43/57	41/59	42/58
Race (% Caucasian/other)	99/1	99/1	99/1
Age (years) ^a	61 (11)	62 (10)	61 (10)
BMI (kg/m ²) ^a	30 (5)	30 (5)	30 (5)
Duration of diabetes (months) ^a	37 (46)	38 (43)	37 (44)
HbA _{1c} (%) ^a	8.1 (1.5)	8.4 (1.6)	8.2 (1.5)

FBG: patients randomized to dose titration by fasting blood glucose; PPBG: patients randomized to dose titration by post-prandial blood glucose.

^a Mean (S.D.).

of the patients who did not complete the study had a follow up visit where the assessment was done ($n = 5$). Patient baseline characteristics are summarised in Table 2. The overall demographic profile of the two groups was similar except for HbA_{1c} which was significantly higher in the PPBG group than in the FBG group (Tables 2 and 3). However, this difference was adjusted for in the analysis by including the baseline value as co-variate.

In the two groups the total duration of exposure to repaglinide was similar; patients were exposed for a mean time of 17.1 and 16.6 weeks in the FBG and PPBG groups, respectively. At the end of the study the mean dose was statistically significantly higher in the FBG group: 1.9 mg per meal versus 1.4 mg per meal in the PPBG group ($P < 0.001$). The dose ranged from 0.5 to 6 mg per meal in both groups. Two patients, one in each group, received treatment with the 6 mg per meal dose for 3 and 10 weeks, respectively; neither recorded any adverse events or hypoglycaemic episodes during that period.

3.2. Glycaemic control

During the study HbA_{1c} improved in both groups (Table 3), decreasing by 1.38 and 1.22% in the FBG and PPBG group, respectively. HbA_{1c} decreased significantly more in the FBG group compared to the PPBG group ($P = 0.03$). The mean difference between groups was -0.16% , with a 95% confidence interval ranging from -0.30 to -0.02% . Further analysis indicates that the between groups difference in

Table 3
Change in HbA_{1c} (based on the intention to treat population)

	FBG (<i>n</i> = 171) (%)	PPBG (<i>n</i> = 179) (%)	FBG – PPBG (%)
Baseline HbA _{1c}			
Mean	8.02	8.42	
S.D.	1.51	1.56	
Minimum	5.5	5.8	
Maximum	13.8	14.8	
Change from baseline to end of study			
Mean	–1.38	–1.22	–0.16*
95% confidence limits	[–1.48, –1.27]	[–1.32, –1.12]	[–0.30, –0.02]

FBG: patients randomized to dose titration by fasting blood glucose; PPBG: patients randomized to dose titration by post-prandial blood glucose.

* $P = 0.03$, FBG vs. PPBG.

HbA_{1c} reduction remained after correcting for the different dose distributions ($P < 0.001$).

Table 4 shows the proportion of patients who did not meet the target levels for glycaemic control and the reasons why. When dose titration was completed, 57% in the FBG group and 86% in the PPBG group had met their targets ($P < 0.001$), giving an overall percentage of 72%. The reasons for patients not reaching the titration targets were similar for the two groups (Table 4).

The fasting and the post-prandial blood glucose time profiles were compared over the 12 weeks treatment period. The mean level was consistently lower in the FBG group (6.3 before start of treatment, 6.4 after 6 weeks and 6.3 mmol/l after 12 weeks of treatment) compared to the PPBG group (6.8, 6.9 and 7.1 mmol/l) ($P < 0.001$). There was however no statistically sig-

nificant time trend in blood glucose ($P = 0.31$), and no statistically significant difference between the groups with regard to time trend ($P = 0.13$).

The within-patient variability expressed as the coefficient of variation was used to describe the day-to-day variation in blood glucose within a patient. The CV differed considerably between the two groups; 10.5 and 18.9 in the FBG and PPBG group, respectively ($P < 0.001$).

Exploratory analyses were made to assess if PPBG was a better predictor of HbA_{1c} than FBG. Two analyses were made and both gave similar results. When the mean values per patient throughout the study were used, the Pearson correlation was estimated as 0.64 for the FBG group and 0.65 for the PPBG group ($P = 0.88$). When the BG values obtained in the 12 weeks treatment period were used, the corresponding figures

Table 4
Glycaemic control targets (met/not met/reason)

	FBG (<i>n</i> = 190)		PPBG (<i>n</i> = 190)		Total (<i>n</i> = 380)	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Met target levels	109	57	163	86	272	72
Did not meet target levels	81	43	27	14	108	28
Reason						
Adverse event	1	1	0	0	1	1
Hypoglycaemic episodes	6	8	3	11	9	8
Reached the 4 mg per meal max dose without meeting target levels	52	64	19	70	71	66
Unknown	22	27	5	19	27	25

FBG: patients randomized to dose titration by fasting blood glucose; PPBG: patients randomized to dose titration by post-prandial blood glucose.

were 0.62 versus 0.65 ($P = 0.56$). Each correlation coefficient in itself was statistically significantly different from zero ($P < 0.001$).

3.3. Hypoglycaemia, adverse events and weight change

During the course of the study, 269 hypoglycaemic episodes were recorded in 96 (25%) patients. In the FBG group, 169 episodes were recorded in 53 patients (28%) and in the PPBG group, 100 episodes were recorded in 43 patients (23%). Only one patient had major hypoglycaemic episodes. Of the 96 patients who reported hypoglycaemic episodes, 75 did not change their dose as a result. Nine patients stopped dose titration because of hypoglycaemic episodes, six patients reduced their dose, and three patients were withdrawn. There was no statistically significant difference in time to first hypoglycaemic episode ($P = 0.24$).

Adverse events were recorded in 51% of the patients in the FBG group and 55% of the patients in the PPBG group. The frequency of adverse events in the two groups was similar (Table 5). The adverse events reported by more than 5% of the patients were influenza-like symptoms (7.4 and 6.8% in the FBG and PPBG group respectively), respiratory tract infection (5.7 and 6.3%) and headache (8.4 and 8.9%). Of these, three (all headache) were recorded as possibly

or probably related to study medication. Only 16 serious events were reported (six patients in the FBG group and nine in the PPBG group).

There was a mean weight increase in both groups during the study of 0.6 kg (range -10 to 23 kg) in the FBG group and 0.4 kg (range -6 to 8 kg) in the PPBG group ($P = 0.63$).

4. Discussion

Repaglinide is a short-acting oral hypoglycaemic agent with a fast onset, taken with main meals. Theoretically, due to the pharmacokinetic profile of repaglinide, PPBG measurements should be as good a guide for adjusting dose as FBG measurements. Patients would have greater flexibility of treatment optimisation if they could monitor glycaemic control with both FBG and PPBG levels. This study was designed to compare the ability of FBG and PPBG measurements to act as a guide for the dosing of repaglinide in patients with type 2 diabetes who are naïve to oral hypoglycaemic drug therapy.

The result of this study shows that repaglinide effectively decreased HbA_{1c} in both groups. Surprisingly, HbA_{1c} was significantly more decreased in the FBG group compared to the PPBG group, however the difference was small and may be of limited clinical relevance.

The repaglinide dose was titrated according to limits quite similar to the limits recommended as short term treatment goals for type 2 diabetic patients by IDF and the St. Vincent declaration. The upper FBG limit (4.4–6.1 mmol/l) was almost 2 mmol/l lower than that used for PPBG group (4.4–8.0 mmol/l). Since fewer patients met their treatment target in the FBG group and as a result received a higher dose it can be concluded that the two targets were not comparable. The primary analysis was repeated to investigate if the result could be explained by the different dose distributions, but the between groups difference in HbA_{1c} remained. This indicates that the result could not be explained by a pure dose-response relationship.

During the 12 weeks treatment period the blood glucose profiles were parallel but separated. Mean FBG was stable whereas mean PPBG increased slightly over time; this tendency was however not statistically significant but it may indicate that the patients in the

Table 5
Summary of adverse events

	FBG		PPBG	
	Events	Patients	Events	Patients
No. of exposed patients		190		190
No. of adverse events	165	97	177	105
Serious	6	6	10	9
Related to study drug				
Impossible	8	4	8	4
Unlikely	142	79	153	87
Possible	12	11	10	8
Probable	3	3	6	6
Severity				
Mild	116	58	120	63
Moderate	45	35	51	37
Severe	4	4	6	5

FBG: patients randomized to dose titration by fasting blood glucose; PPBG: patients randomized to dose titration by post-prandial blood glucose.

PPBG group needed to be further titrated in order to maintain short term glycaemic control.

The day-to-day blood glucose variability was significantly lower in the FBG group than in the PPBG group, which could indicate that FBG is more stable/reproducible and thereby more clinically relevant to use for dose titration. The higher variability in the PPBG measurements may be caused by additional food and drink intake, and problems with timing. It is therefore important for the reliability of the PPBG measurements that variation is minimised through a standardised setting.

A weakness in our study was that investigators were asked to continue dose titration every second week if repaglinide was well tolerated and if targets for the blood glucose were not yet met. However, it was not specified in the protocol whether the target for dose titration was fulfilled if: both BG values were within the target; just the last one was or if it was sufficient with the mean of the two values were within target. In our study, it appears that the same method was used in all patients within a centre. To maintain consistency between centres it is important to have clear guidelines for how to achieve the targets for dose titration.

It could be questioned that if a lower and/or narrower range had been used for the PPBG group then the decrease in HbA_{1c} would have been of the same magnitude for both groups. The patients in our study were only asked to measure BG according to randomisation to help the investigators to be unbiased when assessing whether or not patients had achieved their targets. However, it would have been interesting to make a direct comparison of the FBG values.

The relative contributions of FPG and PPG to HbA_{1c} have studied recently and reported in the ADA position paper [18]. It was concluded that there are insufficient data to accurately determine the relative contribution of the FPG and PPG to HbA_{1c}. It appears, however, that FPG is somewhat better than PPG in predicting HbA_{1c}, especially in type 2 diabetes. Exploratory analyses were performed with our data to investigate whether FBG or PPBG was the better predictor of HbA_{1c}. Both FBG and PPBG were strongly correlated to HbA_{1c} but the correlation was similar. The level of correlation was similar to the correlation shown for the FPG referred to by ADA. The results from our study do not support FBG as a better predictor of HbA_{1c} than PPBG, or vice versa.

The low incidence of hypoglycaemic episodes, together with the safety data and high study completion rate, show that repaglinide was well tolerated and this is in agreement with previous observations [13,17]. This finding suggests that the greater mean repaglinide dose required to meet the FBG target level used in this study was not associated with an increase in the overall risk of hypoglycaemia. The weight increase observed in both groups was expected as it is a common observation when initiating treatment with insulin secretagogues.

In conclusion, the results show that repaglinide effectively and safely reduces HbA_{1c}, in drug-therapy naïve type 2 diabetic patients. The HbA_{1c} decrease was slightly greater in the FBG group than in the PPBG group however the blood glucose targets were met by fewer patients in the FBG group, resulting in a higher mean dose. This suggests that the target set for glycaemic control in the FBG group was more difficult to reach than that in the PPBG group. Self-monitored FBG is a suitable parameter for titrating a repaglinide and this is supported by the lower within-patient variability in the FBG group. The effect of a lower upper limit for the PPBG target on titration of repaglinide should be addressed in a future study.

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