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Effect of adding sitagliptin, a dipeptidyl peptidase-4 inhibitor, to metformin on 24-h glycaemic control and β-cell function in patients with type 2 diabetes

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Aim: The aim of this study was to assess the effect of sitagliptin, a dipeptidyl peptidase-4 inhibitor, on 24-h glucose control when added to the regimen of patients with type 2 diabetes who had inadequate glycaemic control on metformin therapy.

Methods: In a double-blind, randomized, placebo-controlled, two-period crossover study, patients with type 2 diabetes with inadequate glycaemic control on metformin monotherapy (i.e. on a stable dose of ≥1500 mg/day for ≥6 weeks prior to the screening visit and an haemoglobin A_{1c} (HbA_{1c}) ≥6.5% and <10% and fasting plasma glucose (FPG) ≤240 mg/dl) were recruited for participation. A total of 28 patients (baseline HbA_{1c} range = 6.5–9.6%) receiving metformin were randomized into one of two treatment sequences: the addition of placebo for 4 weeks followed by the addition of sitagliptin 50 mg twice daily (b.i.d.) for 4 weeks, or vice versa. At the end of each treatment period, patients were domiciled for frequent blood sampling over 24 h. The primary endpoint was 24-h weighted mean glucose (WMG) and secondary endpoints included change in FPG, mean of 7 daily self-blood glucose measurements (MDG) and fructosamine. β-cell function was assessed from glucose and C-peptide concentrations were measured during the 5-h period after a standard breakfast meal by using the C-peptide minimal model.

Results: Despite a carryover effect from period 1 to period 2, the combined period 1 and period 2 results for glycaemic endpoints were statistically significant for sitagliptin relative to placebo when added to ongoing metformin therapy. To account for the carryover effect, the period 1 results were also compared between the groups. Following period 1, there were significant least-squares (LS) mean reductions in 24-h WMG of 32.8 mg/dl, significant LS mean reduction from baseline in MDG of 28 mg/dl, FPG of 20.3 mg/dl and fructosamine of 33.7 mmol/l in patients treated with sitagliptin relative to placebo ($p < 0.05$). When added to ongoing metformin therapy, parameters of β-cell function were significantly improved with sitagliptin compared with placebo. No weight gain or increases in gastrointestinal adverse events or hypoglycaemia events were observed with sitagliptin relative to placebo during this study.

Conclusions: In this study, the addition of sitagliptin 50 mg b.i.d. to ongoing metformin therapy improved 24-h glycaemic control and β-cell function, and was generally well tolerated in patients with type 2 diabetes.

Keywords: beta cell function, DPP-IV inhibitor, incretin, glycaemic control, MK-0431
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Introduction

Sitagliptin is an oral, potent and highly selective dipeptidyl peptidase-4 (DPP-4) inhibitor for the treatment of type 2 diabetes [1]. DPP-4 inhibitors offer a new therapeutic approach for the treatment of type 2 diabetes and act by inhibiting DPP-4-mediated degradation of the incretin hormones glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), thus increasing concentrations of the intact, active hormones. Both incretins enhance glucose-dependent insulin release, and GLP-1 is also known to suppress glucagon concentrations in response to a meal [2–4]. In a clinical study in patients with type 2 diabetes, single doses of sitagliptin increased active GLP-1 and GIP levels by twofold, increased insulin and C-peptide concentrations, lowered glucagon levels and decreased the glucose excursion after a glucose challenge that was administered 2 h following dosing [5]. The effects observed at 2 h following sitagliptin administration were also observed to a similar extent after a glucose challenge administered 24 h after the sitagliptin dose [5]. Thus, a single dose of sitagliptin enhanced active incretin concentrations and lowered glucose concentrations after a glucose challenge for 24 h.

Treatment with a single antihyperglycaemic agent is often unsuccessful at achieving and/or maintaining glycaemic control [6]. As a result, many patients require a combination of agents with different mechanisms to achieve adequate control. Metformin is the most commonly used first-line antihyperglycaemic agent and acts primarily by reducing hepatic glucose production, and may also improve insulin sensitivity [6].

Since sitagliptin and metformin target different metabolic defects in the pathogenesis of hyperglycaemia in type 2 diabetes, co-administration of these two agents may be a beneficial therapeutic approach. Moreover, in a phase I clinical study, there was no evidence of a pharmacokinetic interaction between sitagliptin and metformin [7]. Therefore, the present study examined the glycaemic efficacy, effect on β-cell function and tolerability of sitagliptin in patients who had inadequate control on metformin monotherapy.

Methods

Patients

Men and women (aged 25–75 years) with type 2 diabetes and inadequate glycaemic control on metformin monotherapy at a stable dose of $\geq$1500 mg/day for $\geq$6 weeks and an haemoglobin A_{1c} (HbA_{1c}) $\geq$6.5% and <10% and fasting plasma glucose (FPG) $\leq$240 mg/dl at screening were entered into a 5-week, screening/diet run-in period. Major exclusion criteria included a history of type 1 diabetes; C-peptide levels $\leq$0.8 ng/dl; hepatic transaminases or creatine phosphokinase (CPK) more than twofold upper limit of normal (ULN); elevated serum creatinine; body mass index <22 kg/m^2 or >40 kg/m^2; or any medically significant cardiovascular event within 6 months.

Study Design

This was a double-blind, randomized, placebo-controlled, two-period, crossover study (Sitagliptin Protocol no. 015). After completing the 5-week, run-in period and if HbA_{1c} was still $\geq$6.5% and <10% and FPG was $\geq$126 mg/dl and <240 mg/dl, patients were randomized in a 1 : 1 ratio to one of two treatment sequences, which included two 4-week treatment periods. Patients randomized to treatment sequence 1 received placebo in period 1 for 4 weeks followed by sitagliptin 50 mg b.i.d. in period 2 for 4 weeks, whereas patients randomized to treatment sequence 2 received sitagliptin 50 mg b.i.d. in period 1 for 4 weeks followed by placebo in period 2 for 4 weeks. Sitagliptin or matching placebo was taken twice daily, before morning and evening meals, along with metformin maintained at the same dose and dose regimen as the patient had been on prior to enrolment in the study. Treatment compliance to study drug was assessed by pill count.

At the end of each 4-week treatment period, patients were domiciled at the investigational site for a 24-h blood sample collection. Patients were fasted overnight for at least 12 h. Study drug was administered 30 min prior to the standardized morning (07:30 hours) and evening (18:30 hours) meals. Blood samples were collected for glucose, insulin and C-peptide at 30 min and immediately prior to the morning meal (08:00 hours) and 15, 30, 60, 90, 120 and 180 min after the meal. Blood samples for glucose and C-peptide were collected prior to the midday meal (13:00 hours) and evening meal (19:00 hours); 30, 60, 120 and 180 min after these meals; and at midnight, 03:00 hours, and at 07:30 hours the next morning to complete the 24-h blood collection. At the investigational site, patients received standardized meals consisting of a total of 2400 kcal divided into three meals, with 32% of total kilocalories consumed at the morning meal (765 kcal with 44% fat, 42% carbohydrate and 14% protein).

Study Endpoints

The primary endpoint was 24-h weighted mean glucose (WMG) calculated as an integrated assessment of glycaemic

exposure over a 24-h period at the end of each study period. This parameter is estimated by dividing the area under the 24-h glucose curve (AUC_{0-24}) by 24 h. The 24-h WMG was collected only at the end of each treatment period and not at baseline. Secondary endpoints included FPG, fructosamine, and mean daily glucose (MDG), calculated as the mean of 7 daily, fingerstick glucose measurements (premeal, 2-h postmeal and at bedtime). Fingerstick glucose measurements for MDG were collected in a 2- to 3-day period, when the patient was at home, prior to the collection of the 24-h blood samples.

Exploratory endpoints included 24-h weighted mean C-peptide and AUC for total and incremental insulin concentrations following a standardized morning meal. In a post hoc analysis, β-cell function was assessed from glucose and C-peptide concentrations measured in the 5-h period after the standard breakfast meal, by using the C-peptide minimal model [8]. The model assumes that insulin secretion is made up of three components. The dynamic component represents secretion of promptly releasable insulin and is proportional to the rate of increase of glucose through a parameter, Φ_d, which defines the dynamic responsivity index. The static component derives from provision of new insulin to the releasable pool and is characterized by a static index, Φ_s, and by a delay time constant, T (delay between static phase secretion and glucose concentration). From Φ_d and Φ_s, total β-cell responsivity, Φ_{total} can be calculated. Finally, a basal β-cell responsivity index, Φ_b, can be calculated from basal C-peptide and glucose concentrations [8]. Insulin sensitivity was assessed with a composite index (ISI) [9]. To determine whether insulin secretion was appropriate for the degree of insulin resistance, Φ_d, Φ_s and Φ_{total} were expressed in relation to insulin sensitivity using disposition indices: dynamic (DI_d), static (DI_s) and total disposition indices (DI_{total}). Each of these indices was calculated as the product of the particular β-cell parameter (e.g. Φ_d) multiplied by the ISI.

Safety and tolerability were assessed throughout the study. Physical examinations, vital signs, 12-lead electrocardiograms and safety laboratory measurements comprising routine haematology, serum chemistry (including hepatic transaminase and CPK levels) and urinalysis were performed. Adverse experiences were monitored throughout the study. Investigators evaluated all clinical adverse experiences in terms of intensity (mild, moderate or severe), duration, severity, outcome and relationship to study drug. Adverse experiences of special interest were incidence of hypoglycaemia and gastrointestinal-related adverse experiences. Hypoglycaemia was assessed by reviewing daily glucose logs, self-report of signs and symptoms and glucose values during the 24-h frequent blood sampling period at the end of each treatment period. Body weight was also assessed throughout the study.

All efficacy and safety laboratory measurements were performed at PPD Global Central Labs, LLC (Highland Heights, KY, USA) by technicians who were blinded to study treatment allocation.

Statistical Analysis

The primary efficacy (24-h WMG) and exploratory endpoints were analysed using an appropriate analysis of variance (ANOVA) model for a 2-period crossover design. For the secondary efficacy endpoint (FPG, MDG and fructosamine), a baseline-adjusted analysis of covariance (ANCOVA) model was used to assess between-treatment differences. Between-treatment differences were estimated by the difference in least-squares (LS) mean from the model with a 95% confidence interval (CI). The ANOVA and ANCOVA models included fixed terms for period and treatment. An alpha level of ≤ 0.05 (two sided) was considered statistically significant. For data presented in conventional units, the following SI conversion factors may be used: to convert glucose values to mmol/l, multiply by 0.0551; to convert insulin values to pmol/l, multiply by 6 and to convert C-peptide values to nmol/l, multiply by 0.331.

For changes in β-cell function, log-transformed data were used in an ANOVA model. These data were then back transformed to yield geometric LS means, and geometric mean ratios were computed to estimate between-treatment differences.

Summary statistics were reviewed for changes in baseline values in safety parameters including vital signs, ECG and laboratory values.

Results

Patients

In this two-period crossover study, 28 patients with ongoing metformin therapy were randomized to treatments: 13 in the placebo/sitagliptin treatment sequence (i.e. placebo during period 1 and sitagliptin during period 2) and 15 in the sitagliptin/placebo treatment sequence. Baseline demographics were well matched (except for slight imbalance in gender distribution), and baseline glycaemic characteristics were similar between treatment groups (table 1). One patient from each treatment sequence withdrew consent during period 1 and period 2, while one patient in the sitagliptin/placebo treatment

Table 1 Baseline demographics

	Placebo/sitagliptin 50 mg b.i.d. + metformin (n = 13)	Sitagliptin 50 mg b.i.d./ placebo + metformin (n = 15)	All (N = 28)
Age (years)	56.9 ± 9.2	54.9 ± 9.7	55.9 ± 9.3
Gender, n			
Women	7	11	18
Men	6	4	10
Race, n			
Asian	0	1	1
Black	2	2	4
Hispanic	5	5	10
White	6	7	13
BMI (kg/m^2)	30.9 ± 4.0	32.5 ± 5.6	31.8 ± 4.9
Known duration of diabetes (years)	6.8 ± 7.6	6.5 ± 4.2	6.6 ± 5.9
HbA_{1c} (%) (range)	7.8 ± 0.8 (6.9–9.2)	7.7 ± 0.8* (6.5–9.0)	7.7 ± 0.8* (6.5–9.2)
FPG (mg/dl)	152.2 ± 21.3	151.4 ± 25.8	151.8 ± 23.4
Fructosamine (mmol/l)	289.8 ± 40.0	275.2 ± 40.9*	282.2 ± 40.4*
MDG (mg/dl)	178.8 ± 30.8	180.2 ± 35.4*	179.5 ± 32.6*
Serum insulin (μIU/ml)†	11.7 (5.7, 17.9)	10.5 (7.3, 19.7)	11.1 (6.5, 18.8)

BMI = body mass index; HbA_{1c} = glycosylated haemoglobin; FPG = fasting plasma glucose; MDG = mean daily glucose from 7 daily self-blood glucose measurements.
Data are expressed as mean ± s.d. or frequency unless otherwise noted.
To convert glucose values to mmol/l, multiply by 0.0551; to convert insulin values to pmol/l, multiply by 6.
*n = 14 for sitagliptin/placebo group and N = 27 for all.
†Data are presented as median (interquartile range).

sequence refused to participate in the 24-h blood collections at the end of each period.

Efficacy

In the design of this two-period crossover study, it was expected that 4 weeks would be sufficient for the effects of the period 1 drug treatment to wash off. This was not achieved in the present study, as the glycaemic endpoints, including 24-h WMG, FPG and MDG at the end of period 2 in patients who received sitagliptin during period 1 (followed by placebo during period 2) were substantially lower than those at the end of period 1 in patients who received placebo during period 1. For 24-h WMG, patients receiving sitagliptin or placebo had a mean (s.d.) value of 125.0 mg/dl (14.5) or 157.9 mg/dl (25.6), respectively, following period 1, whereas following period 2, patients receiving sitagliptin or placebo had a mean value (s.d.) of 136.3 mg/dl (23.1) or 138.0 mg/dl (15.3) respectively. In a post hoc analysis, the treatment by period interaction term trended towards significance ($p = 0.055$) for 24-h WMG. The lack of significance for this interaction term may be due to lack of power, even when the carryover effects were apparent with the 24-h WMG results. Since carryover effects were observed, the analysis of the first-period data was also performed to avoid the potentially biased crossover analysis.

However, despite the carryover effect from period 1 to period 2, the between-treatment difference in 24-h WMG was statistically significant ($p < 0.001$) when the two-period data were combined (table 2). The combined period results for all secondary efficacy endpoints including FPG, MDG and fructosamine were also statistically significantly different between treatment groups (table 2).

As described above, the results of period 1 were further explored to avoid the confounding influence of the carryover effect. The 24-h mean glucose profiles after 4 weeks (i.e. at the end of period 1) of sitagliptin or placebo treatment when added to ongoing metformin therapy are shown in figure 1. Compared with the placebo group, sitagliptin treatment provided sustained glucose lowering over the 24-h period, with substantially lower premeal glucose concentrations and smaller glucose excursions after all three meals. Following period 1, 24-h WMG was significantly lower with sitagliptin relative to placebo [between-treatment difference in LS means (95% CI) = −32.8 mg/dl (−49.7, −16.0); $p < 0.001$] (table 3). Relative to placebo, sitagliptin produced significantly greater changes from baseline in FPG [between-treatment differences in LS mean change from baseline (95% CI) = −20.3 mg/dl (−31.1, −9.6); $p < 0.001$], MDG [−28.0 mg/dl (−55.5, −0.6); $p = 0.046$] and fructosamine [−33.7 mmol/l (−54.5, −12.9); $p = 0.003$] (table 3).

Table 2 The 24-h weighted mean glucose results and change from baseline in mean daily glucose measurements, fasting plasma glucose and fructosamine after 4 weeks of treatment (for periods 1 and 2 combined)

	Periods 1 and 2 combined			
Parameter	**Sitagliptin + metformin (n = 27)**	**Placebo + metformin (n = 27)**	**Difference in LS means (95% CI)**	**p value**
24-h WMG (mg/dl)	130.5 (121.9, 139.1)	148.4 (140.0, 156.9)	−17.2 (−22.3, −12.1)	<0.001
MDG (mg/dl)*	−17.6 (−30.8, −4.5)	−2.7 (−15.7, 10.3)	−15.0 (−24.6, −5.4)	0.004
FPG (mg/dl)*	−23.1 (−29.9, −16.3)	−7.7 (−14.5, −0.9)	−15.4 (−21.7, −9.2)	<0.001
Fructosamine (mmol/l)*	−24.8 (−34.1, −15.4)	−6.5 (−15.8, 2.7)	−18.3 (−28.0, −8.5)	<0.001

WMG, weighted mean glucose; MDG, mean daily glucose; FPG, fasting plasma glucose.
Data are expressed as between-treatment differences in LS means (95% CI) or *LS mean change from baseline (95% CI).
To convert glucose values to mmol/l, multiply by 0.0551.

The 24-h C-peptide profiles are shown in figure 2 for both treatments after period 1. Compared with placebo, the C-peptide levels were numerically reduced after the midday meal and increased after the evening meal with sitagliptin. Overall, the 24-h weighted mean C-peptide was not different between treatment groups at the end of period 1 [between-treatment difference in LS mean 24-weighted mean C-peptide (95% CI) = −0.1 ng/ml (−1.7, 1.5]); p = 0.9]. Following the morning meal, incremental AUC of insulin was slightly, but not significantly, reduced with sitagliptin compared with placebo after period 1 [LS means (95% CI) = 86.9 μIU/ml (41.8, 132.0) and 100.9 μIU/ml (55.8, 146.0) respectively]. Similar results were observed with total insulin AUC (data not shown).

β-cell function, as assessed by the model-based analysis, was significantly improved after treatment with sitagliptin compared with placebo. In particular, the static and total β-cell responsivity indices were statistically significantly higher after sitagliptin treatment than with placebo when added to ongoing metformin therapy (table 4). Dynamic and basal indices were numerically, but not statistically significantly, increased with sitagliptin compared with placebo. Insulin sensitivity was also numerically improved with sitagliptin compared with placebo, but this did not achieve statistical significance (table 4). As a result of the improvement in the parameters describing β-cell function combined with the trend towards an improvement in insulin sensitivity, the disposition indices were substantially enhanced, with statistically significant improvements in static and total disposition indices, and a numerical but not statistically significant improvement of the dynamic disposition index (table 4).

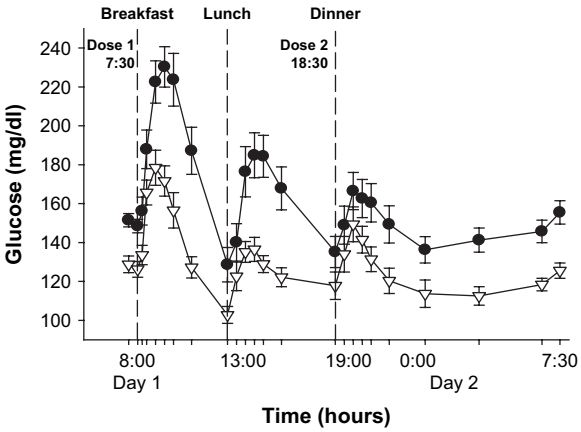

Fig. 1 The 24-h plasma glucose profiles after 4 weeks (i.e. end of period 1) of sitagliptin 50 mg b.i.d. (open triangles) or placebo (closed circles) treatment in patients with inadequate glycaemic control on metformin monotherapy.

Safety and Tolerability

For both periods 1 and 2 combined, the number of patients with one or more adverse experiences was generally similar between sitagliptin (n/N = 11/28) and placebo (n/N = 8/27) treatments when added to ongoing metformin therapy. Adverse experiences were mild to moderate, transient and resolved while patients continued on study drug. There were no discontinuations due to any adverse experiences. Two patients (nausea; abdominal pain, chest pain and vomiting) in the sitagliptin group and one patient (headache) in the placebo group had adverse experiences that were considered drug related by the investigator. No deaths or serious adverse experiences were reported.

Two laboratory adverse events were reported with sitagliptin treatment, but these events were not considered drug related by the investigator. At the end of period 1, one patient in the sitagliptin treatment group had an elevated alanine aminotransferase (ALT) more than three times the ULN with a normal aspartate aminotransferase value. Because this patient was crossed-over to placebo in period 2, repeat ALT measurement while the patient remained on sitagliptin was not possible, but ALT

Table 3 The 24-h weighted mean glucose results and change from baseline in mean daily glucose measurements, fasting plasma glucose and fructosamine after 4 weeks of treatment (i.e. following period 1)

	Following period 1			
Parameter	**Sitagliptin + metformin (n = 13)**	**Placebo + metformin (n = 13)**	**Difference in LS means (95% CI)**	**p value**
24-h WMG (mg/dl)	125.0 (113.1, 136.9)	157.9 (146.0, 169.8)	−32.8 (−49.7, −16.0)	<0.001
MDG (mg/dl)*	−23.1 (−42.2, −4.1)	4.9 (−14.9, 24.6)	−28.0 (−55.5, −0.6)	0.046
FPG (mg/dl)*	−23.8 (−31.1, −16.5)	−3.4 (−11.3, 4.4)	−20.3 (−31.1, −9.6)	<0.001
Fructosamine (mmol/l)*	−28.7 (−43.0, −14.4)	5.0 (−9.8, 19.9)	−33.7 (−54.5, −12.9)	0.003

WMG, weighted mean glucose; MDG, mean daily glucose; FPG, fasting plasma glucose; LS, least square.
Data are expressed as LS mean (95% CI) or *LS mean change from baseline (95% CI).
To convert glucose values to mmol/l, multiply by 0.0551.

returned to normal at the next measurement. No events of hypoglycaemia were reported. The incidence of gastrointestinal-related adverse experiences was similar between treatments [n/N = 2/28 (7.1%) for sitagliptin vs. 3/27 (11.1%) for placebo]. Body weight was not significantly changed with treatment. No meaningful changes in vital signs or ECG measurements were found between treatments.

Discussion

Sitagliptin, a DPP-4 inhibitor, lowers plasma glucose by enhancing active incretin levels in both the fasted state and in response to meals [1,5,10]. The present study examined the glycaemic efficacy and tolerability of sitagliptin in patients with type 2 diabetes who had inadequate control on metformin monotherapy using a placebo-controlled, two-period crossover design. It was expected that patients randomized to sitagliptin in period 1 followed by 4 weeks of placebo treatment during period 2 would have returned to their pretherapy glucose control values (i.e. baseline levels prior to period 1). However, a carryover effect was observed in these patients. This carryover effect may have been related to the reversal of glucotoxicity with sitagliptin treatment or potentially to a prolonged effect of drug treatment with inadequate wash out of drug effects. The present results cannot separate these alternative possibilities. Despite the carryover effect, statistically significant improvements in 24-h WMG and in the secondary efficacy measures were achieved in the analysis of the two periods combined.

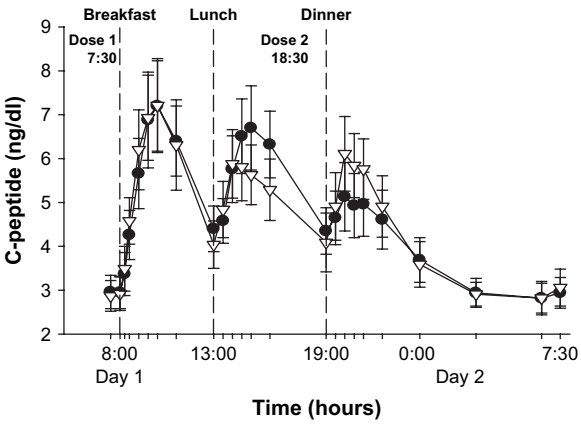

Fig. 2 The 24-h plasma C-peptide profiles after 4 weeks (i.e. end of period 1) of sitagliptin 50 mg b.i.d. (open triangles) or placebo (closed circles) treatment in patients with inadequate glycaemic control on metformin monotherapy.

Since the carryover effect will confound estimation of the extent of glycaemic efficacy with sitagliptin, results from period 1 – in essence, a randomized, parallel group, placebo-controlled 4-week study period – were described in more detail. Although not initially designed as a parallel group study, the two treatment groups started with similar glycaemic control at randomization, supporting the value of the period 1 comparison between groups. For period 1 only, the between-treatment difference for MDG (−28.0 mg/dl) was similar to that for the 24-h WMG (−32.8 mg/dl) despite differences in methodology and, more importantly, differences in the setting in which glucose measurements were obtained (i.e. at home on their usual diet compared with being domiciled at the investigational site on a regimented standard diet).

Incretins, including GLP-1 and GIP, increase the release of insulin in a glucose-dependent manner via specific receptors on pancreatic β-cells [11,12]. In the present study, profiles of 3-h postprandial insulin and 24-h C-peptide levels were similar in the sitagliptin and placebo groups after 4 weeks of treatment. However, an evaluation of insulin response must take into account the concurrent glucose values. To better evaluate this, parameters describing β-cell function were determined with a model-based analysis. Treatment with sitagliptin produced statistically significant and substantial increases

Table 4 Results of β-cell modelling analysis using data from the meal tolerance test (following period 1 data only)

Parameter*	Sitagliptin + metformin (n = 13)	Placebo + metformin (n = 13)	GMR	p value
Φ_s, 10^{-9}/min	28.4 ± 14.3	16.9 ± 12.9	1.68	0.03
Φ_d, 10^{-9}	305.1 ± 733.7	205.1 ± 362.4	1.49	0.44
Φ_b, 10^{-9}/min	7.9 ± 3.5	6.2 ± 3.4	1.26	0.20
Φ_{total}, 10^{-9}/min	31.8 ± 16.1	19.2 ± 13.2	1.66	0.03
T, min	22.5 ± 17.1	22.2 ± 19.3	1.01	0.96
Insulin sensitivity index	4.7 ± 4.7	3.4 ± 3.3	1.40	0.30
DI_s	141.1 ± 131.5	56.5 ± 26.7	2.50	0.001
DI_d	1475.8 ± 6982.1	654.4 ± 2648.5	2.26	0.24
DI_{total}	158.0 ± 150.5	64.3 ± 37.3	2.46	0.003

LS, least square; GMR, geometric mean ratio based on geometric LS mean (sitagliptin/placebo).
Data are presented as geometric LS mean ± s.d. back transformed from log-scale using the analysis of variance model.
*See Methods section for definitions of each parameter.

in several key β-cell parameters, including Φ_s and Φ_{total}, and numerical improvements that did not reach statistical significance in other indices of β-cell function, including Φ_d and Φ_b. The disposition indices, which describe the changes in parameters of β-cell function in the context of changes in insulin sensitivity, were more substantially improved than the β-cell parameters. Confirmation of these improvements in indices, which were numerically but not statistically significantly improved will require larger studies with greater statistical power. Overall, however, the improvements observed confirm a beneficial effect of sitagliptin on β-cell function.

Sitagliptin was generally well tolerated compared with placebo when added to ongoing metformin therapy. The incidence of adverse experiences was similar with both treatments. Since metformin is associated with gastrointestinal intolerance [6] and sitagliptin enhances active GLP-1 levels, which can affect gastric emptying [13], it is important to note that co-administration of sitagliptin and metformin did not increase gastrointestinal-related adverse experiences compared with placebo and metformin in the present study. No events of hypoglycaemia were reported during either study period. Despite enhanced β-cell sensitivity to glucose, the lack of hypoglycaemia observed with sitagliptin treatment indicates that the improvement in β-cell function remains glucose dependent.

In summary, the addition of sitagliptin to ongoing metformin therapy in patients with type 2 diabetes significantly lowered glucose over 24 h, improved β-cell function and was generally well tolerated.

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