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Short report

Efficacy of vildagliptin and sitagliptin in lowering fasting plasma glucose: Results of a randomized controlled trial

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Abstract

Aim. – This study compared the efficacy of vildagliptin and sitagliptin in lowering fasting plasma glucose (FPG) as single-pill combinations (SPCs) with metformin.

Methods. – The randomized crossover, open-label, active-controlled study design assessed the FPG-lowering abilities of a vildagliptin/metformin (50/1000 mg twice daily) SPC compared with a sitagliptin/metformin (50/1000 mg twice daily) SPC after 2 weeks of treatment in 99 type 2 diabetes patients uncontrolled by stable metformin therapy (1000–2000 mg/day).

Results. – The change in FPG from baseline to day 14 was significantly greater ($P < 0.02$, Wilcoxon) with vildagliptin [–21.9 mg/dL (SD 27.0)] than with sitagliptin [–14.5 mg/dL (SD 23.0)]. After 14 days of treatment, the mean FPG was 137.8 mg/dL (SD 28.5) with vildagliptin and 140.1 mg/dL (SD 26.5) with sitagliptin ($P < 0.05$, Wilcoxon).

Conclusion. – Both of these DPP-4 inhibitors, given as SPCs twice daily with metformin, lowered FPG after 14 days of treatment. However, vildagliptin produced a significantly greater reduction in FPG vs baseline compared with sitagliptin, which may translate into clinical relevance.

Keywords: Type 2 diabetes mellitus; Vildagliptin; Sitagliptin; Fasting plasma glucose; Dipeptidyl peptidase inhibitors

1. Introduction

Dipeptidyl peptidase (DPP)-4 inhibitors such as vildagliptin and sitagliptin improve glycaemic control in patients with type 2 diabetes mellitus (T2DM) primarily by increasing both α- and β-cell sensitivity to glucose [1]. This is achieved by DPP-4 inhibition to prevent degradation of incretins glucagon-like peptide (GLP)-1 and gastric inhibitory polypeptide (GIP) [2]. The prolonged incretin effect results in improved glucose control [3].

Vildagliptin is a substrate enzyme blocker, which prevents incretin inactivation, whereas sitagliptin competitively inhibits DPP-4, which reduces the rate of inactivation. Treatment with vildagliptin therefore leads to prolonged meal-induced increases in GLP-1 and GIP levels [4].

Large-scale reviews evaluating DPP-4 inhibitors have revealed no substantial differences in their glucose-lowering potential when used on their own [5], although some data have indicated differences in fasting plasma glucose (FPG)-lowering potential [6] and glycaemic control [7].

In the present study, FPG was chosen as the parameter to define overnight glucose control, as FPG can be assessed acutely and new steady states achieved within 2 weeks.

This study is the first to directly compare the FPG-lowering potential of vildagliptin and sitagliptin in T2DM patients in the form of single-pill combinations (SPCs) with metformin in a twice-daily regimen.

2. Methods

2.1. Study design and procedures

This study (Clinicaltrials.gov identifier: NCT01398592) applied a crossover, open-label, active-controlled design to

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assess the FPG-lowering abilities of a vildagliptin/metformin (50/1000 mg twice daily) SPC vs a sitagliptin/metformin (50/1000 mg twice daily) SPC after a 2-week treatment in T2DM patients uncontrolled by stable metformin therapy (1000–2000 mg/day).

Patients were randomized after their FPG values were assessed by a central laboratory to receive either the vildagliptin/metformin SPC during period 1 and sitagliptin/metformin SPC during period 2, or vice versa, for 14 days, with a 14-day (up to 28-day) washout period using metformin as monotherapy (1000 mg twice daily). For the analysis, patients' data from both periods (vildagliptin/metformin and sitagliptin/metformin) were pooled, and are henceforth referred to as the vildagliptin and sitagliptin groups, respectively.

2.2. Study patients

Female and male subjects (aged 18–85 years) diagnosed with T2DM at least 3 months prior to screening and stable while taking metformin monotherapy (for at least 4 weeks prior to screening) at 1000–2000 mg/day were eligible to participate. Subjects also had to have HbA_{1c} levels of 7.0–9.5% (with metformin $\geq$ 1000 mg/day but < 2000 mg/day) or of 6.5–9.5% (with metformin 2000 mg/day) at screening, and FPG of 126–270 mg/dL (7–15 mmol/L) at screening and at randomization. Women of childbearing potential not using adequate contraception and pregnant or breastfeeding women were excluded. Further relevant exclusion criteria were FPG $\geq$ 270 mg/dL (15 mmol/L), use of any antidiabetic medication other than metformin within the last 12 weeks, clinically significant renal dysfunction (glomerular filtration rate < 60 mL/min/1.73 m^2), acute metabolic conditions, congestive heart failure, myocardial infarction and hepatic disorders.

2.3. Efficacy and safety endpoints

The two efficacy endpoints of this study were the difference in FPG between vildagliptin and sitagliptin, additionally assessed as the decrease from baseline after 2 weeks and after a missed dose of either drug. The safety evaluation consisted of the adverse events (AEs) and serious AEs (SAEs) observed in each treatment group.

2.4. Statistical analyses

Treatment effects of vildagliptin and sitagliptin on FPG were compared with an analysis of variance (ANOVA) model, using centre, period, patients within centre and treatment as factors for endpoint FPG after 2 weeks. Raw as well as adjusted (least-squares) means were provided as point estimates for the pair wise contrast of treatments. A two-sided 95% confidence interval (CI) and *P*-value for the null hypothesis of no treatment difference were calculated. The significance level was 5% (two-sided). For all pair wise comparisons, a non-parametric (Wilcoxon signed-rank) test was calculated.

The difference in FPG between baseline and day 14 was descriptively analyzed post hoc. The study required 83 patients to achieve a power of 90% with a two-sided significance level of 5%, and a (within-patient) standard deviation (SD) of the difference in FPG of 0.83 and a true effect size of 0.3 [mmol/L]. To compensate for dropouts and other protocol deviations, 100 patients were randomized into the trial.

Table 1
Mean fasting plasma glucose (FPG) and change in FPG after 14 days of treatment.

	Vildagliptin	Sitagliptin
FPG	(*n* = 98)	(*n* = 98)
Mean FPG [mg/dL (SD)]	137.8 (28.52)	140.1 (26.51)
Difference sitagliptin – vildagliptin [95% CI]	2.2 [–1.8; 6.2]	
P-value (ANOVA/Wilcoxon)	0.2788/0.0498	
Change in FPG	(*n* = 98)	(*n* = 98)
Least-squares mean change (mg/dL)	–21.2	–14.2
Difference sitagliptin – vildagliptin [95% CI]	7.0 [0.2; 13.7]	
P-value (ANOVA/Wilcoxon)	0.0425/0.0196	

ANOVA model: FPG; Change in FPG: centre, period, patients within centre and treatment.

2.5. Ethics

The study protocol was approved by the ethics committee of Hessen (Germany) and conducted in accordance with good clinical practice guidelines and the declaration of Helsinki. Written informed consent was obtained from each participant.

3. Results

3.1. Patients' demographic and disease characteristics

A total of 99 patients [mean (SD) age: 61.2 (10.1) years; 35.4% female] with T2DM [mean (SD) time since diagnosis: 6.33 (5.79) years] from 15 centres throughout Germany were enrolled. All patients completed the study except one who discontinued due to an AE (see Safety below).

3.2. Efficacy

Mean baseline FPG values in the vildagliptin and sitagliptin groups were 159.5 mg/dL (SD 31.2) and 154.4 mg/dL (SD 26.6), respectively. Mean FPG after 14 treatment days decreased in both groups, but favored vildagliptin: the change in FPG from baseline to day 14 was significantly greater with vildagliptin [–21.9 mg/dL (SD 27.0)] than with sitagliptin [–14.5 mg/dL (SD 23.0); $P < 0.02$, Wilcoxon]. The final FPG values and change in FPG from baseline to day 14 are presented in Table 1.

The post hoc analysis-defined subgroup with baseline $HbA_{1c} > 7.9\%$ showed a mean change in FPG from baseline in the first treatment period of –27.45 mg/dL (SD 28.93) for vildagliptin ($n = 11$) and –12.09 mg/dL (SD 23.45) for sitagliptin ($n = 11$).