ORIGINAL ARTICLE doi: 10.1111/j.1463-1326.2008.00967.x

Introducing a simplified approach to insulin therapy in type 2 diabetes: a comparison of two single-dose regimens of insulin glulisine plus insulin glargine and oral antidiabetic drugs

M. R. Lankisch,[1] K. C. Ferlinz,[2] J. L. Leahy[3] and W. A. Scherbaum[1,4] on behalf of the Orals Plus Apidra and LANTUS (OPAL) study group

[1]German Diabetes Clinic, German Diabetes Centre, Leibniz Centre for Diabetes Research, Heinrich-Heine-University, Düsseldorf, Germany
[2]sanofi-aventis Deutschland GmbH, Berlin, Germany
[3]Department of Medicine, Division of Endocrinology, Diabetes and Metabolism, University of Vermont College of Medicine, Burlington, VT, USA
[4]Department of Endocrinology, Diabetes and Rheumatology, WHO Collaborating Centre for Diabetes and European Training Centre in Endocrinology and Metabolism, University Hospital Düsseldorf, Düsseldorf, Germany

Aim: To investigate whether the addition of a single bolus of insulin glulisine (glulisine), administered at either breakfast or main mealtime, in combination with basal insulin glargine (glargine) and oral antidiabetic drugs (OADs), provides equivalent glycaemic control in patients with type 2 diabetes, irrespective of the time of glulisine injection.

Methods: A national, multicentre, randomized, open-label, parallel-group study of 393 patients with type 2 diabetes who were suboptimally controlled [haemoglobin A_{1c} (HbA_{1c}) >6.5–9.0% and fasting blood glucose (BG) ≤6.7 mmol/l] on their previous glargine and OAD regimen. A single injection of glulisine was added, either at breakfast or at main mealtime, to their existing therapy.

Results: The per-protocol group (n = 316) showed improved HbA_{1c} (baseline vs. end-point) in the breakfast (7.4 vs. 7.0%; p <0.0001) and main mealtime groups (7.3 vs. 6.9%; p <0.0001). Glulisine given at breakfast was equally effective in controlling HbA_{1c} as glulisine given at the main mealtime [adjusted HbA_{1c} mean difference (95% confidence interval): 0.0481% (–0.115 to 0.211); p <0.0001 for equivalence]. Overall, 30.7% of patients achieved HbA_{1c} ≤6.5% at end-point but slightly more patients met this target in the main mealtime group vs. the breakfast group (33.8 vs. 27.8%; p = NS). This trend continued and was more marked when considering only those patients with HbA_{1c} >7.0% at baseline and who reached HbA_{1c} ≤7.0% at end-point (44.1% overall), with 52.2 and 36.5% for main mealtime and breakfast groups, respectively (p = 0.028). Most postprandial BG values improved within each group, while the number of hypoglycaemias was low and comparable between the two treatment groups.

Conclusions: A single bolus of glulisine, added to glargine and OADs, resulted in significantly improved HbA_{1c} levels, irrespective of whether glulisine was administered at breakfast or at main mealtime. These results may represent a simplified and effective approach to treatment intensification in type 2 diabetes patients.

Keywords: antidiabetic drugs, diabetes mellitus, HbA_{1c}, insulin analogue
Received 22 April 2008; accepted 24 June 2008

Correspondence:
Dr Mark Lankisch, Herzzentrum Wuppertal Medizinische Klinik III Abteilung Kardiologie, Arrenbergerstrasse 20, 42117 Wuppertal, Germany.
E-mail:
mark.lankisch@helios-kliniken.de

Introduction

Tight metabolic control, with glycaemic levels as close as possible to the non-diabetic range, has been demonstrated to reduce diabetes-associated complications in type 2 diabetes [1–3]. The most recent glycaemic goals recommended by the American Diabetes Association (ADA) and the International Diabetes Federation (IDF) are haemoglobin A_{1c} (HbA_{1c}) <7% [4] and <6.5% [5], respectively.

The treatment algorithm recently proposed in a consensus statement [6] states that lifestyle intervention, concurrent with the initiation of metformin therapy, should be implemented as the first step in treating new-onset type 2 diabetes, followed by the addition of one to two other oral antidiabetic drugs (OADs). If lifestyle intervention and full tolerated doses of one or two OADs fail to achieve or sustain glycaemic goals, insulin should be initiated with a single injection of basal insulin such as neutral protamine Hagedorn insulin or a long-acting insulin analogue [e.g. insulin glargine (glargine)], with the aim of achieving fasting blood glucose (FBG) ≤5.5 mmol/l [4,6].

Because of the progressive nature of type 2 diabetes, the majority of patients will eventually require such an insulin-based combination therapy [7–11]. The additional administration of rapid-acting insulin with each meal, a component of intensive insulin therapy, may lower postprandial blood glucose (BG) levels close to the normal range [12–14]. An intensive basal–bolus insulin regimen with multiple daily injections requires the effort of multiple daily self-measurements of BG for the appropriate adjustment of insulin dose. While multiple injection, basal–bolus insulin therapy is considered to be the 'gold standard' and is certainly the best choice advocated by diabetes practitioners, it is, unfortunately, not practicable for all patients. Several barriers to the initiation and intensification of insulin therapy exist, including patient fears regarding hypoglycaemia, weight gain and injections [15,16]. Indeed, the method by which insulin is administered has been demonstrated to impact patient acceptability of insulin therapy and quality of life, and may serve as a key barrier [17]. Therefore, other therapeutic regimens that look to improve glycaemic control should be considered and assessed in clinical trials.

In the present study, we sought to apply an intermediate approach that would be less intensive and more convenient to patients: that is, by adding a single dose of a rapid-acting insulin analogue, such as insulin glulisine (glulisine), to an existing therapy of OADs and once-daily basal insulin, such as glargine. Although this individual 'stepwise' approach towards a full basal–bolus regimen is not new, very little data exist in the literature assessing its efficacy and safety [14,18].

The aim of this study was to investigate the success rate of adding a single injection of glulisine to patients who were suboptimally controlled with glargine plus OADs in terms of attaining HbA_{1c} <6.5%, and the relative efficacy of starting the prandial insulin before breakfast or before the main meal. Our hypothesis was that the above-mentioned simplified approach (combining basal insulin with a single injection of prandial insulin) may not only reduce postprandial glucose (PPG) excursions but also improve HbA_{1c} levels, irrespective of the timing of the single prandial injection.

Methods

Study Population

The study population comprised male and female patients with type 2 diabetes, aged ≥18 years. Patients were required to meet the following inclusion criteria at baseline: treatment with glargine plus OADs for ≥3 months with suboptimal glycaemic control (HbA_{1c} >6.5–9.0% and FBG ≤6.7 mmol/l). Patients needed to be willing and able to perform BG monitoring using a BG meter and complete a patient diary. The first subject was enrolled in June 2004, and the last subject completed the study in September 2006. Informed consent was obtained in writing at enrolment into the study. Patients were excluded if they had type 1 diabetes, more than two FBG values >6.7 mmol/l for five consecutive days before the second visit or an irregular daily routine (e.g. shift worker).

Study Design

This national (Germany), multicentre study comprised a stratified, 1 : 1 randomized, open-label, parallel-group design and consisted of a prescreening phase (up to 2 weeks), a screening phase (between 1 and 3 weeks), a randomized treatment phase (24 weeks) and a follow-up phase (1 week). During the screening period, the main mealtime was individually determined by recording the median of mealtime-specific 2-h postprandial (2h-pp) BG values after breakfast (between 06:00 and 09:00 hours), lunch (between 11:00 and 14:00 hours) and dinner (between 18:00 and 21:00 hours) on three different days. The main mealtime was defined as the maximum of the three medians. Patients were stratified according to their main mealtime at the end of the screening period and before randomization.

Patients were randomized, using an interactive voice response system, to inject glulisine subcutaneously either 0–15 min before breakfast or 0–15 min before their main

mealtime (breakfast, lunch or dinner); this injection time was maintained during the 24-week study treatment phase (table 1). The glulisine dosage was individually titrated, at the investigator's discretion, to the titration goal of 2h-pp BG $\leq$7.5 mmol/l and FBG $\leq$5.5 mmol/l in the absence of hypoglycaemia. The previous treatment regimens of once-daily glargine and OAD(s) were continued as concomitant medication. Patients were allowed to administer a single injection of glargine at any time of the day but at the same time every day; dosage was adjusted according to target FBG $\leq$5.5 mmol/l. The study was conducted in accordance with the Declaration of Helsinki and was reviewed and approved by an independent ethics committee.

Table 1 Strata/randomization groups, baseline demographics and characteristics of patients treated with insulin glargine plus oral antidiabetic drugs, plus insulin glulisine injected either at breakfast or at main mealtime (per-protocol population) and previous oral antidiabetic drug therapy

Number of patients according to randomization group stratum	Total	Breakfast injection	Main mealtime injection
Breakfast (n)	100	51	49
Lunch (n)	80	46	34
Dinner (n)	136	65	71
Total (n)	316	162	154
Demographics and characteristics	**Total (n = 316)**	**Breakfast injection (n = 162)**	**Main mealtime injection (n = 154)**
Age (years)	63.3 ± 9.2	62.7 ± 9.2	64.0 ± 9.1
BMI (kg/m^2)	31.3 ± 5.1	31.6 ± 5.2	30.9 ± 5.0
Sex (%)			
Male	56.6	56.2	57.1
Female	43.4	43.8	42.9
Age at onset of diabetes (years)	52.8 ± 9.9	51.9 ± 9.5	53.7 ± 10.1
Diabetes duration (years)	10.5 ± 7.1	10.6 ± 7.1	10.4 ± 7.0
HbA_{1c} (%)	7.3 ± 0.7	7.4 ± 0.7	7.3 ± 0.7
FPG (mmol/l)*	6.8 ± 2.1	6.7 ± 2.0	7.0 ± 2.1
Duration of antidiabetic treatment (years)	8.4 ± 6.0	8.5 ± 6.5	8.3 ± 5.5
Duration of treatment with insulin (years)	2.1 ± 2.1	2.3 ± 2.5	1.9 ± 1.6
Concomitant antidiabetic medication (ATC class)	**Total**	**Breakfast injection**	**Main mealtime injection**
Sulphonamides, urea derivatives (n)	205	98	107
Biguanides (n)	191	96	95
Other oral blood glucose lowering drugs (n)	45	28	17
Oral blood glucose lowering drugs (n)	35	23	12
Thiazolidinediones (n)	4	2	2

ATC, anatomical therapeutic chemical; BMI, body mass index; FPG, fasting plasma glucose; HbA_{1c}, haemoglobin A_{1c}.
*FPG levels were measured by a central laboratory after randomization [when fasting blood glucose (FBC) $\leq$6.7 mmol/l was determined]. The slightly higher values in the table reflect the fact that FPG values typically exceed FBG levels by approximately 10–15%. Data are mean ± s.d. unless otherwise stated.

Study Objectives

The primary objective was to show two-sided equivalence of glargine plus glulisine administered at breakfast vs. glargine plus glulisine given at the main meal, in terms of baseline to end-point change in HbA_{1c} levels. Secondary objectives included a comparison of efficacy between the two treatment arms with regard to response rate (HbA_{1c} $\leq$6.5%) at end-point; baseline to end-point changes in 2h-pp BG; baseline to end-point changes in eight-point BG profiles and baseline to end-point changes in insulin doses. Additionally, subgroup analyses were conducted for those patients with HbA_{1c} >7.0% at baseline.

The eight-point 24-h BG profile included BG measurement in the morning (FBG), 2 h after breakfast, at lunch, 2 h after lunch, at dinner, 2 h after dinner, at bedtime and at 03:00 hours (nocturnal). Safety analyses included the incidence of hypoglycaemic events and adverse events (AEs), including treatment-emergent AEs (TEAEs) and changes in body weight and body mass index (BMI). Hypoglycaemia was confirmed by BG measurement $\leq$3.3 mmol/l.

Statistical Analyses

Descriptive analysis was performed for all data. The full analysis set (FAS) comprised all randomized patients who had received $\geq$1 dose of study insulin, and provided both baseline and at least one on-treatment primary or secondary efficacy variable. The per-protocol set comprised all FAS patients without any major protocol violations and, based on the results of a blinded 'data monitoring' of 158 subjects (recalculation of the variance), a total of 296 patients was calculated to be required for the per-protocol analysis to achieve equivalence. The safety analysis set consisted of all patients who were treated with study glulisine.

The primary efficacy variable was the change in HbA_{1c} from baseline to end-point for each patient. The primary analysis tested the hypothesis of equivalence of the two glulisine therapy regimens (injection at breakfast vs. injection at main mealtime) in the per-protocol population for the primary efficacy variable at the two-sided level of $\alpha = 0.05$ and with a predefined margin for equivalence at $\varepsilon = 0.4\%$ using the confidence interval (CI) inclusion method (95% CI for difference of HbA_{1c} change should be within −0.4 to 0.4%). Adjusted means for HbA_{1c} change from baseline were calculated using an analysis of

covariance model, with therapy group and randomization stratum as fixed factors and baseline HbA_{1c} values as covariate. 95% CI were calculated for changes in HbA_{1c}.

In addition, BG values were analysed using Student's *t*-test including 95% CI. The number of hypoglycaemic events per patient and per patient-year was calculated and summarized as a quantitative variable. Comparisons between treatment groups were performed using an analysis of variance model.

Results

Study Population

A total of 395 patients were randomized to receive glargine and OADs with a breakfast (n = 196) or main meal (n = 197) injection of glulisine. Two patients, one from each group, were accidentally randomized after failing to meet the inclusion criteria at screening but did not receive glulisine injections and were subsequently excluded from the study. The majority of patients (177 in each group) completed the study; a total of 19 and 20 patients in the breakfast and main meal glulisine groups, respectively, withdrew from the study. For both the breakfast and main meal group, the most frequently reported reason for withdrawal was 'patient not wishing to continue' (11 and 10 patients, respectively).

A total of 198 major protocol deviations occurred in 77 patients (breakfast group: 34; main meal group: 43); these patients were, therefore, excluded from the per-protocol analysis set. The main protocol deviations were a failure to have FBG $\leq$6.7 mmol/l for at least three measurements (n = 73) and allocation to the wrong stratum (n = 42). Thus, a total of 316 patients comprised the per-protocol treatment group; all results included here, except the safety data, comprise the per-protocol analysis set.

Patient baseline characteristics and demographics, including glycaemic control, duration of diabetes and previous treatment regimens [including concomitant OAD(s)], were comparable between the two treatment arms (per-protocol group; table 1).

The time taken to achieve the glulisine titration goal (2h-pp BG $\leq$7.5 mmol/l) for the first time was 34.0 $\pm$ 34.6 days overall and was 33.9 $\pm$ 34.4 days and 34.0 $\pm$ 35.0 days in the breakfast and main meal glulisine groups, respectively.

Efficacy

Changes in HbA_{1c} Levels

Baseline to end-point HbA_{1c} improvements were observed in the overall per-protocol population and in both glulisine injection arms. Mean $\pm$ s.d. for HbA_{1c} improved from 7.32 $\pm$ 0.70 to 6.99 $\pm$ 0.83% overall, from 7.35 $\pm$ 0.71 to 7.03 $\pm$ 0.79% in the breakfast and from 7.29 $\pm$ 0.69 to 6.94 $\pm$ 0.87% in the main meal glulisine injection groups ($p < 0.0001$ vs. baseline for all) (figure 1). Similarly, the adjusted means in baseline to end-point change in HbA_{1c} were comparable between the breakfast (−0.31%) and main mealtime (−0.36%) glulisine injection groups.

The subgroup of patients with HbA_{1c} >7.0% at baseline (n = 188), with similar numbers of patients in the breakfast (n = 96) and main mealtime (n = 92) groups, showed an even more pronounced relative improvement in HbA_{1c} from baseline to end-point. The adjusted means in baseline to end-point change in HbA_{1c} for the overall, breakfast and main meal glulisine injection groups were −0.5, −0.5 and −0.6%, respectively ($p < 0.0001$ vs. baseline for all).

The primary efficacy analysis performed on the per-protocol analysis set demonstrated significant therapeutic equivalence of the two study glulisine treatment regimens. The breakfast treatment regimen differed from the main mealtime treatment arm by 0.0481% (95% CI: −0.115 to 0.211) in the effect on absolute HbA_{1c} change from baseline to end-point ($p < 0.0001$ for equivalence). As the 95% CI for the treatment group difference lies within the predefined range equivalence

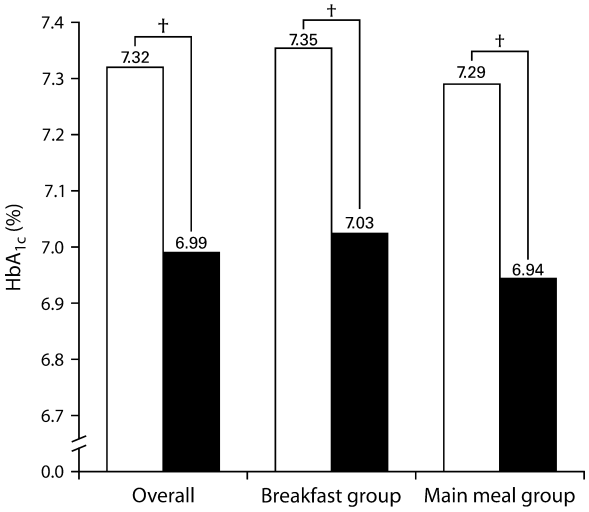

Fig. 1 Change in HbA_{1c} (%) in the overall group and within each treatment arm. †$p < 0.0001$ within each group vs. baseline. HbA_{1c} at baseline (□) and end-point (■) in the per-protocol analysis set. Predefined margin for equivalence between the breakfast and main mealtime groups at $\varepsilon = 0.4\%$, ΔHbA_{1c} change (95% CI) = 0.048 (−0.115 to 0.211).

region [two-sided (−0.4 to 0.4%)], the two treatment groups were considered to be equivalent.

Equivalence was also demonstrated, irrespective of an intrinsic study design bias towards patients who were stratified to the breakfast stratum and who, therefore, injected glulisine at breakfast independent of their randomization; that is, the 95% CI of difference of adjusted ΔHbA_{1c} of patients who injected glulisine 'at main meal' vs. those who administered glulisine 'not at main meal' was also entirely within the predetermined equivalence margin (data not shown).

There was a tendency towards a slightly higher proportion of patients achieving $HbA_{1c} \leq 6.5\%$ at end-point (30.7% overall) who were administering glulisine injections at main mealtime (33.8%) compared with those injecting at breakfast (27.8%; p = NS) (table 2). Moreover, this trend continued and was more pronounced for the subgroup of patients with $HbA_{1c} > 7.0\%$ at baseline (n = 188). Therefore, although 44.1% overall in this subgroup achieved $HbA_{1c} \leq 7.0\%$ at end-point, a significantly higher proportion of patients achieved this goal in the main meal vs. breakfast group (52.2 vs. 36.5%; p = 0.028).

Blood Glucose

Overall, circadian BG control was comparable between the two glulisine treatment regimens. Mean daily BG decreased from baseline to end-point in both the breakfast (8.3 ± 1.5 to 7.7 ± 1.3 mmol/l) and main mealtime (8.3 ± 1.4 to 7.6 ± 1.5 mmol/l) injection groups. Over the course of the study, baseline to end-point FBG levels increased in both the breakfast (6.0 ± 0.8 to 6.7 ± 1.4 mmol/l) and main mealtime (5.9 ± 0.8 to 6.3 ± 1.4 mmol/l) glulisine arms. However, central laboratory data demonstrated that fasting plasma glucose (FPG) levels remained stable throughout the study period (data not shown). By contrast, eight-point BG profiles over 24 h were similar between the two treatment groups at baseline.

Improvements in BG control were similar between the two treatment groups, irrespective of whether the main mealtime injection was administered at breakfast or at main meal (figure 2A, B). Moreover, in the breakfast arm, BG levels at end-point were not only significantly lower in the postprandial period immediately following breakfast but also extended to the prelunch period (figure 2A). As would be expected, better BG control was achieved in the circadian period following the individual time of study glulisine injection (figure 2C–E). Group analyses also revealed that glycaemic control was equivalent in both groups of patients who injected glulisine at breakfast, irrespective of whether breakfast was their main meal (data not shown).

Table 2 Responder rates of patients who achieved $HbA_{1c} < 6.5\%$ and $HbA_{1c} \leq 7.0\%$ at the end of the study

	Total	Breakfast injection	Main mealtime injection
Patients with $HbA_{1c} > 6.5$–9.0% at screening (n)	316	162	154
Patients who achieved $HbA_{1c} \leq 6.5\%$ at end-point, n (%)	97 (30.7)	45 (27.8)	52 (33.8)
Patients with $HbA_{1c} > 7.0\%$ at baseline (n)	188	96	92
Patients with $HbA_{1c} > 7.0\%$ at baseline achieving $HbA_{1c} \leq 7.0\%$ at end-point, n (%)	83 (44.1)	35 (36.5)*	48 (52.2)*

HbA_{1c}, haemoglobin A_{1c}.
*p = 0.028 for differences between the two treatment groups.

Insulin Doses

The mean ± s.d. glulisine dose increased between study start and end-point in both the breakfast [4.6 ± 1.9 to 11.2 ± 6.4 U/day (range at end-point: 2–34 U/day)] and the main mealtime [5.0 ± 2.3 to 12.0 ± 7.0 U/day (range at end-point: 2–40 U/day)] glulisine injection groups. However, the mean ± s.d. glargine dose increased only slightly from baseline to end-point in the breakfast group (30.9 ± 24.9 to 32.4 ± 28.8 U/day) and remained unchanged in the main mealtime group (26.5 ± 13.2 to 26.9 ± 13.2 U/day), as reflected by the nearly constant FBG/FPG levels over the study period.

Body Weight and BMI

Body weight was virtually unchanged from baseline to end-point for both the breakfast [89.7 ± 16.6 to 90.7 ± 16.5 kg (+1.0 kg)] and the main mealtime [89.4 ± 17.6 to 90.3 ± 17.6 kg (+0.9 kg)] glulisine injection groups. Similarly, BMI remained stable in both treatment groups over the study period [breakfast injection: 31.5 ± 5.2 to 31.8 ± 5.2 kg/m^2 (+0.4 kg/m^2) and main mealtime injection: 30.8 ± 5.0 to 31.1 ± 5.0 kg (+0.3 kg/m^2)].

Safety

Most types of hypoglycaemic events occurred at a similar frequency in the two treatment groups; very few of these were classified as being severe. Overall, confirmed hypoglycaemia occurred at similar rates in the breakfast (n = 67;

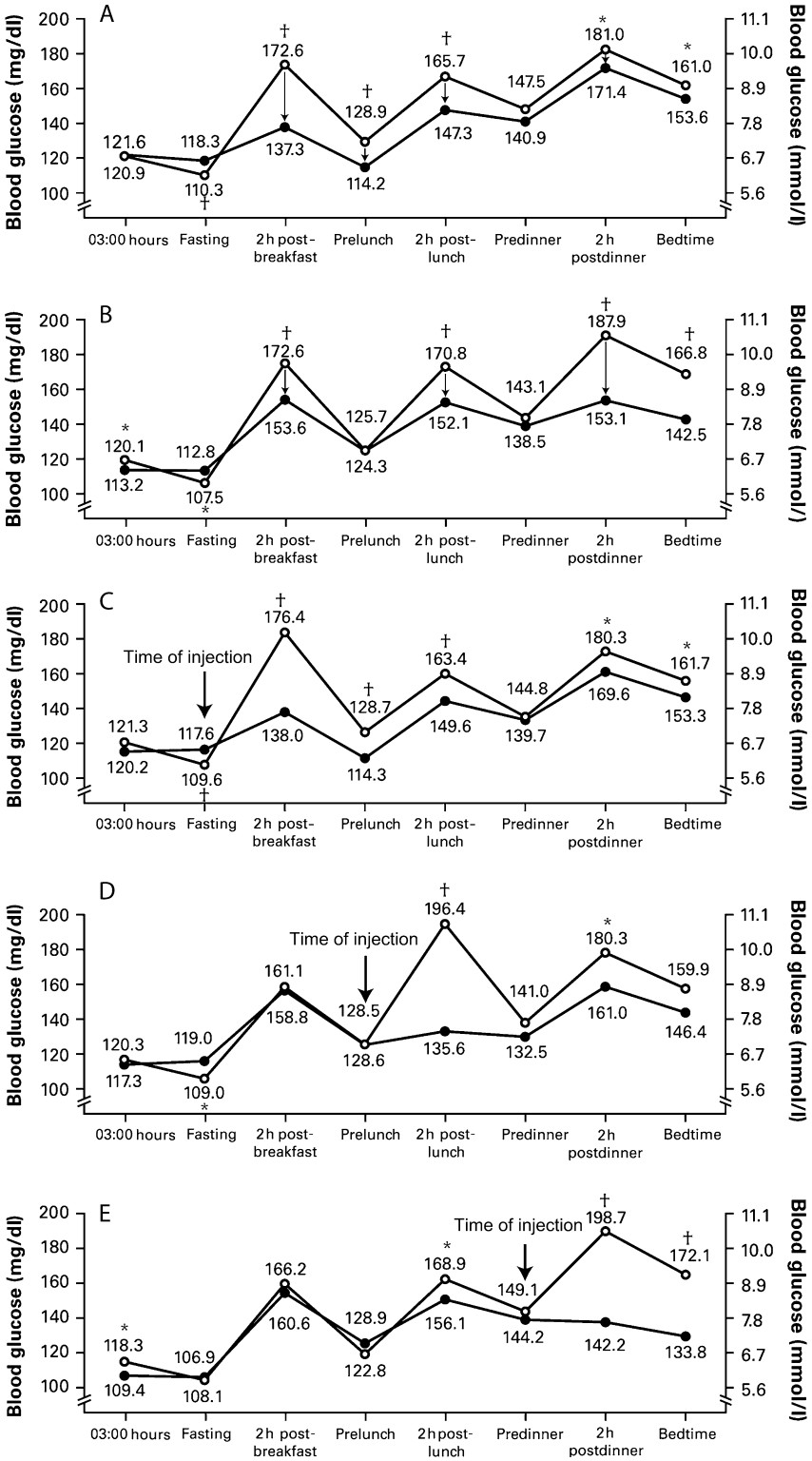

Fig. 2 Eight-point blood glucose profiles for glulisine injection at breakfast (A) and main mealtime (B); and according to the glulisine injection time at the main mealtime at breakfast (C); lunch (D) and dinner (E) (independent of strata and randomization group). Blood glucose at baseline (○) and end-point (●) in the per-protocol analysis set. *$p < 0.05$; †$p < 0.0001$ vs. baseline.

34.2%) and the main mealtime (n = 73; 37.1%) injection groups (2.72 ± 6.11 vs. 3.69 ± 10.96/patient-years; p = 0.314). The total rate of confirmed severe hypoglycaemic events was low in the breakfast (n = 1; 0.5%) vs. the main mealtime (n = 4; 2.0%) injection groups (0.01 ± 0.15 vs. 0.04 ± 0.30 events/patient-years; p = 0.191). There was no statistically significant difference in the incidence of confirmed nocturnal hypoglycaemia in patients injecting glulisine at main mealtime (n = 24; 12.2%) vs. breakfast (n = 16; 8.2%) (0.52 ± 2.19 vs. 0.27 ± 0.99 events/patient-years; p = 0.176).

The proportion of patients experiencing TEAEs was comparable between the two treatment regimens. The overall incidence was 169 TEAEs in 87 (44.4%) of the patients treated at breakfast, and 161 TEAEs in 92 (46.7%) of the patients treated at main mealtime. The majority of TEAEs were not considered to be treatment related; two (1.0%) patients treated at breakfast and four (2.0%) patients treated at main mealtime reported TEAEs, which were possibly related to treatment medication. Possibly related TEAEs included weight increase in two patients and serious hypoglycaemia in one patient. Withdrawal because of a TEAE occurred at low rates: three (1.5%) patients treated at breakfast and six (3.1%) patients treated at main mealtime withdrew from the study because of a TEAE.

Discussion

The results from this study indicate that a single daily injection of glulisine, in combination with glargine and OADs, improves HbA_{1c} and PPG levels in type 2 diabetes patients with suboptimal glycaemic control. Furthermore, this simplified approach was effective in controlling glycaemia irrespective of whether glulisine was administered at breakfast or at the main mealtime, as demonstrated by equivalent improvements in HbA_{1c} levels, and with equivalent risk of hypoglycaemia. These data provide evidence of the efficacy and safety for a stepwise approach to intensive insulin therapy in a clinical study.

An important finding of this study was that 30% of all patients achieved an HbA_{1c} target of $\leq$6.5%, while no statistically significant difference was observed between the two treatment arms. For patients with HbA_{1c} >7.0% at baseline, 44% achieved HbA_{1c} $\leq$7.0% at study end and, although significantly more patients reached this HbA_{1c} target in the main meal group compared with the breakfast group, this should be interpreted with caution owing to the small numbers overall and within each treatment arm. Nonetheless, injecting glulisine at the main meal should be considered for patients who clearly show a predominant daily main mealtime or for those who regularly skip breakfast. Although the 2h-pp BG value may not accurately determine the largest meal of the day owing to patient dietary variations and does not necessarily compare PPG with premeal BG levels, it does provide a simple method for physicians to decide at which meal to begin prandial treatment.

Both FBG and PPG contribute to HbA_{1c} levels and, therefore, inadequate control of either parameter will have a negative impact on overall glycaemic control. Normalizing FBG is a long-established goal of basic glycaemic control in the treatment of type 2 diabetes. However, evidence suggests that PPG levels are the major contributor to overall glycaemic control in patients with well-to-moderately controlled (HbA_{1c} <7%) type 2 diabetes [19]. Furthermore, a recent study demonstrated that deterioration of glucose homeostasis progresses from loss of PPG control in early type 2 diabetes to deteriorating fasting glucose control with more advanced type 2 diabetes [20].

Indeed, recent guidelines stress the importance of early and aggressive intervention in the treatment of type 2 diabetes, with the rapid addition of medications and early transition to new regimens such as insulin therapy, when target glycaemic goals are not achieved or sustained [6]. The intensification of a basal insulin (plus OAD) regimen by the addition of a single bolus insulin injection would be expected to resemble more closely normal physiological insulin secretion patterns [21], with a potentially reduced risk of hypoglycaemia when compared with a traditional intensive basal–bolus regimen. Detailed studies addressing this important issue are ongoing.

Furthermore, the titration of prandial insulin doses to a single target meal would be expected to facilitate the attainment of glycaemic goals set by the ADA [22] and the IDF [5], and supported by a recent consensus statement [6], and also enable further addition of prandial insulin at non-target meals.

Of note, it is well documented that patients with diabetes who participate in clinical trials may experience improvements without any therapeutic intervention [23], and we acknowledge that the lack of a control arm in the study makes it difficult to assess the net effect of the addition of once-daily glulisine. A moderate decrease in HbA_{1c} of approximately equal magnitude was seen in the overall group and in both treatment arms between the time of screening and randomization at baseline (up to 3 weeks before baseline/randomization). This improvement in HbA_{1c}, before the addition of once-daily glulisine, is in accordance with recently published data [23] and, thus, may be at least partially ascribed to the Hawthorne effect. By contrast, the

ΔHbA_{1c} observed from baseline to end-point may be, for the most part, a therapy-driven effect, although an additional study effect component cannot be excluded.

The approach of adding a single injection of prandial insulin to an existing regimen of basal insulin plus OAD, as described in our trial, is not new and many diabetologists in clinical practice advocate this method, particularly in patients with poor compliance. Indeed, it is perhaps even predictable that the addition of a third agent, glulisine, to glargine and OADs can only improve glycaemic control. Nonetheless, there are currently no clinical trial data available regarding the extent of improvement that can be expected from this stepwise approach to treatment intensification, and our study goes some way to addressing this issue.

In conclusion, the results of our study suggest that a simplified basal–bolus regimen with a single injection of rapid-acting insulin analogue before breakfast or before the main mealtime may be used for treatment intensification in patients with type 2 diabetes who are not optimally controlled on glargine plus OADs. Further studies are currently ongoing to assess formally the benefit of adding further doses of prandial insulin.

Acknowledgements

This study was sponsored by sanofi-aventis. Editorial support for this article was provided by the Global Publications Group of sanofi-aventis.

References

1 UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; **352:** 837–853.

2 UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; **352:** 854–865.

3 Ohkubo Y, Kishikawa H, Araki E *et al.* Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract 1995; **28:** 103–117.

4 American Diabetes Association. Standards of medical care in diabetes – 2007. Diabetes Care 2007; **30:** S4–S41.

5 International Diabetes Federation. Global Guidelines for Type 2 Diabetes. Brussels: 2005.

6 Nathan DM, Buse JB, Davidson MB *et al.* Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2006; **29:** 1963–1972.

7 DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. JAMA 2003; **289:** 2254–2264.

8 Hirsch IB. Insulin analogues. N Engl J Med 2005; **352:** 174–183.

9 Wright A. Sulfonylurea inadequacy: efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the UK. Prospective Diabetes Study (UKPDS 57). Diabetes Care 2002; **25:** 330–336.

10 Nelson SE, Palumbo PJ. Addition of insulin to oral therapy in patients with type 2 diabetes. Am J Med Sci 2006; **331:** 257–263.

11 Kuritzky L. Addition of basal insulin to oral antidiabetic agents: a goal-directed approach to type 2 diabetes therapy. MedGenMed 2006; **8:** 34.

12 Hirsch IB, Bergenstal RM, Parkin CG, Wright E Jr, Buse JB. A real-world approach to insulin therapy in primary care practice. Clin Diabetes 2005; **23:** 78–86.

13 Leahy JL. Basal-prandial insulin therapy: scientific concept review and application. Am J Med Sci 2006; **332:** 24–31.

14 Monnier L, Colette C. Addition of rapid-acting insulin to basal insulin therapy in type 2 diabetes: indications and modalities. Diabetes Metab 2006; **32:** 7–13.

15 Cryer P, Childs BP. Negotiating the barrier of hypoglycemia in diabetes. Diabetes Spectr 2002; **15:** 20–27.

16 Korytkowski M. When oral agents fail: practical barriers to starting insulin. Int J Obes Relat Metab Disord 2002; **26:** S18–S24.

17 Meece J. Dispelling myths and removing barriers about insulin in type 2 diabetes. Diabetes Educ 2006; **32:** 9S–18S.

18 Raccah D, Bretzel RG, Owens D, Riddle M. When basal insulin therapy in type 2 diabetes mellitus is not enough–what next? Diabetes Metab Res Rev 2007; **23:** 257–264.

19 Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA(1c). Diabetes Care 2003; **26:** 881–885.

20 Monnier L, Colette C, Dunseath GJ, Owens DR. The loss of postprandial glycemic control precedes stepwise deterioration of fasting with worsening diabetes. Diabetes Care 2007; **30:** 263–269.

21 Bethel MA, Feinglos MN. Basal insulin therapy in type 2 diabetes. J Am Board Fam Pract 2005; **18:** 199–204.

22 American Diabetes Association. Standards of medical care in diabetes–2006. Diabetes Care 2006; **29** (Suppl. 1): S4–S42.

23 Gale EA, Beattie SD, Hu J, Koivisto V, Tan MH. Recruitment to a clinical trial improves glycemic control in patients with diabetes. Diabetes Care 2007; **30:** 2989–2992.