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Optimal timing of injection of once-daily insulin glargine in people with Type 1 diabetes using insulin lispro at meal-times

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Abstract

Aims To compare blood glucose control when insulin glargine is given at lunch-time, dinner-time, and bed-time in people with Type 1 diabetes using insulin lispro at meal-times.

Methods In this 16-week, three-way, cross-over study, 23 people with Type 1 diabetes were randomized to insulin glargine injection at lunch-time (L) [mean 12.37 ± 00.34 (± SD) h], dinner-time (D) (18.12 ± 00.40 h), or bed-time (B) (22.29 ± 00.40 h), each plus meal-time insulin lispro. Each 4-week treatment period concluded with a 24-h inpatient metabolic profile.

Results Insulin doses, HbA_{1c}, and fructosamine concentration did not differ between treatment periods. Pre-breakfast self-monitored blood glucose (SMBG) concentration was higher with injection of glargine at lunch-time than at other times [L: 9.2 ± 0.3 (± SE) vs. D: 8.2 ± 0.3 or B: 8.0 ± 0.3 mmol/l, $P = 0.016$], as probably was pre-lunch SMBG (L: 8.6 ± 0.7 vs. D: 6.4 ± 0.7 or B: 6.4 ± 0.8 mmol/l, $P = 0.051$). Pre-dinner SMBG level was higher with dinner-time glargine than other injection times (D: 9.4 ± 0.9 vs. L: 4.9 ± 0.9 or B: 7.4 ± 1.1 mmol/l, $P = 0.007$). For 22.00 to 02.00 h, mean inpatient plasma glucose concentration was higher with injection of glargine at bed-time than other times (B: 9.1 ± 0.6 vs. L: 7.8 ± 0.6 or D: 6.7 ± 0.6 mmol/l, $P = 0.023$). Plasma free insulin concentration was lower at the end of the afternoon with dinner-time glargine than other injection times (D: 11.5 ± 1.4 vs. L: 20.2 ± 1.3 or B: 16.5 ± 1.3 mU/l, $P < 0.001$). Frequency of hypoglycaemia was not different, but timing of hypoglycaemia differed between treatment periods.

Conclusions Blood glucose levels rise around the time of injection of insulin glargine whether given at lunch-time, dinner-time or bed-time. Bed-time injection leads to hyperglycaemia in the early part of the night which is improved by giving insulin glargine at lunch-time or dinner-time.

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Keywords glargine, insulin glargine, timing, Type 1 diabetes

Abbreviations B, bed-time; D, dinner-time; DTSQ, Diabetes Treatment Satisfaction Questionnaire; L, lunch-time; SMBG, self-monitored blood glucose.

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Introduction

Early pharmacokinetic studies with insulin glargine in healthy volunteers reported a duration of action of up to 30 h [1,2]. However, the duration was significantly shorter in 20% of the study population [1]. Later studies in people with Type 1 diabetes also reported a substantially shorter duration of action, with mean plasma glucose levels in a euglycaemic clamp study rising from approximately 16 h after insulin glargine injection [3]. The mean duration of action of insulin glargine for the whole population of that study was 20.5 h.

Whilst insulin glargine and rapid-acting insulin analogues have complementary benefits when used in combination [4], the brief duration of action of rapid-acting analogues may exacerbate relative insulin deficiency around the time of injection of insulin glargine.

There is a 3–6-h delay from injection until insulin glargine reaches a plateau of metabolic effect [1–3,5]. In the pivotal clinical trials, insulin glargine was injected at bed-time [6–9]. However, this exacerbates the problem of relative insulin deficiency at the time of injection, as little rapid-acting insulin is available by this time [10]. Thus, delay of the insulin glargine injection for any time after dinner would be expected to result in relative hyperglycaemia 3–6 h later.

Injecting insulin glargine earlier might improve this situation. However, blood glucose escape might still occur before the injection if the duration of action of insulin glargine is less than 24 h. A study comparing insulin glargine injection at dinner-time, bed-time and breakfast-time in people with Type 1 diabetes showed rising self-monitored blood glucose levels (SMBG) around the time of injection in all groups [11].

The aim of the present study was to compare blood glucose control, particularly in the early part of the night, with injection of insulin glargine at lunch-time, dinner-time, and bed-time in people with Type 1 diabetes using a rapid-acting insulin analogue at meal-times.

Participants and methods

A 16-week, single-centre, open, randomized, three-way cross-over clinical trial in people with Type 1 diabetes managed with a multiple insulin injection regimen was conducted. The study was approved by the local ethics committee, and written informed consent was obtained from all participants.

Participants

Twenty-four people were recruited. One did not fulfil study inclusion criteria, thus 23 were randomized (13 male). Three withdrew during the study: one through perception of deteriorating hyperglycaemia, one felt unable to complete all 24-h inpatient profiles, and one suffered an episode of severe hypoglycaemia as a result of an insulin dose error. Twenty thus completed the study.

The people recruited were men and women aged 18–65 years with Type 1 diabetes and no previous experience of insulin glargine, who had been using a multiple insulin injection regimen for at least 1 year, and who had a random C-peptide concentration ≤ 0.18 nmol/l and HbA_{1c} 6.0–9.5% (non-diabetic reference range < 5.9%). Women of childbearing potential had to be using adequate contraception. People with proliferative retinopathy, recurrent severe hypoglycaemia, impaired hepatic or renal function, or who worked night shifts were excluded from the study. Participants were age 39.3 ± 10.6 (± SD) years, had body weight of 80.6 ± 17.2 kg, body mass index (BMI) of 27.8 ± 4.2 kg/m^2, and baseline HbA_{1c} 8.3 ± 0.9%. They had had diabetes for 21.1 ± 10.8 years and had used multiple insulin injections for 8.9 ± 4.8 years.

Design

After a 2-week screening period during which previous insulin therapy was continued, participants commenced insulin glargine (Lantus®; Aventis Pharma, Frankfurt, Germany) and meal-time insulin lispro (Humalog®; Lilly, Indianapolis, IN, USA). People were requested to measure blood glucose concentration before breakfast daily and perform an 8-point 24-h SMBG profile each week (pre-meal, post-meal, bed-time, and 03.00 h) using the Medisense® Optium™ blood glucose meter (Abbott Laboratories, Bedford, MA, USA). The first 4 weeks consisted of a dose titration run-in period, during which insulin glargine was injected at bed-time, and all insulin doses were titrated at weekly study visits according to target SMBG levels.

After 4 weeks, people were randomized by a third party (concealed randomization) to insulin glargine injection at lunch-time (L), dinner-time (D) or bed-time (B), using a Williams cross-over design to define the treatment sequence for the entire study. The commencing insulin doses for all treatment periods were defined at randomization. Study visits occurred weekly during each 4-week treatment period. At each consultation, SMBG levels, episodes of hypoglycaemia and insulin doses were reviewed and insulin glargine and insulin lispro doses were titrated using target blood glucose levels that were identical for each treatment period: pre-breakfast and preprandial 4.0–6.5 mmol/l, and postprandial 4.0–7.5 mmol/l, in the absence of hypoglycaemia.

Treatment satisfaction was assessed at the end of each treatment period using the Diabetes Treatment Satisfaction Questionnaire (DTSQ) [12].

24-h inpatient metabolic profile

At the end of each 4-week treatment period, participants attended at 17.00 h for a 24-h inpatient metabolic profile. Blood was taken using a polytetrafluoroethylene (PTFE) intravenous catheter (Vasofix®, Braun, Melsungen, Germany) for measurement of plasma glucose and plasma free insulin concentration every 30 min at meal-times (from meal-time –0.5 to +2 h) and every hour at other times, except during the period 22.00 to 02.00 h during which blood was taken to measure plasma glucose concentration every 30 min. Dinner was given at 18.00 h and lunch at 12.30 h. Breakfast was given at the participants' usual time. A snack was given before bed in all studies, without rapid-acting insulin. Nutritional intake was kept identical for the three studies by assessment of intake at the first study. Insulin lispro was given immediately before meals and insulin

glargine as determined by study period, both at the doses used in the 5 days preceding the inpatient profile.

At the end of each 24-h profile participants moved to the next randomized treatment period.

Hypoglycaemia

Hypoglycaemia was classified as any-time symptomatic (appropriate symptoms confirmed by SMBG concentration < 2.8 mmol/l and self-treated), any-time severe (requiring third-party assistance), and nocturnal (from bed-time until measurement of pre-breakfast blood glucose concentration).

Biochemical analysis

Blood was collected for plasma glucose analysis into fluoride oxalate tubes during the 24-h inpatient studies and immediately centrifuged at 4 °C for 5 min. Plasma glucose concentration was immediately determined using the glucose oxidase method (YSI model 2300 Stat Plus, Yellow Springs Instrument, Yellow Springs, OH, USA). Blood was also collected into lithium–heparin tubes for measurement of plasma free insulin concentration. The sample was immediately centrifuged at 4 °C for 5 min, 0.5 ml of plasma was pipetted into 0.5 ml polyethyleneglycol buffer, vortexed and then centrifuged at 4 °C for 30 min. The supernatant was frozen at −40 °C. Plasma free insulin concentration was determined by immuno-chemiluminometric assay (Molecular Light Technology Research, Cardiff, UK). HbA_{1c} was measured by HPLC.

Statistical analysis

The primary efficacy assessment was mean inpatient plasma glucose concentration at 22.00–02.00 h. Secondary efficacy assessments included 8-point 24-h SMBG levels, pre-breakfast SMBG concentration, 24-h inpatient plasma glucose and free insulin levels, hypoglycaemia, insulin doses, HbA_{1c} and fructosamine concentration at end of the treatment period, and treatment satisfaction (from the DTSQ).

Mean self-monitored pre-breakfast blood glucose concentration was determined from levels on the final 14 days of each treatment period. Self-monitored 8-point 24-h blood glucose profiles were determined from the final two profiles in the last 2 weeks of each treatment period. Within-person variability of pre-breakfast SMBG concentration was determined using the SD of pre-breakfast blood glucose levels in the final 2 weeks of the treatment period.

A three-way analysis of variance (ANOVA) model, including patient, treatment and period effects was used to compare all variables between treatment periods. Where a statistically significant three-way treatment effect was detected ($P < 0.05$), two-way ANOVA was performed to assess pair-wise comparison between treatment periods, using the same model. Descriptive data alone were used to compare the number of people reporting hypoglycaemia, and the timing of hypoglycaemia.

Nineteen people were required to demonstrate a 1.0-mmol/l difference in mean inpatient plasma glucose concentration at 22.00–02.00 h, assuming a standard deviation for this measure of 1.5 mmol/l based on the results of previous studies, a power of 80%, and a type 1 error of $\alpha = 5\%$.

All data are expressed as mean ± SE unless otherwise stated.

Results

Insulin doses and injection times

Insulin glargine was given at 12.37 ± 00.34, 18.12 ± 00.40, and 22.29 ± 00.40 h (± SD) with lunch-time, dinner-time and bed-time injection, respectively. Insulin glargine doses did not differ between treatment groups (L: 30.2 ± 0.6 vs. D: 28.6 ± 0.6 and B: 28.8 ± 0.6 U/day, NS). Similarly, insulin lispro and total daily insulin doses did not differ between groups.

HbA_{1c} and fructosamine concentration

There was no difference in HbA_{1c} (L: 6.9 ± 0.1, D: 7.0 ± 0.1 and B: 6.8 ± 0.1%, NS), or fructosamine concentration (L: 2.9 ± 0.1, D: 2.8 ± 0.1, and B: 2.8 ± 0.1 mmol/l, NS) at the end of the 4-week treatment period between treatment groups.

Mean pre-breakfast blood glucose concentration

Pre-breakfast SMBG concentration was higher with injection of glargine at lunch-time than other times (L: 9.2 ± 0.3 vs. D: 8.2 ± 0.3, or B: 8.0 ± 0.3 mmol/l, $P = 0.016$). In pair-wise comparison pre-breakfast SMBG concentration was higher with lunch-time glargine compared with both dinner- ($P = 0.033$) and bed-time injection ($P = 0.017$). Within-person variability of pre-breakfast SMBG concentration was equal in the three treatment periods (3.9 ± 0.2, 3.9 ± 0.2 and 3.9 ± 0.3 mmol/l).

Eight-point 24-h self-monitored blood glucose profiles

Pre-dinner SMBG concentration was higher with dinner-time glargine than other injection times (D: 9.4 ± 0.9 vs. L: 4.9 ± 0.9 or B: 7.4 ± 1.1 mmol/l, $P = 0.007$) (Fig. 1). In pair-wise comparison, pre-dinner SMBG concentration was higher with dinner-time glargine compared with lunch-time ($P = 0.008$) but not bed-time injection ($P = 0.069$).

Pre-lunch SMBG concentration was probably higher with injection of glargine at lunch-time than other times (L: 8.6 ± 0.7 vs. D: 6.4 ± 0.7 or B: 6.4 ± 0.8 mmol/l, $P = 0.051$). In pair-wise comparison, pre-lunch SMBG concentration was higher with lunch-time insulin glargine compared with both dinner- ($P = 0.046$) and bed-time injection ($P = 0.050$).

In all treatment periods, blood glucose concentration rose around the time of injection of insulin glargine (Fig. 1).

Twenty-four-hour inpatient plasma glucose profile

Plasma glucose concentration 3–5.5 and 8–10 h after dinner (approximately 21.15 to 23.45 h and 02.15 to 04.15 h, respectively) was significantly higher with bed-time insulin glargine compared with the other groups (Fig. 2). Mean plasma glucose concentration at 22.00–02.00 h (4–8 h after dinner), the

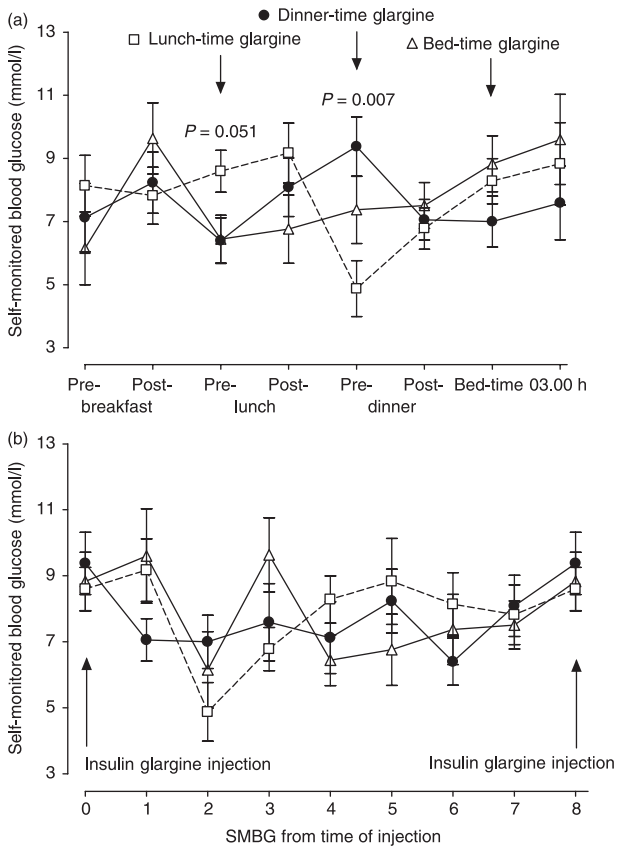

Figure 1 Eight-point 24-h self-monitored blood glucose levels [mean ± SE (mmol/l)] plotted relative to time of day (a) and time of insulin glargine injection (b) in 23 people with Type 1 diabetes managed with insulin glargine taken at lunch-time (□), dinner-time (●) or bed-time (△), plus meal-time insulin lispro.

primary endpoint, was higher with injection of insulin glargine at bed-time than other times (B: 9.1 ± 0.6 vs. L: 7.8 ± 0.6 or D: 6.7 ± 0.6 mmol/l, respectively, $P = 0.023$). In pair-wise comparison, mean plasma glucose concentration at 22.00 to 02.00 h was higher with bed- compared with dinner-time ($P = 0.001$), but not lunch-time insulin glargine.

Twenty-four-hour plasma free insulin concentration

Plasma free insulin concentrations from the three treatment periods diverged from 2 h after lunch, and at 4 h after lunch became significantly lower with dinner-time insulin glargine than the other treatment groups (D: 11.5 ± 1.4 vs. L: 20.2 ± 1.3 or B: 16.5 ± 1.3 mU/l, $P < 0.001$) (Fig. 2). Plasma free insulin concentration did not differ between treatment periods at any other time point of the 24-h profile.

Hypoglycaemia

There were 113, 126 and 113 episodes of symptomatic hypoglycaemia with lunch-, dinner-, and bed-time glargine, respectively. There was no difference between treatment periods in the number of episodes of hypoglycaemia or in the number of people reporting hypoglycaemia.

The timing of hypoglycaemia differed between treatment periods with each period displaying a distinct peak and trough time for hypoglycaemia (Fig. 3). Lunch-time insulin glargine was associated with a peak in hypoglycaemia 3.5–7.5 h after injection at 16.00 to 20.00 h, but a trough at the end of the night and through the morning. With dinner-time injection, the highest rates were seen from 4 to 14 h after injection, namely at 22.00 to 10.00 h, and the lowest rates before injection and through the afternoon. Bed-time insulin glargine was associated with highest rates 9.5–15.5 h after injection at 10.00 to 16.00 h, but notably low rates in the evening up to midnight.

Treatment satisfaction

There was no difference in overall treatment satisfaction, in any individual items of the DTSQ between treatment periods, or in perceived convenience of timing of injection of insulin glargine (data not shown).

Discussion

This study compared blood glucose control in people with Type 1 diabetes managed with a multiple insulin injection regimen with insulin glargine given at lunch-time, dinner-time, or bed-time in combination with meal-time insulin lispro. Hyperglycaemia in the early part of the night (22.00–02.00 h) was improved by a mean of 2.4 and 1.3 mmol/l with dinner-time and lunch-time insulin glargine, respectively, compared with bed-time injection. Whilst 24-h mean plasma glucose and fructosamine concentrations did not differ between treatment periods, a consistent trend to higher blood glucose concentrations around the time of insulin glargine injection was observed. This was found, in the afternoon, to relate to waning basal insulin levels in the period approaching 24 h after insulin glargine injection. Each time of injection of insulin glargine was associated with a distinct peak and trough time for hypoglycaemia.

Self-monitored, but not inpatient glucose profiles, demonstrated pre-dinner hyperglycaemia with dinner-time insulin glargine. However, a significantly lower plasma free insulin concentration and a non-significant rise in inpatient plasma glucose concentration in the late afternoon were observed in this group. This discrepancy is likely to have resulted from a methodological flaw resulting in the discontinuation of some of the initial inpatient studies (that all commenced before dinner) just before 24 h. Data for the last 1–2 h of the 24-h profiles were thus not obtained from all participants.

Plasma free insulin concentration 4 h after lunch was lower with dinner-time glargine than the other groups. This difference is unlikely to arise as a result of insulin lispro effect as lunch-time rapid-acting insulin doses did not differ between

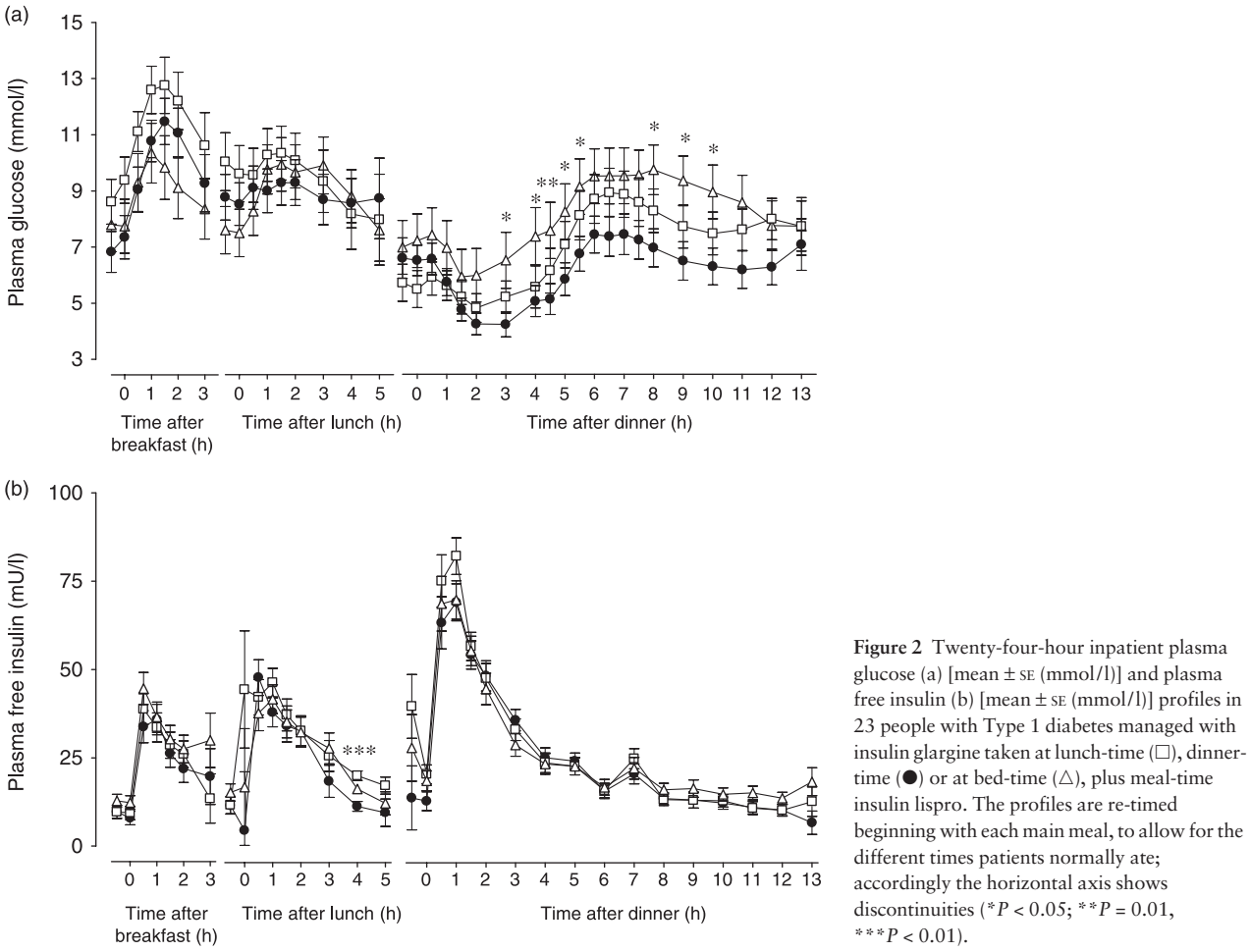

Figure 2 Twenty-four-hour inpatient plasma glucose (a) [mean ± SE (mmol/l)] and plasma free insulin (b) [mean ± SE (mmol/l)] profiles in 23 people with Type 1 diabetes managed with insulin glargine taken at lunch-time (□), dinner-time (●) or at bed-time (△), plus meal-time insulin lispro. The profiles are re-timed beginning with each main meal, to allow for the different times patients normally ate; accordingly the horizontal axis shows discontinuities (*$P < 0.05$; **$P = 0.01$, ***$P < 0.01$).

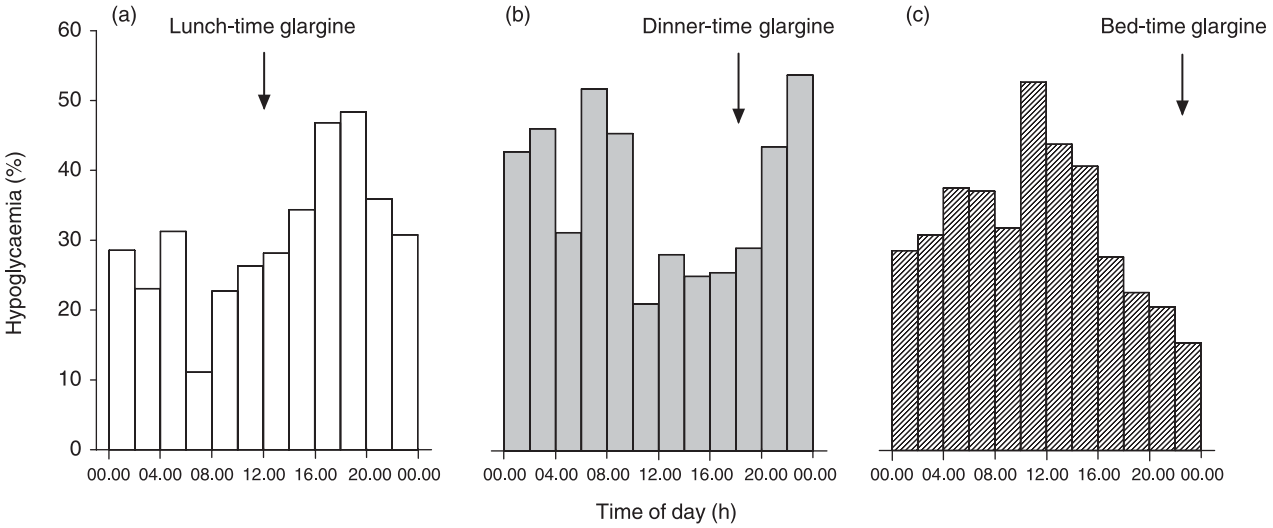

Figure 3 Timing of hypoglycaemia: proportion of all episodes of hypoglycaemia that occurred during each treatment period (%) during 2-h intervals over 24 h, in 23 people with Type 1 diabetes managed with insulin glargine taken at lunch-time (a), dinner-time (b), or bed-time (c), plus meal-time insulin lispro.

treatment periods, and little rapid-acting insulin would be available by this time [10]. It is therefore likely to represent plasma levels of insulin glargine waning approximately 22 h after its injection. Pre-meal hyperglycaemia, especially before dinner, could be attributed to absorption of carbohydrate ingested at the previous meal persisting for longer than the duration of action of the rapid-acting insulin analogue. However the plasma free insulin data suggest that waning basal insulin levels in the period approaching 24 h after insulin glargine injection is a significant contributor to this effect.

Pre-breakfast SMBG, but not 24-h inpatient plasma glucose concentration, was higher with lunch-time insulin glargine than the other groups. This may be an artefact of the short duration of the treatment periods resulting in inadequate insulin glargine dose titration in this group who may have required larger doses and did not suffer the highest levels of nocturnal hypoglycaemia.

Treatment satisfaction did not differ between groups, but satisfaction scores were generally high and a ceiling effect may have limited the ability to observe any difference, a problem that might have benefited from use of the DTSQ change version [13].

These data support those of Hamann and co-workers who compared insulin glargine injection at breakfast-, dinner-, or bed-time in a large group of people with Type 1 diabetes [11]. Self-monitored blood glucose concentration consistently rose around the time of injection of insulin glargine in all groups, but HbA_{1c} did not differ. Insulin glargine was not given at breakfast-time in the present study as it was felt that this time of injection is limited by pre-breakfast hyperglycaemia, and thus does not provide optimal 24-h blood glucose control in most people with Type 1 diabetes. Additionally, it was felt that the addition of a further treatment period to the present study might have had a negative impact on recruitment of the study population, when breakfast-time glargine has already been studied.

In a smaller study, 24-h inpatient plasma glucose and plasma free insulin levels were measured in people with Type 1 diabetes managed with insulin glargine injected at bed-time or dinner-time, and compared with NPH insulin given four times-daily, plus meal-time insulin lispro [14]. Here, the difference between plasma glucose levels in the early part of the night with dinner- and bed-time insulin glargine were not statistically significant and there were no differences in 8-point SMBG levels between the two groups. However the inpatient plasma glucose data in that study come from only eight people in each group, and are taken from a study population who eat dinner later than those in the present study. These factors will have reduced the power to detect a difference between dinner- and bed-time insulin glargine.

It is claimed that insulin glargine provides a peakless metabolic profile. The present study, however, provides evidence of a significant maximum in glucose-lowering activity (giving increased rates of hypoglycaemia), and waning before the next injection is due. Injection at both lunch- and dinner-time was associated with a peak incidence of hypoglycaemia around 5 h later. This is consistent with pharmacokinetic data that describe a small peak in plasma free insulin levels and metabolic activity at this time [3]. Differences in 24-h hypoglycaemia profiles between treatment groups could be attributable to the effect of meal-time insulin. However, neither clinically nor statistically significant differences in rapid-acting insulin doses between treatment groups were observed. Thus, any differences in hypoglycaemia profiles are likely to reflect differences in basal insulin profiles. The consistent patterns in 24-h hypoglycaemia profiles suggest that different individuals may benefit from different times of injection of insulin glargine. For example, where night-time hypoglycaemia is a problem bed-time injection may help; where morning hypoglycaemia is a problem, however, lunch-time glargine injection may be helpful.

The results of the present study, together with those from previous work [11], strongly suggest that, in some people with Type 1 diabetes using insulin glargine, the profile of action is insufficient to prevent some hyperglycaemia at, or after, the end of each 24-h period from injection, when used with a meal-time rapid-acting insulin analogue. This effect appears to be particularly marked with bed-time injection, and suggests that once-daily insulin glargine should not routinely be given at this time in people with Type 1 diabetes. We would suggest that the injection should be given earlier, at a time that is convenient for the individual. However, pre-injection hyperglycaemia might still occur in some people in whom basal insulin levels wane towards the end of the 24-h period after insulin glargine injection, as shown in the present study. Indeed, hyperglycaemia in the early evening might become an increasing problem in the UK as the pattern of meal-times changes with some people eating later in the evening. Pre-injection hyperglycaemia might be avoided by twice-daily injection of insulin glargine and this might be expected to additionally reduce within-person variability in blood glucose levels. Alternatively, an additional interprandial injection of rapid-acting insulin could be given towards the end of the 24-h period after insulin glargine injection, or unmodified human insulin could be used for the meal prior to the insulin glargine injection. These interventions require investigation.

In conclusion, blood glucose levels rise around the time of injection of insulin glargine whether given at lunch-time, dinner-time, or bed-time, suggesting that once-daily insulin glargine does not provide completely optimal 24-h basal insulin supply when used with a meal-time rapid-acting insulin analogue in some people with Type 1 diabetes. Bed-time injection leads to hyperglycaemia in the early part of the night, which is improved by giving insulin glargine at lunch-time or dinner-time.

Competing interests

SGA has received speaker fees from Sanofi Aventis. The University of Newcastle has received financial support to support the research activities of SGA. PDH, on behalf of the University of Newcastle upon Tyne, has provided lecturing and consultancy services and received research support from insulin manufacturers, including Sanofi Aventis.

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