Abstract

Aim. – The pharmacodynamic properties of a single dose of 0.5 U/kg insulin detemir and insulin glargine were compared during two 24-h isoglycaemic clamps, one week apart.

Methods. – The order of treatments was randomised. At approximately 08:30 h, persons with T2DM received subcutaneous administration of a 0.5 U/kg dose of either insulin detemir or insulin glargine into the anterior abdominal wall. Plasma glucose was measured at 10-min intervals throughout the 24-h clamp period and isoglycaemia was maintained by variable infusion of 20% glucose. Glucose infusion rates (GIR) and plasma C-peptide were determined throughout each 24-h period.

Results. – Eleven persons with type 2 diabetes (8 male) with mean (SD) age 58.5 years (8.5), BMI 30.8 kg/m² (2.8) and HbA₁c 7.5% (0.6) were studied. Plasma glucose remained constant during the clamp (CV: insulin detemir 3.7%; insulin glargine 3.8%). Following injection of insulin detemir, GIR increased, reaching a mean peak of 2.29 mg/kg/min (95% CI 1.64, 2.94) at 11.6 h (range 8.9 to 14.3) compared to 1.71 mg/kg/min (95% CI 1.4, 2.0) at 10.2 h (8.1 to 12.3) for insulin glargine (P = 0.025 for GIR_max). Plasma C-peptide decreased during the study period, remaining significantly lower than the fasting level at the study end after both analogues, insulin detemir (P = 0.01) and insulin glargine (P = 0.02).

Conclusion. – In persons with T2DM, no difference in duration of action following a single subcutaneous dose of insulin detemir and insulin glargine could be observed. Insulin detemir showed greater between subject variability and achieved a significantly higher maximum GIR than insulin glargine.

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Keywords: Insulin; Detemir; Glargine; Glucose infusion rate; Variability

Résumé

Une comparaison des propriétés pharmacodynamiques de l’insuline detemir et glargine : étude de clamp après une dose unique chez des diabétiques de type 2.

But. – Les propriétés pharmacodynamiques d’une dose unique de 0.5 U/kg d’insuline detemir et d’insuline glargine ont été comparées lors de 2 clamps euglycémiques de 24 heures réalisés à 7 jours d’intervalle.

Méthodes. – L’ordre des traitements était tiré au sort. À 8 h 30, les diabétiques de type 2 recevaient en sous cutanée dans l’abdomen une injection de 0.5 U/kg, soit de l’insuline detemir ou de l’insuline glargine. La glycémie plasmatique était mesurée toutes les 10 minutes pendant les 24 heures du clamp et l’euglycémie était maintenue par une perfusion de glucosé à 20 %. La quantité de glucose perfusé et la concentration du peptide-C étaient mesurées sur 24 heures.

Résultats. – Onze diabétiques de type 2 (8 hommes et 3 femmes) ont été inclus avec un âge moyen de 58,5 ± 8,5 ans, IMC de 30,8 ± 2,8 kg/m² et une HbA₁c de 7,5 ± 0,6 %. La glycémie est restée stable durant le clamp. Suivant l’injection de detemir, le débit de perfusion du glucose (GIR) a augmenté, atteignant un pic à 2,29 mg/kg/min (95 % IC 1,64, 2,94) à 11,6 heures (intervalle 8,9–14,3) comparé à 1,71 mg/kg/min (95 % IC 1,4, 2,0) à 10,2 heures (intervalle 8,1–12,3) pour la glargine (P = 0.025 pour GIR_max). La concentration du peptide-C a diminué au cours du clamp avec les deux insulines, restant significativement plus faible que la valeur à jeun.
1. Introduction

Two basal insulin analogue preparations were introduced in the first decade of the 21st century. The absorption and action of insulin detemir is retarded by reversible albumin binding [1] whereas insulin glargine achieves its protracted action through retarded absorption, following isoelectric precipitation after subcutaneous injection [2]. These two alternative mechanisms were developed in an attempt to improve upon the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of protaminated (NPH) or zinc-saturated (Ultralente) human insulin-based preparations which have well documented inappropriate time-action characteristics for once a day administration and/or unacceptable levels of variability [3–6]. Several glucose clamp studies have demonstrated that these two analogues have clear advantages over NPH insulin, in terms of time-action profile and day-to-day variability [4–8]. Clinical trials have also demonstrated safety benefits from using the insulin analogues [9]. However, how insulin detemir and glargine compare to each other, remains a subject for debate. The earliest clamp study of insulin detemir in persons with type 1 diabetes mellitus (T1DM) [7] suggested a dose-dependent mean duration of action, this being longer than NPH insulin, but approaching 24 h only at clinically high doses. As a result of this, most of the original clinical studies of insulin detemir, especially in T1DM, were conducted using twice daily dosing and insulin detemir was therefore initially licensed for once or twice daily dosing. For insulin glargine, an early clamp study in type 1 diabetes mellitus (T1DM) [4] demonstrated that this analogue had a prolonged and flat action profile, mimicking continuous subcutaneous insulin infusion (CSII) and lasting for approximately 24 h. This insulin analogue has subsequently been clinically applied predominantly using once-daily dosing, and licensed accordingly [2].

Once-daily dosing feasibility is perhaps more of a consideration in type 2 diabetes (T2DM), where insulin is often initiated quite late in the natural history of T2DM by the simple addition of a once-daily basal-only insulin dose to oral antidiabetic drug (OAD) therapy in an attempt to make acceptance of insulin injection therapy as easy as possible for the patient [10]. Some head-to-head comparative clinical trials have been conducted comparing insulin glargine with detemir, but the data are difficult to interpret due to the unequal dosing algorithms used [9–13]. In persons with type 2 diabetes, insulin glargine is predominantly used once-daily whereas insulin detemir is prescribed once or twice daily.

Clearly many of the outcomes reported from clamp studies are dependent on the methodologies adopted [14] and the different populations studied.

We have therefore undertaken our own single-centre clamp study using standard techniques with the goal of shedding further light on the pharmacodynamic action profiles of insulin detemir and glargine in insulin-naïve persons with T2DM.

2. Methods

The study was conducted as a randomised, open labelled, single-centre, single dose two-way crossover study. Eligible participants were men or women aged 18–75 years with a confirmed medical history of T2DM having not previously received insulin therapy and with an otherwise normal clinical examination. Glycated haemoglobin (HbA1c) was in the range 7.0 to 11.0% (53 to 97 mmol/mol) inclusive, and body mass index (BMI) ≤ 35 kg/m².

The study consisted of a screening visit followed by two 24-h in-house study days, separated by a 7-day washout interval. Patients attended each study day fasting and, on the first of these days, they were randomised to receive via subcutaneous injection into the anterior wall of the abdomen, a total dose of 0.5 U/kg of either insulin detemir (12 nmol/kg) or insulin glargine (3 nmol/kg) at 0h. Individuals received the comparator insulin on their second study day one week later. Subjects remained fasted and in a semi-recumbent position throughout the study period, and smoking was prohibited. They were instructed to refrain from alcohol in the previous 24 h, and blood glucose-lowering drugs were not taken after the evening preceding each study day.

An intravenous cannula was inserted into an ante-cubital fossa vein in the forearm and attached via a three-way tap to a slow running saline (0.154 nmol/L) infusion to maintain the patency of the vein. A second cannula was inserted into a warmed dorsal hand vein of the contralateral arm for repeated “arterialised” blood sampling and was also attached via a three-way tap to a slow running saline infusion.

At approximately 0830, the bolus dose of basal insulin was administered into the abdomen (time 0h). Each insulin preparation was administered by a subcutaneous injection at 45° into a skin fold of the anterior abdominal wall, midway between the umbilicus and the anterior superior iliac spine. A 20% glucose infusion was administered via the cannula in the forearm. Samples for the determination of plasma glucose concentrations were measured every 10 min. At each sample time, the infusion was stopped and the first 2 mL blood withdrawn from the cannula in the hand vein and discarded, prior to obtaining the sample for assay. The samples were separated using a microcentrifuge, and plasma glucose was determined. The GIR was then adjusted to maintain the plasma glucose concentrations at just below (0.3 mmol/L) isoglycaemic (mean of –30, –20, –10 and
0 min samples) levels. Further samples were taken at frequent intervals for determination of C-peptide.

The second study day was conducted after an interval of one week with a follow-up assessment after a further one to two weeks.

Plasma glucose was assayed using a glucose oxidase method on a benchtop Analox GM7 glucose analyser (Analox Instruments, London, UK). Plasma C-peptide was measured using immuno-chemiluminometric assay (ICMA) kits (Invitron, Monmouth, UK).

Pharmacodynamic endpoints assessed during the 24-hour clamps, which included plasma glucose, GIR in response to the insulin analogue, and plasma C-peptide.

3. Statistical methods

Plasma glucose and C-peptide levels were summarised by treatment and visit using descriptive statistics. The results are presented as mean (95% CI), unless otherwise stated. The primary efficacy variable was the GIR (mg/kg/min), and for the statistical analysis, the area under curve (AUC) of GIR, calculated by the trapezoidal rule, within each treatment group was compared between the two study days. Data were analysed, using apaired t-test or Wilcoxon signed rank test on non-parametric data, at the 5% level of significance.

Between subject variability was calculated by means of 3rd order polynomial fitting [15] to each individual time series and calculating the sum of the squares of the residuals (SSR) from this fitted curve.

4. Results

A total of 14 subjects with type 2 diabetes, aged 44–69 years (inclusive) were enrolled, of which 11 completed both glucose clamp study days (8 male; 3 female). No serious adverse events occurred during the study however, three did not complete due to problems with cannulation. The mean (SD) age of those who completed was 58.5 (8.5) years (range: 44–69), BMI 30.8 kg/m² (2.8) (range: 26.5–34.7). The HbA_{1c} was 7.5 (0.6) (range: 7.0–8.6)% (59 (7) mmol/mol [range: 53–70]) (reference range < 6.0% and 42 mmol/mol, respectively). Mean fasting C-peptide on the first study day was 1.25 (0.53) nmol/L (range: 0.47–2.06). One subject was treated by diet alone, 4 by metformin, and 6 by metformin in combination with a sulphonylurea (5 gliclazide; 1 glibenclamide).

4.1. Glucose

Fasting plasma glucose concentrations were similar on both the insulin detemir and insulin glargine study days (8.1 [7.1 to 9.0] vs 8.3 [7.4 to 9.3] mmol/L; \( P = 0.31 \)), respectively. Mean plasma glucose remained relatively constant during each isoglycaemic clamp; for insulin detemir, the mean CV from the target glucose concentration was 3.7% and for insulin glargine was 3.8% (Fig. 1a). The absolute and relative deviations reported by root mean square for insulin detemir were 0.11 mmol/L and 1.43%, respectively and for insulin glargine 0.12 mmol/L and 1.48%, respectively.

4.2. C-peptide

C-peptide remained low and relatively constant throughout the duration of the clamp (Fig. 1b) with both insulin analogues and there were no clinically relevant increases in C-peptide levels in the individual clamps. No statistically significant differences were found in mean (95% CI) AUC over the first (AUC_{0–12h} [13.7 (9.9 to 17.6)] vs 15.1 (9.5 to 20.7) mmol.h/L; \( P = 0.31 \)) or second (AUC_{12–24h} [8.4 (6.8 to 10.1)] vs 10.1 (6.7 to 13.6) mmol.h/L; \( P = 0.12 \)) 12-h periods between insulin detemir and insulin glargine, respectively. Over the total study period of 24 h, the differences in AUC were not statistically significant (AUC_{0–24h} [22.1 (17.1 to 27.2)] vs 25.2 (16.4 to 34.0) mmol.h/L; \( P = 0.18 \)).

4.3. Glucose infusion rate

Measured pharmacodynamic parameters are summarised in Table 1. As expected, the GIR gently rose and fell again over the 24-h period following the injection of either insulin analogue (Fig. 2). Following injection of insulin detemir, the average GIR rose gradually to reach a maximum rate of 2.29 mg/kg/min (1.64 to 2.94) at 11.62 hours (range 8.9 to 14.3), before falling gradually to 0.44 mg/kg/min (0.16 to 0.73) at the end of the 24-h study. Following injection of insulin glargine, the average GIR rose gradually to reach a maximum of 1.71 mg/kg/min (1.40 to 2.03) at 10.21 h (8.09 to 12.34) before falling gradually to 0.47 mg/kg/min (0 to 0.95) at the end of the 24-h study period.

There was no statistical difference between the mean differences GIR_{AUC} over the total study period (AUC_{0–24h} 0.218 g/kg (–0.092 to 0.529); \( P = 0.148 \)), over the first 12 h (AUC_{0–12h} 0.049 g/kg (–0.093 to 0.188); \( P = 0.638 \)) or over the second 12 h (AUC_{12–24h} 0.169 g/kg (–0.048 to 0.387); \( P = 0.113 \)) between insulin detemir and insulin glargine, respectively.

<table>
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<tr>
<th></th>
<th>Detemir</th>
<th>Glargine</th>
<th>( P ) value</th>
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<tbody>
<tr>
<td>GIR_{0–end} (24h) (g/kg)</td>
<td>1.62 (1.15 to 2.09)</td>
<td>1.40 (1.08 to 1.73)</td>
<td>0.148</td>
</tr>
<tr>
<td>AUC_{0–12h} (g/kg)</td>
<td>0.85 (0.63 to 1.06)</td>
<td>0.80 (0.64 to 0.96)</td>
<td>0.638</td>
</tr>
<tr>
<td>AUC_{12–end} (g/kg)</td>
<td>0.77 (0.47 to 1.08)</td>
<td>0.60 (0.40 to 0.81)</td>
<td>0.113</td>
</tr>
<tr>
<td>GIR_{max} (mg/kg/min)</td>
<td>2.29 (1.64 to 2.93)</td>
<td>1.71 (1.40 to 2.03)</td>
<td>0.025</td>
</tr>
<tr>
<td>T_{max} (h)</td>
<td>11.62 (8.90 to 14.34)</td>
<td>10.21 (8.09 to 12.34)</td>
<td>0.290</td>
</tr>
</tbody>
</table>
A statistically significant difference in $GIR_{\text{max}}$ between insulin detemir and insulin glargine was observed 2.29 (1.64 to 2.93) vs 1.71 (1.40 to 2.03) mg/kg/min, respectively ($P = 0.025$).

4.4. Between subject variation

The between subject variation for each treatment modality, calculated from the sum of the squares of the residuals from fitted curves (Table 2), showed a statistically significant difference between insulin detemir and insulin glargine 59.2 ± 99.2 vs 29.5 ± 38.0; $P < 0.023$, respectively.

5. Discussion

This single-centre head-to-head isoglycaemic clamp study was undertaken in order to better understand the
pharmacodynamic action profiles of insulin detemir and glargine in insulin-naïve persons with T2DM. Although the confounding influences of insulin and glucose infusion on the insulin action profile can be corrected using mathematical formulae [11], in persons with type 2 diabetes, however, we considered it more straightforward to clamp the blood glucose at the individuals’ fasting level (rather than a pre-defined target) so as not to be confounded by counter-regulatory responses. Insulin-naïve subjects with type 2 diabetes were chosen as they represent the target group that is most likely to require treatment by the addition of a once-daily basal-only insulin regimen to prior OAD therapy.

The results show a similar time-action profile for insulin detemir and insulin glargine over 24 h when dosed with a single subcutaneous injection at 0.5 U/kg in our insulin-naïve participants with T2DM. At 24 h, the mean GIR (and also GIR in most individual clamps) was still elevated from baseline and the insulin analogues were still readily detectable in blood samples, with suppression of C-peptide. These observations imply that both insulin analogues were still exerting a small glucose-lowering effect 24 h after dosing.

C-peptide levels remained at or below baseline throughout the glucose clamps, indicating the GIR curves obtained are due to the blood glucose-lowering activity of the exogenous insulin injection with no contribution by endogenous insulin secretion. The resulting GIR curves for the two analogues were similar to each other. It should be noted however that although equipotent clinical doses were used for each insulin (0.5 U/kg), the actual concentrations of administered insulins were different: insulin detemir 12 nmol/kg and insulin glargine 3 nmol/kg. It is accepted that there were a relatively small number of subjects included in our study, which will affect the power of the study to achieve statistical significance, however, our observations are broadly consistent with those of Klein et al. [12] who also obtained similar 24 h GIR curves for insulin detemir and insulin glargine at doses of 0.4 and 0.8 U/kg in persons with type 2 diabetes. There were some differences between this study and ours, most notably by clamping glycaemia at a pre-set level of 5 mmol/L and comparing the analogues in a parallel-group protocol. Our data are consistent with those of Sørensen et al. [13] who also showed very similar profile for insulin glargine and insulin detemir in healthy volunteers, the only difference being a tendency for both the onset and decline of action to occur sooner with insulin detemir. Their crossover study used a similar approach to ours in that the clamp level was based on the subjects’ individual fasting glucose level but set at 0.3 mmol/L lower, and being a volunteer study, the range of clamp values was small. Of interest, the Sørensen study did not show any major differences between the PK/PD profiles of the two basal insulin analogues and NPH insulin, contrasting with earlier work and clinical experience. The apparently atypically prolonged action of NPH in this study may reflect the use of insulin-sensitive non-diabetic volunteers kept fasted for 24 h and the diligent efforts of the investigators to thoroughly re-suspend NPH insulin before injection.

Our observations are not in accordance of those of a previous crossover study that we undertook in a different category of diabetes i.e. type 1 diabetes in collaboration with Porcellati et al. [11]. This earlier study compared the profiles of insulin glargine and insulin detemir in 24 h clamps (∼5.5 mmol/L) given as 0.35 U/kg doses at the end of a two-week treatment period during which the test analogue had been used as part of basal-bolus therapy for people with T1DM. Here, a greater waning of effect was seen with detemir in the second 12–24 h interval of the clamp, with this difference in finding to our present study, possibly reflecting the lower dose level, the residual contribution of previous doses of study basal insulins and the T1DM cohort.

Although the pharmacodynamic profiles of the study basal insulin analogues were similar in most respects in the present study, we did find one statistically significant difference between insulin detemir and insulin glargine, this being the higher GIRmax (P < 0.05) of insulin detemir. Between subject variation was also greater following insulin detemir compared to insulin glargine. Previous studies have suggested a less variable blood glucose-lowering effect with insulin detemir than insulin glargine [5,12], however, as we did not use a repeat-clamp protocol in this study, we cannot comment on this finding. The differences may also be due to the greater binding of insulin detemir to albumin at high doses, unfortunately, there is a paucity of information regarding the free to bound ratio of insulin detemir in the circulation.

Clinical studies suggest little difference between the two basal insulin analogues, in terms of hypoglycaemia risk when used in either basal plus OAD [16] or basal-bolus regimens [17–20], although as noted there are no published comparisons that have used equal dosing protocols. A meta-analysis of insulin detemir versus insulin glargine when used in people with type 2 diabetes mellitus did not show any significant differences with respect to changes in HbA1c, or number of hypoglycaemic events, but small differences were observed for weight gain (in favour of insulin detemir) and for daily insulin doses (in favour of insulin glargine), although insulin detemir may need to be administered twice daily [21].

<table>
<thead>
<tr>
<th>Subject</th>
<th>SSR</th>
<th>Detemir</th>
<th>Glargine</th>
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<tr>
<td>1</td>
<td>80.6</td>
<td>47.0</td>
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<tr>
<td>2</td>
<td>12.0</td>
<td>16.5</td>
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<td>4</td>
<td>44.7</td>
<td>6.9</td>
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<td>5</td>
<td>11.4</td>
<td>18.9</td>
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<tr>
<td>7</td>
<td>72.0</td>
<td>22.0</td>
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<tr>
<td>8</td>
<td>12.2</td>
<td>18.3</td>
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<tr>
<td>9</td>
<td>34.8</td>
<td>14.0</td>
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<tr>
<td>10</td>
<td>60.3</td>
<td>31.3</td>
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<tr>
<td>11</td>
<td>20.1</td>
<td>12.8</td>
<td></td>
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<tr>
<td>13</td>
<td>81.9</td>
<td>35.6</td>
<td></td>
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<tr>
<td>14</td>
<td>220.9</td>
<td>100.7</td>
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</tr>
<tr>
<td>Mean</td>
<td>59.2</td>
<td>29.5</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>99.2</td>
<td>38.0</td>
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In summary, our data using a clamp protocol based upon the participants’ own fasting blood glucose values suggest that a single subcutaneous dose of 0.5 U/kg insulin detemir and insulin glargine have very similar action profiles in insulin-naive type 2 diabetes when administered by subcutaneous injection in the morning. No difference in duration of action between insulin detemir and insulin glargine could be observed although insulin detemir had a more variable and significantly higher GIR_max than insulin glargine and showed greater between subject variability.

Disclosure of interest

S.D.L. has received honoraria for consultancy from Sanofi-Aventis. D.R.O. has received honoraria for consultancy and lectures from Novo Nordisk and Sanofi-Aventis, Eli Lilly and Boehringer Ingelheim. G.J.D. and M.A. have no conflicts of interest.

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References