Is insulin detemir able to favor a lower variability in the action of injected insulin in diabetic subjects?

P Valensi, E Cosson

SUMMARY
Insulin treated diabetic patients have often to contend with variability in the action of injected insulin and to some unpredictibility in glycemic control. The variability in blood glucose control seems particularly important with long-acting insulins. Insulin detemir belongs to a new class of non-crystalline form of long-acting insulin analogs. Absorption of insulin detemir is dependent on neither appropriate resuspension before injection and dissolution of crystals in the subcutaneous tissue, as is the case for NPH insulin, nor on formation and dissolution of microprecipitates, as is the case for insulin glargine. In euglycemic glucose clamp studies, insulin detemir was associated with significantly less within-subjects variability for the pharmacodynamic endpoints than both NPH insulin and insulin glargine. Three, up to 6 months trials, carried out in patients with type 1 diabetes have shown that the day-to-day within-subject variations in plasma glucose were significantly lower with insulin detemir than with human NPH insulin. Similar results have been reported in patients with type 2 diabetes. Nightly 8-h plasma glucose recordings showed a smoother and more stable profile with insulin detemir than with NPH insulin. In patients with type 1 diabetes the combination of insulin detemir with mealtime insulin aspart, a fast-acting insulin analog, provides a smoother and more stable profile with lower post-prandial plasma glucose levels that the combination of NPH insulin with regular human insulin before each meal. In several trials, the risk of hypoglycemia, particularly of nocturnal hypoglycemia, was significantly lower with insulin detemir than with NPH insulin. In conclusion insulin detemir offers a better reproducibility as compared with other basal insulins, reduces the risk of hypoglycemia, and may lead the patients to titrate their insulin doses more easily and therefore to achieve more often glycemic objectives. The combination of rapid- and long-acting insulin analogs reproduces a more physiological insulin secretion and thereby reduces the risk of hypoglycemia and improves the overall 24-h glycemic profile.

Key-words: Insulin effects · Reproducibility · Glycemic variability · Insulin analogs · Insulin detemir · Insulin glargine · NPH insulin.

Valensi P, Cosson E. Is insulin detemir able to favor a lower variability in the action of injected insulin in diabetic subjects? Diabetes Metab 2005,31,4S34-4S39

RéSUMÉ
L’insuline détémir peut-elle favoriser une plus faible variabilité d’action de l’insuline injectée chez les patients diabétiques?
Les patients diabétiques traités par l’insuline sont souvent confrontés à une variabilité dans l’action de l’insuline injectée et à une certaine imprédictibilité du contrôle glycémique. La variabilité du contrôle glycémique semble particulièrement importante avec les insulines de longue durée d’action. L’insuline détémir appartient à une nouvelle classe de forme non cristalline d’analogues de l’insuline de longue durée. Son absorption ne dépend ni de la qualité de la remise en suspension avant injection ni d’une dissolution des cristaux dans le tissu sous-cutané comme c’est le cas pour l’insuline NPH, ni de la formation ou de la dissolution des microprécipités comme c’est le cas pour l’insuline glargine. Au cours des études menées par clamps euglycémiques, l’insuline détémir présentait une moindre variabilité intra-individuelle de ses effets pharmacodynamiques comparativement à l’insuline NPH et à l’insuline glargine. Trois essais menés chez les diabétiques de type 1 et ayant duré jusqu’à six mois ont montré que les variations intra-individuelles jour après jour de la glycémie étaient significativement plus faibles avec l’insuline détémir qu’avec l’insuline humaine NPH. Des résultats similaires ont été rapportés chez des diabétiques de type 2. Les enregistrements nocturnes de la glycémie ont montré un profil plus étalé et plus stable sous insuline détémir que sous insuline NPH. Chez les diabétiques de type 1, la combinaison de l’insuline détémir avec l’insuline aspart, un analogue rapide de l’insuline, avant chaque repas, fournit aussi un profil plus étalé et plus stable avec de moindres excursions glycémiques postprandiales que la combinaison de l’insuline NPH avec l’insuline humaine rapide avant chaque repas. Au cours de plusieurs essais thérapeutiques, le risque d’hypoglycémie, en particulier nocturne, était significativement plus faible sous insuline détémir que sous insuline NPH. En conclusion, l’insuline détémir offre une meilleure reproductibilité comparativement aux autres insulines basales, réduit le risque d’hypoglycémie et peut conduire les patients à titrer leurs doses d’insuline plus aisément et devrait permettre ainsi d’atteindre plus souvent les objectifs glycémiques. La combinaison d’un analogue rapide et d’un analogue de longue durée de l’insuline reproduit un profil d’insulinosécrétion plus physiologique, réduit le risque d’hypoglycémie et améliore l’ensemble du profil glycémique des 24 heures.

Mots-clés : Effets de l’insuline · Reproductibilité · Variabilité glycémique · Analogues de l’insuline · Insuline détémir · Insuline glargine · Insuline NPH.

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Insulin treated diabetic patients have often to contend with variability in the action of injected insulin and to some unpredictability in glycemic control, prone to influence their therapeutic compliance. Among the factors involved in glycemic response to insulin, some are related to the conditions of injections: depth, site of administration, importance of subcutaneous tissue blood flow, the time lapse before withdrawing the needle, the quantity of injected insulin, and the quality of shaking to create a suspension before injection when using crystallised insulins [ref. 1 for review]. Other factors are related to insulin itself since the variability in the pharmacokinetics of insulin may contribute to the variability in glycemic responses. This variability increases the risk of hypoglycemia and some fears expressed by some patients. An association between glycemic variability and an increase in mortality has also been reported in patients with type 2 diabetes [2].

The variability in blood glucose control seems particularly important with long-acting insulins, and relatively lower with fast-acting insulins [3, 4]. Recently, two slow-acting analogs, detemir and glargine, have been developed and raised the hope of lower within-subject variability. Some trials have tested this variability with detemir, using accurate methods.

### Lower within-subject variability of glycemic responses with detemir

Detemir belongs to a new class of non-crystalline form of slow-acting insulin analogs. Its prolonged duration of action is attributable to a combination of increased self-association (hexamer stabilization and hexamer-hexamer interaction) and albumin binding due to acylation of the amino acid lysine in position B29 with a 14C fatty acid (myristic acid). Insulin detemir is highly albumin bound in the interstitial fluid and in plasma [5]. It has been shown to elicit a protected metabolic action, with a slow onset of action and a less pronounced peak of action compared with that for NPH insulin [6, 7].

### Absorption of insulin detemir

Absorption of insulin detemir is dependent on neither appropriate resuspension before injection and dissolution of crystals in the subcutaneous tissue, as is the case for NPH insulin, nor on formation and dissolution of microprecipitates, as is the case for insulin glargine. Therefore, insulin detemir is expected to provide a more constant and reliable basal insulin supply than other basal insulin preparations.

Within-subject variability of hypoglycemic effects of insulin detemir has been compared with NPH insulin and insulin glargine in type 1 diabetic patients, in a double-blind parallel group study. Each subject received four single subcutaneous doses of 0.4 units/kg of either insulin detemir (n = 18), insulin glargine (n = 17), or human NPH insulin (n = 16) on four identical study days [8]. The pharmacodynamic and pharmacokinetic properties of the basal insulin preparations were evaluated under euglycemic glucose clamp conditions (with a target blood glucose concentration 5.5 mmol/l).

Insulin detemir was associated with significantly less within-subject variability than both NPH insulin and insulin glargine, as assessed by the coefficients of variation for the pharmacodynamic endpoints studied (glucose infusion rates for 12 and 24 hours after insulin injection). Insulin detemir also provided less within-subject variability in the pharmacokinetic endpoints (maximal concentration) (Table I) [8].

Several studies have analyzed within-subject variability during long-term trials comparing insulin detemir with NPH insulin. A 6-month multinational open parallel-group study was conducted at 46 centers in five countries and included 448 patients with type 1 diabetes randomized to insulin detemir or NPH insulin, injected twice daily (before breakfast and bedtime), with rapid-acting analog insulin aspart injected before each main meal [9]. At baseline mean HbA1c was similar in the two groups. Mean HbA1c decreased slightly in both treatment groups (0.55% point) and was comparable after 6 months. The day-to-day fluctuation in fasting self-measured blood glucose profiles within a subject, based on home-measured blood glucose during the past

### Table I

Reproducibility of pharmacodynamic and pharmacokinetic parameters of 3 treatment groups: insulin detemir, NPH insulin and insulin glargine. Data obtained from euglycemic glucose clamp (target blood glucose concentration 5.5 mmol/l) on four identical study days, in 18, 17 and 16 type 1 diabetic patients, respectively [from ref. 8].

<table>
<thead>
<tr>
<th></th>
<th>Detemir</th>
<th>NPH</th>
<th>Glargine</th>
<th>Detemir</th>
<th>NPH</th>
<th>Glargine</th>
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<tr>
<td><strong>Pharmacodynamics</strong></td>
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<tr>
<td>GIR-AUC (0-12 h) (mg/kg)</td>
<td>1,130 ± 312</td>
<td>1,280 ± 559</td>
<td>886 ± 325</td>
<td>27</td>
<td>59*</td>
<td>46*</td>
</tr>
<tr>
<td>GIR max (mg/kg/min)</td>
<td>2.3 ± 0.5</td>
<td>2.7 ± 1.1</td>
<td>1.8 ± 0.6</td>
<td>23</td>
<td>46*</td>
<td>36*</td>
</tr>
<tr>
<td><strong>Pharmacokinetics</strong></td>
<td></td>
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<tr>
<td>Cmax (pmol/l)</td>
<td>2,865 ± 626</td>
<td>147 ± 40</td>
<td>99 ± 33</td>
<td>18</td>
<td>24</td>
<td>34</td>
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GIR-AUC and GIR max: glucose infusion rate-area under the curve for 12 h and maximum level, after subcutaneous insulin injection.

Cmax: peak of plasma insulin concentration.

* p < 0.001 vs insulin detemir. CVs: coefficients of variation.
7 days of treatment, was significantly lower with insulin detemir than with NPH insulin (3.37 vs 3.78; p < 0.001). The risk of hypoglycemia during the last 5 months of treatment was 22% lower in the detemir group than in the NPH insulin group, with an estimated hazard ratio (detemir/NPH insulin) of 0.78 (p < 0.05).

In a similarly designed study, 408 patients with type 1 diabetes were randomized in an open-labelled parallel-group trial of 16-week treatment duration using either insulin detemir or NPH insulin. Insulin detemir was administered twice daily using two different regimens, either before breakfast and at bedtime or at a 12-h interval. NPH insulin was administered before breakfast and at bedtime. Mealtime insulin was given as the rapid-acting insulin analog insulin aspart [10]. At the end of the trial, HbA1c for the pooled insulin detemir groups was significantly lower than for the NPH group (mean difference –0.18%; p = 0.027). According to self-monitored prebreakfast plasma glucose measurements on the last 7 days of treatment, mean plasma glucose was 8.28 and 8.26 mmol/l in the two detemir groups, and 9.05 mmol/l in the NPH group (p < 0.005), mean within-patient standard deviations (for 7 values/patient) were 2.95, 2.91 and 3.49, respectively (p < 0.001). The risk of minor hypoglycemia was lower in detemir-treated patients compared with NPH insulin in the last 12 weeks of treatment, which was mainly attributable to a 53% reduction in nocturnal hypoglycemia in the patients treated by insulin detemir before breakfast and at bedtime.

Another trial compared the efficacy and tolerability of two types of basal-bolus therapy, using either insulin detemir in combination with the rapid-acting analog insulin aspart before each meal, or NPH insulin in combination with mealtime regular human insulin [11]. In this 18-week randomised, open-labelled, parallel trial, 595 patients with type 1 diabetes received insulin detemir or NPH insulin in the morning and at bedtime. The day-to-day within-subject variation in plasma glucose, based on self-measured 8-point plasma glucose profiles during four normal week days within the last week of treatment, was significantly lower with insulin detemir/insulin aspart than with NPH/regular human insulin (CVs: 36.9% vs 39.6%; p < 0.001). The occurrence of hypoglycemic episodes per person-year was significantly lower in the insulin detemir insulin aspart group than that in the NPH/regular human insulin group, with a risk of hypoglycemia 21% lower in the former group than in the latter (p = 0.036).

In another 6-month trial which included 749 patients with type 1 diabetes, fasting blood glucose, but not HbA1c levels, was significantly lower in the insulin detemir group than in the NPH insulin group [12]. Within-patient day-to-day variability was measured by self-recorded prebreakfast blood glucose on each of the last 7 days of treatment. Within-patient variability was significantly lower in patients receiving insulin detemir than in those receiving NPH insulin (CVs: 37.4% vs 43.0%; p < 0.001).

The variability of glycemic response has also been examined in patients with type 2 diabetes in a multicenter multinational study. In this open-labelled, parallel-group trial, 294 patients were included and randomly assigned to 22 weeks of treatment with insulin detemir once or twice daily associated with the fast-acting insulin analog aspart before each main meal, or NPH insulin once or twice daily combined with fast-acting human insulin before each main meal. The decrease in HbA1c levels was similar in the two groups (–0.65 and –0.58%, respectively). At the end of the trial, mean fasting blood glucose was also similar (7.3 mmol/l for both groups), but the day-to-day within-patient variability of fasting blood glucose was significantly lower in insulin detemir-treated group than in the NPH insulin-treated group (SD values 1.2 vs 1.5; p < 0.001) [13].

**Variability of nocturnal blood glucose profiles with insulin detemir**

The nocturnal glycemic profile has been examined by recording plasma glucose between 11:00 pm and 7:00 am at the end of an above mentioned trial [9] which compared insulin detemir and NPH insulin, injected before breakfast and bedtime, in patients with type 1 diabetes. Nightly 8-h plasma glucose profiles were significantly different between the two treatment groups (p = 0.05), and a smoother and more stable profile was observed with insulin detemir (Fig. 1). The effect of insulin detemir appeared to be longer lasting than that of NPH insulin and was still evident at 7:00 am [9]. In addition, the risk of nocturnal hypoglycemic episodes was 34% lower for the detemir group (p < 0.005).

In another trial the reduction in nocturnal hypoglycemia in patients treated by insulin detemir twice daily as compared with NPH insulin twice daily was even 53% [10].

Russell-Jones et al. [12] have examined 24-h blood glucose profiles obtained from continuous blood glucose monitoring (CGMS) after 5 months of treatment with insulin detemir (n = 99) or NPH insulin (n = 39) injected at bedtime. The overall shapes of the mean glucose profile were different, and showed a prominent peak in the mean glucose levels with NPH insulin from 10:00 pm to 2:00 am. In addition, the glucose-lowering action of insulin detemir appeared to persist longer than with NPH insulin. Mean glucose fluctuations from individual mean levels were significantly lower with insulin detemir than with NPH insulin, both nocturnally and over 24 hours (Fig. 2).

**Glycemic profile when on the combination of a long-acting insulin analog and a fast-acting insulin analog**

Fast-acting insulin analogs were developed in order to provide a peak and duration of insulin action more similar to the physiological pattern, and to reduce post-prandial glycemic increase [14]. The fast-acting insulin analogs (insulin aspart, insulin lispro) differ from regular human
Figure 1
Night-time 8-h plasma glucose profiles in type 1 diabetic patients treated by insulin detemir (●) or NPH insulin (■) twice daily before breakfast and bedtime [from ref 9].

Figure 2
Continuous glucose profiles (CGMS recordings) among patients with type 1 diabetes after 5 months of treatment with insulin detemir or NPH insulin injected at bedtime. Part A: mean 24-hour glucose profile. Part B: mean fluctuation from individual mean glucose level over the same period [from ref. 12].
insulin by having changes in amino acid sequence or composition in the B chains of the insulin molecule. These alterations reduce the stability of the insulin monomer-monomer interaction, leading to a more rapid subunit dissociation and subcutaneous absorption of the insulin. In insulin aspart, the proline at position B28 has been replaced by aspartic acid. Due to this modification, its onset of action occurs in 10-20 min, with maximal serum concentrations reached in around 45 min [15].

Several clinical trials in healthy subjects and in patients with type 1 diabetes have shown that insulin aspart has a faster onset and shorter duration of action than does regular human insulin [16, 17]. The improved glycemic control was not associated with an increase in the incidence of hypoglycemic episodes [18].

The combination of a fast-acting insulin analog with a long-acting insulin analog has been tested in an already mentioned study [11] where patients with type 1 diabetes were randomized to insulin detemir in the morning and at bedtime in combination with mealtime insulin aspart, or NPH insulin in the morning and at bedtime with regular human insulin before each meal. After 18 weeks of treatment, the mean daily doses of basal insulin and bolus insulin were very similar in the two groups. Self-measured 8-point plasma glucose profiles differed between treatment groups (p < 0.001), and a smoother and more stable profile with lower post-prandial plasma glucose levels was observed in the group treated by insulin detemir and insulin aspart (Fig. 3). Changes in HbA1c from baseline to the end of treatment was –0.50% in this group compared with –0.28% in the second group. At the end of treatment, mean HbA1c was significantly lower in the insulin detemir/insulin aspart group than in the NPH/regular human insulin group (7.88% vs 8.11%; p < 0.001). Risk of nocturnal hypoglycemia was 55% (p < 0.001) lower in the insulin detemir/insulin aspart group than in the NPH insulin/regular human insulin group. Body weight was 1 kg lower in the former than in the latter group [11].

The DCCT documented that intensive insulin treatment is associated with an increased risk of hypoglycemia. Each 10% reduction in HbA1c resulted in a 26% increase in the risk of severe hypoglycemia [19]. Reaching tight glycemic objectives evaluated by HbA1c levels below 7%, or better below 6.5%, requires optimisation of both fasting and post-prandial blood glucose levels. The basal-bolus regimen is the most often necessary to achieve these goals. The combination of two analogs, insulin detemir as a long-acting basal insulin analog, and insulin aspart as a fast-acting insulin analog, appear able to improve the overall glycemic control, with a more potent reduction in post-prandial blood glucose due to a more marked effect for insulin aspart than for regular human insulin. This combination reduces the risk of hypoglycemia due to a more stable and reproducible profile of action with insulin detemir as compared with NPH insulin.

**Conclusion**

The variability in insulin resorption alters the confidence of the patients in their treatment. It may also alter their quality of life and compliance to treatment. The above summarized studies provide altogether evidence for a better reproducibility in the action of insulin detemir as compared with other basal insulins. The risk of hypoglycemia is significantly reduced. This may lead the patients to titrate their insulin doses more easily and therefore to reach more often glycemic objectives. Another advantage mentioned in several of these studies consists of a slight weight loss which may be attributable to slightly lower food intake, mainly due to less hypoglycemic episodes and less defensive snacking, but also possibly to other more complex mechanisms. The combination of rapid- and long-acting insulin analogs reproduces a more physiological insulin secretion and thereby reduces the risk of hypoglycemia and improves the overall 24-h glycemic profile.

![Figure 3](image_url)

**Figure 3**

Eight-point plasma glucose profiles for insulin detemir/insulin aspart (●) and NPH insulin/regular human insulin (■). Detemir and NPH were injected morning and bedtime, aspart and regular insulin before each meal. BB, BL and BD: before breakfast, lunch and dinner, respectively. B90, L90 and D90: 90 min after breakfast, lunch and dinner, respectively. Data are means ± 2 SE [from ref. 11].
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References