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Higher dose requirements with insulin detemir in type 2 diabetes - three cases and a review of the literature

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Abstract
We report on three type 2 diabetic patients whose daily basal insulin dose requirements were substantially reduced after switching from insulin detemir to insulin glargine. Meta-analysis of three randomised trials of basal insulin initiation confirmed this increased insulin detemir dose requirement in type 2 patients. Potential explanations are discussed.
Introduction
Insulin detemir is a long-acting insulin analogue associated with less hypoglycaemia and reduced weight gain compared with NPH insulin (1-3). Two studies found that type 2 diabetic patients require higher detemir doses to obtain the same level of glycaemic control as with other basal insulin preparations (1,4), whereas another trial reported similar dosages (3). In this paper we describe three patients with type 2 diabetes whose daily dose requirements of basal insulin were substantially reduced after changing basal insulin treatment from insulin detemir to insulin glargine.

The cases
Patient A (female, 63 years, diabetes duration 5 years, insulin-naive, body mass index [BMI] 40 kg/m²) participated in a 6-month treat-to-target trial comparing insulins detemir and glargine (ClinicalTrials.gov number: NCT00405418). During the trial insulin detemir was titrated to 97 units twice-daily, reaching mean fasting plasma glucose (FPG) concentrations of 9.0 mmol/l. HbA1c improved from 9.2 to 8.0% while she gained 3 kg. After study completion prandial insulin was added and the insulin requirement increased to 230 units/day. Seven weeks after the switch to glargine, daily insulin need had decreased to 124 units, due to reduced basal doses (from 206 units detemir to 104 units glargine). HbA1c decreased to 7.4%, average FPG to 7.6 mmol/l, without weight change. After this observation we asked two further type 2 diabetic patients with high detemir dose requirements to change their basal insulin to insulin glargine.

Patient B’s dose of once-daily detemir (female, 42 years, diabetes duration 15 years, basal/bolus therapy, HbA1c 7.4%, BMI 32 kg/m²) was titrated twice-weekly for 6 weeks, using an algorithm targeting FPG <5.6 mmol/l, without adjustment of prandial insulin. The detemir dose increased from 80 to 102 units, reaching mean FPG of 6.3 mmol/l, without an effect on HbA1c, but accompanied by 1 kg weight reduction. Subsequently, the basal insulin was changed to glargine and after another 6 weeks of systematic titration using the same FPG target, the daily glargine dose was 81 units, without changes in HbA1c, FPG, or weight.

Patient C (male, 51 years, diabetes duration 2 years, once-daily basal insulin, HbA1c 7.5%, BMI 32 kg/m²) underwent detemir dose titration from 80 to 126 units, reaching an average FPG of 7.4 mmol/l and resulting in an HbA1c improvement
of 0.2% with a weight reduction of 4 kg. After 6 weeks of insulin glargine, the basal insulin need had decreased to 104 units, reaching lower FPG levels (around 6.0 mmol/l) and with a further 0.2% improvement of HbA1c and 1 kg weight gain.

Discussion

Insulin detemir is produced by removal of the amino acid threonine from position B30 of the human insulin molecule and attachment of a 14-carbon fatty acid chain (myristic acid) to position B29. These modifications result in increased self-association and albumin binding at the injection-site and plasma albumin binding, which are responsible for the prolonged duration of action (5). However, since the myristic acid is sufficiently close to the receptor recognition site to interfere with receptor binding, insulin detemir has a lower affinity (18%) for the human insulin receptor than other insulins (5). In order to compensate for the reduced potency, detemir is formulated at a higher molar concentration: 2400 nmol/ml vs. 600 nmol/ml for all other insulin preparations. This ratio was based on type 1 diabetes trials showing comparable glycaemic control with detemir and NPH, provided that four times the molar dose was used (2,7). However, our observations suggest that this unit dose equivalence does not apply to patients with type 2 diabetes.

To further explore this hypothesis we compared the mean daily detemir dose with the mean daily dose of other basal insulins (NPH insulin or insulin glargine) at the completion of the three published randomised trials investigating basal insulin initiation with insulin detemir in type 2 diabetes (Table 1). The weighted mean daily dose of basal insulin was greater for patients treated with insulin detemir than for those treated with another basal insulin preparation (0.64 vs. 0.46 units/kg, corresponding to a 39% higher dose for insulin detemir). When using a random effects model for meta-analysis, the weighted mean difference of endpoint daily insulin dose was estimated to be 0.21 units (95% confidence interval: 0.04 to 0.39 units) in favour of NPH/glargin. Of note, there was significant heterogeneity across the three included studies (p<0.00001 and I²=97.8%). This heterogeneity could be related to many factors, e.g. to the fact that in one of the trials detemir was dosed once-daily vs. twice-daily in the other two studies (1,4) or to the relatively high endpoint HbA1c attained in this once-daily trial (Table 1) (3).

The 0.64 vs. 0.46 units/kg difference in average daily insulin need corresponds to a six-fold greater dose requirement on a molar basis, a ratio that was also found
in a pharmacodynamic (PD) study (8). Further analysis by the U.S. Food and Drug Administration of these PD data, in which the PD response was plotted against BMI, showed parallel regression lines for detemir and NPH (i.e. for both insulins the PD response decreased as BMI increased), which suggests that the dose ratio difference found in type 1 and type 2 diabetes is not related to obesity (9). It is possible that the reduced receptor binding affinity of insulin detemir and/or its longer residence at the site of injection allows a greater fraction of detemir than of other insulins to undergo non-receptor mediated clearance (6). Alternatively, as more than 98% of insulin detemir is bound to albumin and only free detemir is physiologically active, increased protein binding in type 2 diabetes is a theoretically possible explanation.

Regardless of the explanation, clinicians should be aware of potentially increased insulin dose requirements when prescribing insulin detemir to their type 2 diabetic patients. In addition to the resulting elevated health care cost, high daily detemir doses may be a reason to change basal insulin treatment in individual patients. Also, changes in basal insulin need should be anticipated when switching from insulin detemir to insulin glargine or NPH insulin, and vice versa, to avoid hypoglycaemia or deterioration in glycaemic control.

Table 1 Mean endpoint daily dose of insulin detemir compared with the mean endpoint daily dose of other basal insulin preparations in three randomised trials comparing basal insulin initiation with insulin detemir to insulin glargine or NPH insulin in patients with type 2 diabetes.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients on detemir</th>
<th>Insulin detemir dose (units/kg)</th>
<th>Endpoint HbA1c (%)</th>
<th>Number of patients on comparator</th>
<th>Other basal insulin dose (units/kg)</th>
<th>Endpoint HbA1c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hermansen et al. (1)a</td>
<td>227</td>
<td>0.78</td>
<td>6.8</td>
<td>225</td>
<td>0.53 (NPH)</td>
<td>6.6 (NPH)</td>
</tr>
<tr>
<td>Philis-Tsimikas et al. (3)</td>
<td>334</td>
<td>0.45</td>
<td>7.5</td>
<td>164</td>
<td>0.40 (NPH)</td>
<td>7.4 (NPH)</td>
</tr>
<tr>
<td>Rosenstock et al. (4)</td>
<td>227</td>
<td>0.78</td>
<td>7.2</td>
<td>248</td>
<td>0.44 (glargine)</td>
<td>7.1 (glargine)</td>
</tr>
<tr>
<td>Weighted mean daily insulin dose (units/kg)</td>
<td>0.64</td>
<td></td>
<td></td>
<td>0.46</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No differences in end-of-study HbA1c levels were found in these trials.

aThis study did not report mean endpoint daily insulin dose as units/kg. We calculated this from mean endpoint insulin dose reported as units/day and mean body weight at study completion.
Duality of interest
Sanne G.H.A. Swinnen is employed by the Department of Internal Medicine of the Academic Medical Centre, Amsterdam, the Netherlands, partly through funding from Novo Nordisk and sanofi-aventis for the conduct of clinical trials. J. Hans DeVries has received honoraria for consultancy work as well as research funding from Novo Nordisk and sanofi-aventis.
References


