INSULIN DETEMIR - A NOVEL BASAL INSULIN

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SUMMARY

Insulin detemir is a soluble long-acting insulin analog developed to provide low, constant and reproducible plasma insulin supply for up to 24 hours. Acylation of a 14-carbon chain fatty acid (myristic acid) to the lysine residue at position B29 of the insulin molecule results in delayed absorption due to both increased self-association at the injection site and a high degree of reversible albumin binding. The combination of protracted absorption from the injection site and delayed action due to albumin binding provides a prolonged and predictable action profile with low within-subject day-to-day variation. From the published phase III trials, the effect of insulin detemir as a basal insulin is the same or better in comparison with NPH in terms of achieving glycemic control estimated by HbA1c. There is clearly a lower within-subject variability of insulin effect with insulin detemir than with NPH or glargine, thus making the effect more predictable. In most studies, the number of hypoglycemic events, especially nocturnal, was lower with insulin detemir than with NPH. In comparison to NPH insulin, insulin detemir was associated with less weight gain. A designed basal insulin should be peakless with low variability, i.e. with more predictable action, thus enabling better glycemic control with less hypoglycemia, safe and easy to handle. Insulin detemir seems to meet these requirements.

INTRODUCTION

Modern concept of insulin replacement therapy is the basal-bolus regimen aimed to mimic the physiologic insulin secretion: low insulinemia fasting and between meals, and rapid increase of insulinemia after meal (1,2). So far, the most appropriate insulin replacement is obtained by continuous subcutaneous insulin infusion (CSII) with a changeable rate of infusion by insulin pumps (3). However, the majority of patients take insulin by syringes or 'pen' devices. In them, the basal-bolus regimen is provided by multiple insulin injections. In this regard, conventional insulin preparations have limitations: short and rapid acting insulins are not that short or rapid (the time of action is up to 6 hours after sc application, whereas a variable time from 30 to 60 min is needed for absorption), and prolonged action insulins for basal replacement do have peaks of action. Furthermore, the variability of action within applications in the same individual for prolonged action insulins, especially NPH, is substantial (4,5).

So far, there are two successful strategies to obtain an insulin analog of a protracted action profile. One is modification of the isoelectric point making the insulin soluble in a suitable medium while crystallizing into a slowly-absorbed precipitate depot in the neutral pH of the subcutaneous tissue. This method has been used in
insulin glargine (6). Another strategy is acylation of fatty acid residues to the insulin molecule, enabling the resulting analog to bind to albumin (7,8).

PHARMACOLOGY

Insulin detemir is a soluble long-acting insulin analog developed to provide low, constant and reproducible plasma insulin supply for up to 24 hours. Acylation of a 14-carbon chain fatty acid (myristic acid) to the lysine residue at position B29 of the insulin molecule (des-arginine + myristic acid (mir)) (Figs. 1 and 2) results in delayed absorption due to both increased self-association at the injection site and a high degree of reversible albumin binding (9). The combination of protracted absorption from the injection site and delayed action due to albumin binding provides a prolonged and predictable action profile with low within-subject day-to-day variation (10,11). Soluble formulation of insulin detemir with homogeneous concentration makes agitation before the application unnecessary. Receptor binding studies have shown that insulin detemir has a lower affinity for insulin and IGF receptors than human insulin (12,13).

The time-action profile of insulin detemir has been shown to be dose-dependent, protracted, smooth and predictable (14). In comparison with NPH and another long-acting peakless insulin analog, glargine, its action is less variable (Fig. 3) (7,8).

CLINICAL USE

A number of phase III trials were conducted with insulin detemir. The following is a brief summary regarding its efficacy and potential beneficial effects: glycemic control, variability of action, hypoglycemia rate, and weight gain.

Glycemic control

A meta-analysis of three trials comparing insulin detemir and NPH as basal insulin in basal-bolus treatment in type 1 diabetics (17-19) reveals a slight but significant (-0.11% HbA1c) improvement with detemir in 4- and 6-month treatment in 983 patients. Data on the use of insulin detemir in type 2 patients are fewer, so far showing equal glycemic control in terms of HbA1c as NPH (20).

Variability

As stated earlier (16), clamp studies have shown lower within-subject variability of insulin effect with insulin detemir than with NPH or glargine. To make clear the implication of variation in clinical practice, a prediction interval containing 95% of the predicted
values for an average patient is calculated. The lower and upper limits of this prediction interval are calculated for a given insulin preparation by subtracting and adding the observed standard deviation multiplied by 1.96. The predicted clinical consequences of these calculations are illustrated in Table 1. It is clear that in 15-16 of 100 cases a patient on NPH will experience half his usual effect, whereas this is the case for a patient on insulin detemir in only 1 of 200 cases. At the same time, a patient has substantially less chance (1 out of 1000) to experience the usual effect which can lead to hypoglycemia if on insulin detemir in comparison with NPH (6-7 out of 100).

Table 1. Implications of within-subject pharmacodynamic variability

<table>
<thead>
<tr>
<th>Insulin detemir</th>
<th>Insulin glargine</th>
<th>NPH insulin</th>
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<tbody>
<tr>
<td>The subject’s risk of experiencing less than half their mean overall insulin effect (hypoglycemic risk)</td>
<td>0.5%</td>
<td>7.5%</td>
</tr>
<tr>
<td>The subject’s risk of experiencing more than twice their mean maximal insulin effect (hypoglycemic risk)</td>
<td>0.1%</td>
<td>2.7%</td>
</tr>
</tbody>
</table>

(Heise et al., Diabetes, 2003, Heise et al, Diabetologia 2003)

**Hypoglycemia**

Recently published data from a 6-month longitudinal study (21) have revealed that the hypoglycemic risk reduction seen with insulin detemir is not a transitory phenomenon attributable to differences during the dose titration period. Statistical analysis of the rate of hypoglycemic events for each month in a 6-month comparison of twice daily insulin detemir or NPH insulin in basal-bolus treated type 1 diabetics revealed a significant advantage regarding hypoglycemias for insulin detemir. The risk of having a hypoglycemic episode was significantly reduced in the insulin detemir group compared to the NPH group, being by 22% lower in the insulin detemir group. Moreover, the risk of nocturnal (23:00-06:00) hypoglycemia was by 32% lower with insulin detemir than with NPH insulin when data from the 6-month extension phase were included (22).

**Weight gain**

Weight gain accompanying insulin treatment is considered as an inevitable side effect (23,24). Besides compromising compliance, it may potentially increase the cardiovascular risk. A consistent difference in terms of weight change was found in a number of phase III studies of insulin detemir in both type 1 (17-19,21,22) (Fig. 4) and type 2 (20) diabetics (Fig. 5). In comparison with NPH, insulin detemir was associated with less weight gain in all type 1 studies cited. In type 2 weight gain was minimal, significantly different from NPH. The possible explanation for this is a reduced threat of hypoglycemia, and thus the lessened need of compensatory snacks.
CONCLUSION

There are two main pitfalls of conventional NPH insulin: its time action profile is neither smooth nor predictable. As a result, hypoglycemics occur in an unpredictable manner and make the glycemic control more difficult. A designed protracted insulin analog is expected to obtain the same or better mean glycemic control reflected in better HbA1c, with less hypoglycemics. To obtain this, it should be peakless with a low variability, i.e. with a more predictable action. In addition, any novel insulin should be safe and easy to use. Insulin detemir seems to meet these requirements.

Acknowledgment. The authors who participated in the NN304-1375 trial acknowledge the assistance of Željko Metelko, Nikica Car, Marjana Vučić-Lovrenčić from the Vuk Vrhovac Institute and Novo Nordisk, especially of Marija Perić from Novo Nordisk Croatia.

REFERENCES


