Drugs of the Future 2003, 28(8): 747-753

CCC: 0377-8282/2003

Insulin Detemir

Antidiabetic

Prop INN, USAN

NN-304
Levemir™

[(*N*ε-Tetradecanoyl)Lys(B29),des-Thr(B30)]-insulin (human)

CAS: 169148-63-4
EN: 239855

Abstract

Insulin detemir is a soluble, basal insulin analogue which has a prolonged duration of action due to its insulin binding properties. The potential clinical advantages of treatment with insulin detemir in patients with diabetes mellitus have been demonstrated in pharmacological studies in pigs and dogs with smoother glucose disposal curves generated in euglycemic clamp studies. Pharmacodynamic studies in healthy volunteers and diabetic subjects confirmed the potential therapeutic advantages of this analogue, but indicated that a higher molar dose of insulin detemir would be required to achieve corresponding glycemic control to conventional NPH insulin. A number of clinical studies in both type 1 and type 2 diabetic subjects have demonstrated that insulin detemir provides comparable glycemic control to conventional basal insulins, with the advantages of lower intrasubject variability in fasting blood glucose, some evidence for fewer hypoglycaemic episodes and less weight gain. The therapeutic advantage of this longer-acting insulin is, therefore, to enable patients to achieve better glycemic control than is possible with NPH insulin.

Introduction

Conventional basal insulins, Neutral Protamine Hagedorn (NPH) and Lente-type, are crystalline preparations which dissolve slowly in the subcutaneous tissue fluid. The absorption rates of these products vary from day to day, making normalization of blood glucose in patients with diabetes mellitus difficult to achieve (1). Insulin detemir (NN-304) is a soluble, basal insulin analogue which has a prolonged duration of action due primarily to its insulin binding properties. In clinical practice this should confer advantages over conventional insulins and improve glycemic control in diabetic patients. Insulin detemir has been synthesized from a single-chain, biosynthetic precursor produced in yeast (2).

Pharmacological Actions

The potential therapeutic advantage of insulin detemir has been demonstrated in pigs. The time for 50% disappearance from the subcutaneous injection site ($T_{50\%}$) for insulin detemir was significantly longer than that of NPH insulin, 14.3 ± 2.2 h *versus* 10.5 ± 4.3 h. Intravenous bolus injections of insulin detemir also showed a protracted blood glucose lowering effect compared to that of human insulin. Euglycemic glucose clamp studies showed that the glucose disposal curve for insulin detemir was steadier, without the pronounced peak at 3 h caused by NPH. In addition, histological studies showed that insulin detemir, unlike NPH insulin, did not elicit invasion of macrophages at the site of injection. These studies showed that some disadvantages of the crystalline suspensions had been overcome by insulin detemir (1).

The metabolic effects and interstitial fluid profiles of insulin detemir have been studied in dogs using euglycemic clamps. Equivalency of steady-state action was found at equimolar physiologic infusions of insulin detemir and human insulin. The studies also showed that the binding of insulin detemir to plasma albumin resulted in its slower appearance in the interstitial compartment compared with human insulin (3).

The mode of transcapillary transport of insulin detemir has been studied in the dog hindlimb using euglycemic clamps. The appearance of insulin detemir in skeletal muscle interstitial fluid was constant whether in the absence or presence of human insulin concentrations sufficient to saturate the endothelial insulin receptors. These results supported the hypothesis that the

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transcapillary transport of insulin occurs primarily via a nonsaturable process such as passive diffusion. There was no evidence to support receptor-mediated transport in skeletal muscle (4). Compartmental modeling studies in dogs confirmed this slow transendothelial mode of transport (5).

Pharmacokinetics and Metabolism

The pharmacokinetic and pharmacodynamic properties of insulin detemir following subcutaneous injection were investigated during euglycemic glucose clamp studies in 11 healthy volunteers. In this open, randomized, crossover study, 3 doses of insulin detemir (0.15, 0.3 and 0.6 U/kg body weight) were administered on 3 days and time-action profiles compared with NPH insulin. Injection of insulin detemir resulted in a linear and proportional dose-response effect with maximal concentrations reached after 4-6 h. The metabolic response as shown by the maximal glucose infusion rates did not show the pronounced peak seen with NPH insulin (1); however, no clear dose-response was demonstrated for metabolic effect. The time to reach maximal concentrations (t_{max}) was also significantly higher for insulin detemir, indicating its slower onset of action (6).

In a double-blind, randomized, crossover, placebo-controlled study, the pharmacokinetic and pharmacodynamic properties of 2 doses of insulin detemir (0.3 and 0.6 U/kg) were compared to NPH insulin in 10 healthy volunteers. Similar results to those in the previous study were obtained, with a clear dose-response relationship for area under the insulin curve. The AUCs of glucose infusion following administration of insulin detemir were only 36% and 24% for doses of 0.3 and 0.6 U/kg, respectively, of those observed for corresponding doses of NPH insulin. Again, no clear dose-response was observed. The results indicated that insulin detemir and NPH insulin could not be considered equipotent in humans (7). A further study in healthy volunteers demonstrated that this lesser equimolar effect of insulin detemir in comparison to human insulin was not due to enhanced liver extraction of insulin detemir (8).

The intrasubject variability in pharmacokinetic parameters in healthy subjects who received single doses of insulin detemir was shown to be about half that of subjects who received NPH insulin. Healthy subjects were studied in a double-blind, randomized, crossover trial. The coefficient of variation was significantly less for insulin detemir for the parameters AUC, C_{max} and $T_{50\%}$AUC, indicating that insulin detemir could result in an improved ratio between glucose control and the risk of hypoglycemia (9).

The pharmacokinetics and pharmacodynamics of insulin detemir have also been investigated in a number of euglycemic clamp studies in patients with type 1 diabetes. The duration of action and intersubject variability for 5 doses (0.1-1.6 U/kg) of insulin detemir were studied in a double-blind, six-period, crossover study in 12 subjects. Glucose infusion rate curves indicated that a dose of 0.3 IU/kg of NPH insulin corresponded to a dose of between 0.2 and 0.4 U/kg insulin detemir, with a flatter and less variable profile. The duration of action for insulin detemir was dose-dependent; the mean glucose infusion rate at 0.4 U/kg of insulin detemir was approximately 1 mg/kg/min and the duration of action was 20 h. The study demonstrated a lower intersubject variability for insulin detemir compared with NPH insulin (10).

A randomized, double-blind, controlled, parallel-group study in 54 subjects showed that intrasubject variability for insulin detemir, as demonstrated by coefficients of variations, was significantly lower for the area under the glucose infusion rate curve and maximum glucose infusion rate, compared with NPH insulin and insulin glargine. Insulin detemir had a 2.5-fold lower coefficient of variation for $AUC_{0\text{-}24h}$ than NPH insulin (27% *vs.* 68%). Similar results were obtained for the pharmacokinetic parameters. The study indicated that insulin detemir could provide a more predictable therapeutic effect than either NPH insulin or insulin glargine (11).

A study in 25 type 1 diabetic patients showed that steady-state conditions were likely to be reached with insulin detemir after 2-3 days, depending on dose and dose frequency. Subjects received injections of either insulin detemir or NPH insulin at 0 and 12 h, followed by twice-daily treatment for 7-14 days. Insulin detemir showed a significantly lower metabolic effect compared to NPH insulin after the first 2 injections, but a comparable overall metabolic effect. The glucose infusion rate curve for insulin detemir was also flatter and without the initial pronounnced peak, in accordance with earlier studies (12).

Further studies in special groups of patients have indicated that individual dose titration of insulin detemir can be based on uniform guidelines for children and adolescents (13) and for diabetic subjects with renal or hepatic impairment (14). Two studies investigating insulin detemir in healthy Caucasian and Japanese subjects found that the pharmacokinetic profiles for insulin detemir were similar in the two groups, but that there was a trend towards a higher metabolic overall effect of insulin detemir in Japanese compared with Caucasian subjects (15, 16).

The distribution of insulin detemir in adipose and muscle tissue was investigated in 20 diabetic patients using open-flow microperfusion in a randomized, open, three-period, crossover trial. Relative interstitial insulin concentrations were significantly lower with insulin detemir compared to human insulin, 3.8 ± 1.2 compared with 53.8 ± 15.4 (% of serum) for adipose tissue in type 1 diabetic patients. Similar results were obtained in muscle tissue and in type 2 diabetic patients. The results showed a higher concentration gradient for insulin detemir across the capillary wall than for human insulin, indicating a reduced transcapillary transport of insulin detemir to the peripheral tissues (17). A study with identical design in healthy male volunteers also showed that the relative

concentration of insulin detemir in interstitial fluid was lower than that of human soluble insulin (18).

Clinical Studies

The efficacy and safety of insulin detemir have been demonstrated in a number of randomized trials in both type 1 and type 2 diabetes mellitus patients.

Insulin detemir was compared with NPH insulin in a multicenter, open, crossover trial in 59 subjects with type 1 diabetes. The treatments were evaluated for intrasubject variability in fasting blood glucose and incidence of hypoglycemia over two 6-week periods of optimized basal bolus therapy with either once-daily insulin detemir or NPH insulin. The AUCs derived from 24-h serum glucose profiles on the last day of each treatment period were not significantly different for insulin detemir and NPH insulin. The intrasubject variability in fasting blood glucose was significantly lower for insulin detemir than for NPH insulin during the last 4 days of treatment and significantly fewer subjects also experienced hypoglycemic episodes during the last week of treatment with insulin detemir (60% *vs.* 77%). However, a higher molar dose of insulin detemir, in the order of 2.35, was required to maintain glycemic control, corresponding to findings in pharmacodynamic studies in healthy volunteers (7). Around one-third of subjects in both treatment periods experienced adverse events, the majority of which were mild and considered unrelated to either insulin product (19). The results of this study and other clinical studies that follow are summarized in Table I.

In a 6-month, open, parallel-group study conducted in 5 countries, 448 patients with type 1 diabetes were randomized to receive insulin detemir or NPH insulin (2:1) twice daily. Rapid-acting insulin aspart was given at main meals. Glycemic control, risk of hypoglycemia and effect on body weight were compared between the treatment groups. Self-measured blood glucose profiles were recorded by patients during the last 7 days of treatment and on the last day of treatment a representative sample of patients was hospitalized for the recording of a nighttime 8-h plasma glucose profile. Intrasubject variation in fasting blood glucose was significantly lower with insulin detemir than with NPH insulin; the mean fasting blood glucose was 8.80 and 9.23 mmol/l for insulin detemir and NPH insulin, respectively, with corresponding intrasubject variation (SD) of 3.37 and 3.78. The overall risk of hypoglycemia and the risk of nocturnal hypoglycemia were also significantly lower with insulin detemir than with NPH insulin (22% and 34% lower, respectively). Patients on insulin detemir also had a significantly lower body weight at the end of the trial. The mean daily molar dose requirement of basal insulin at the end of the trial was approximately 3.8 times higher in the insulin detemir group than the NPH insulin group. The adverse event profile was similar between the groups and the majority of events were considered mild and unrelated to the treatments (20). Following a 6-month extension period to the study, glycemic control was similar in the two groups and the risk of nocturnal hypoglycemia was significantly lower (32%) in the insulin detemir group, although there was no significant difference in the overall risk (21).

In another 6-month, open, parallel-group study, 747 subjects with type 1 diabetes received either insulin detemir or NPH insulin (2:1) once daily with human soluble insulin before meals. After 6 months, fasting plasma glucose and intrasubject variation in self-measured fasting blood glucose were significantly lower in the insulin detemir group than the NPH insulin group (SD for self-measured blood glucose 2.8 mM *vs.* 3.6 mM, respectively). After 5 months treatment, overall and nighttime glucose fluctuations were significantly lower in the insulin detemir group than the NPH insulin group; the risk of nighttime hypoglycemia was 26% less in the insulin detemir group. There was also a significant mean difference in body weight between the two groups at the end of the study, with a relative decrease in favor of subjects receiving insulin detemir (22).

A study in 460 subjects with type 1 diabetes found that insulin detemir provided comparable glycemic control to NPH insulin. This was a 6-month, open, parallel-group study with a twice-daily bolus regimen and human soluble insulin before meals. The difference between the treatment groups in fasting plasma glucose was not significantly different, although there was a trend towards lower intrapatient variation in overall fasting blood glucose in the insulin detemir group. The safety profiles were comparable between treatment groups (23). Following a 6-month extension period, glycemic control was comparable between the two groups and there was a trend towards a lower risk of nocturnal hypoglycemia in the insulin detemir group. There was also a significant and clinically relevant difference in body weight between the two groups following 12 months of treatment (24).

Two studies have been reported in patients with type 2 diabetes. In an open, 2-period, dose relationship study, 58 subjects were switched from NPH insulin to insulin detemir or from human premixed insulin to insulin detemir plus human soluble insulin. Comparable mean blood glucose profiles were obtained when molar doses of insulin detemir approximately 4 times higher than insulin NPH were used (25).

In a 6-month, open, parallel-group trial, 505 subjects received either insulin detemir or NPH insulin (2:1) and insulin aspart before meals. Frequency of dosing was once or twice daily according to previous treatment. Similar glycemic control was maintained in both treatment groups; however, there was a significantly lower intrasubject variation in self-measured fasting blood glucose in the insulin detemir group compared with the NPH insulin group. The risk of hypoglycemia and incidence of adverse events were similar between groups (26).

The timing of administration of insulin detemir was investigated in an open, parallel-group study in 400 subjects with type 1 diabetes. Similar glycemic control was achieved with insulin detemir administered either in the morning and before dinner or in the morning and at

Table I: Clinical studies of insulin detemir (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Diabetes mellitus type 1	Randomized, open, crossover, multicenter	NPH insulin bolus x 2 wk → Insulin detemir basal-bolus treatment x 6 wk NPH insulin bolus x 2 wk → NPH insulin basal-bolus treatment x 6 wk	59	Insulin detemir was as effective as NPH in maintaining glycemic control in patients with type 1 diabetes, although it should be administered at a higher molar dose. Insulin detemir demonstrated more predictable fasting blood glucose, low intrasubject variation and a reduced risk of hypoglycemia	19
Diabetes mellitus type 1	Randomized, open, multicenter	Insulin detemir iv bolus bid x 6 mo [+ 6 mo extension period] (n=212) Neutral human insulin iv bolus bid x 6 mo [+ 6 mo extension period] (n=96)	308	Compared to neutral insulin, insulin detemir was as effective in decreasing the risk of nocturnal hypoglycemia in patients with type 1 diabetes, but was associated with a lower body weight after 12 months of treatment	21
Diabetes mellitus type 1	Randomized, open, multicenter	Insulin detemir od + Human soluble insulin [before meals] x 6 mo (n=491) NPH insulin od + Human soluble insulin [before meals] x 6 mo (n=256)	747	Insulin detemir administered for 6 months was more effective than NPH insulin in reducing plasma HbA1c levels, fasting plasma glucose levels, glucose fluctuations, intrasubject variations in self-measured fasting plasma glucose levels, and the risk of nocturnal hypoglycemia in patients with type 1 diabetes. Insulin detemir was also associated with an improved maintenance of stable body weight compared to NPH insulin	22
Diabetes mellitus type 1	Randomized, open, multicenter	Insulin detemir + human soluble insulin (basal-bolus regimen) x 6 mo NPH insulin + human soluble insulin (basal-bolus regimen) x 6 mo	460	Insulin detemir was as safe and effective as NPH insulin in controlling glycemic levels in patients with type 1 diabetes on a basal-bolus regimen	23
Diabetes mellitus type 1	Randomized, open, multicenter	Insulin detemir + Human soluble insulin (basal-bolus regimen) x 12 mo (n=154) NPH insulin + Human soluble insulin (basal-bolus regimen) x 12 mo (n=134)	288	Insulin detemir showed similar efficacy to NPH insulin, with a lower risk of nocturnal hypoglycemia, in patients with type 1 diabetes	24
Diabetes mellitus type 2		NPH insulin x 2 wk → Insulin detemir x 5 wk Human premix insulin x 2 wk → Insulin detemir + Human soluble insulin x 5 wk	58	Both regimens were similarly well tolerated and effective in controlling blood glucose required in patients with type 2 diabetes, although higher molar doses of insulin detemir were required	25
Diabetes mellitus type 2	Randomized, open, multicenter	Insulin detemir + Insulin aspart [before meals] x 6 mo (n=341) NPH insulin + Insulin aspart [before meals] x 6 mo (n=164)	505	After 6 months of treatment, insulin detemir plus insulin aspart showed similar glycemic control to NPH insulin plus insulin aspart in patients with type 2 diabetes. Patients treated with insulin detemir showed a lower increase in body weight and more predictable fasting blood glucose levels	26
Diabetes mellitus type 1	Randomized, open, multicenter	Insulin detemir bid [in morning and before dinner] + Insulin aspart [with meals] x 16 wk (n=139) Insulin detemir bid [in morning and bedtime] + Insulin aspart [with meals] x 16 wk (n=129) NPH insulin bid [in morning and evening] + Insulin aspart [with meals] x 16 wk (n=132)	400	Insulin detemir administered in the morning and before dinner or in the morning and at bedtime was associated with greater reductions in body weight and plasma levels of HbA1c and fasting glucose in patients with type 1 diabetes than NPH insulin twice daily. No significant differences were found in the level of glycemic control achieved by the two insulin detemir regimens	27

bedtime for 16 weeks. Fasting plasma glucose was significantly lower in both of these groups than in the group treated with insulin NPH (morning and bedtime). There was also significantly lower intrasubject variation in self-measured fasting blood glucose in both insulin detemir groups compared with the insulin NPH group. However, the risk of hypoglycemia was similar in the 3 groups (27).

In conclusion, pharmacodynamic and clinical studies with insulin detemir have demonstrated the ability of this insulin analogue to maintain glycemic control in diabetic patients, with the advantage over conventional insulins of less intrapatient variability in fasting blood glucose. The studies indicate that insulin detemir may enable patients to achieve better glycemic control than is possible with NPH insulin.

Source

Novo Nordisk A/S (DK).

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