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Insulin detemir used in basal-bolus therapy in people with type 1 diabetes is associated with a lower risk of nocturnal hypoglycaemia and less weight gain over 12 months in comparison to NPH insulin

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Aim: The aim of this study was to compare the long-term safety and efficacy of twice-daily insulin detemir or NPH insulin as the basal component of basal-bolus therapy in people with type 1 diabetes.
Methods: A multicentre, open-label, parallel-group study was conducted over 12 months and completed by 308 people (from an original randomized cohort of 428). Patients were randomized in a 2 : 1 ratio to receive insulin detemir or NPH insulin before breakfast and dinner, with insulin aspart at mealtimes.
Results: Glycaemic control improved in both groups with HbA_{1c} decreasing by 0.64 and 0.56% point in the insulin detemir and NPH insulin groups, reaching baseline-adjusted final values of $7.53 \pm 0.10\%$ and $7.59 \pm 0.13\%$, respectively. No significant difference was apparent between treatments in terms of HbA_{1c}, fasting plasma glucose or 9-point blood glucose profiles. Fewer hypoglycaemic events (major and minor) occurred in association with insulin detemir compared with NPH insulin, but the overall hypoglycaemic risk did not differ statistically significantly (RR for detemir, 0.78 [0.56–1.08]). However, the risk of nocturnal hypoglycaemia during the maintenance phase (month 2–12) was 32% lower in the detemir group ($p = 0.02$) and lower in every month. This risk reduction remained statistically significant after correction for HbA_{1c}. After 12 months, baseline-adjusted mean body weight was significantly lower in the insulin detemir group than in the NPH insulin group ($p < 0.001$).
Conclusions: In long-term basal-bolus therapy, insulin detemir with insulin aspart as mealtime insulin is well tolerated and reduces the risks of nocturnal hypoglycaemia and weight gain compared to NPH insulin.

Keywords: basal-bolus therapy, insulin detemir, nocturnal hypoglycaemia, NPH insulin, type 1 diabetes
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Introduction

In basal-bolus therapy, once- or twice-daily injections of an insulin preparation with protracted absorption are given in addition to premeal bolus injections of a rapidly absorbed preparation. Yet, the ability and willingness of patients to undertake intensive therapy to meet strict

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glycaemic targets has been limited by the associated fear and increased risk of hypoglycaemia [1,2]. Hypoglycaemia may also contribute to the common insulin-associated problem of weight gain, as patients anticipating hypoglycaemia may compensate by increasing carbohydrate intake. The Diabetes Control and Complications Trial (DCCT) showed that patients experiencing one or more episodes of severe hypoglycaemia gained 6.8 kg in weight, while those without severe hypoglycaemia gained 4.7 kg [3].

Hypoglycaemia is not an inevitable consequence of good glycaemic control; it results solely from the inability to recreate appropriate insulin profiles in individuals with diabetes using currently available treatments. Given that improved glycaemic control achieved through intensive treatment reduces and delays long-term morbidity from late diabetic complications [4–8], it is desirable that insulin regimens are developed that can reproduce the kinetic profiles of non-diabetic physiology in a better way. The rapid-acting insulin analogues, insulin aspart (IAsp) and insulin lispro, provide superior postprandial glycaemic control to soluble human insulin [9–15], due to their ability to mimic the physiological prandial insulin response rather well. The problem of hypoglycaemia, particularly nocturnal hypoglycaemia, however, probably relates mainly to the variable and inappropriate kinetic profiles of traditional basal insulin preparations. These poorly recreate the rather constant, low-level overnight plasma insulin concentrations seen in normal physiology. For example, NPH insulin, is characterized by high within-person variability in absorption and action and undesirable peaks in plasma concentration some 4–6 h post injection [16–19]. This can result in evening injections being unpredictably followed by nocturnal episodes of hypoglycaemia and/or hyperglycaemic escape before breakfast the following morning due to insufficient duration of effect.

Recently, two analogues of human insulin have been developed in an attempt to refine basal exogenous insulin therapy. The first to be marketed, insulin glargine is, however, associated with formation of a microprecipitate in the subcutaneous depot, which may account for observations of limited reproducibility between injections [19–21].

Insulin detemir is the first clinically available soluble acylated analogue. It has a protracted action that is achieved through a combination of increased self-association and albumin binding via a 14-carbon fatty acid chain attached to the insulin B-chain [22]. Insulin detemir has a more prolonged time–action profile than NPH insulin that is less variable between individuals [23]. It has also shown lower within-person variability in various pharmacokinetic and pharmacodynamic parameters in comparison to both NPH insulin and insulin glargine [20].

In clinical trials lasting up to 6 months, reduced variability has been manifest as a greater within-person consistency in fasting plasma glucose in comparison to NPH insulin [24–27], associated with a risk reduction for nocturnal hypoglycaemia [24–27]. The present study therefore sought to assess the relative safety and efficacy over a 1-year period of insulin detemir in comparison to NPH insulin, with IAsp as mealtime insulin.

Methods

Design

This was a 12-month, multinational, open parallel-group comparison of twice-daily insulin detemir vs. NPH insulin, in combination with mealtime IAsp in people with type 1 diabetes.

The trial involved 42 sites in Europe, and comprised an initial 6-month treatment period, results of which have been published [25], followed by a 6-month extension period. Patients (n = 428) were randomized (in a 2 : 1 ratio) to receive subcutaneous insulin detemir or NPH insulin as their basal insulin; all received IAsp before main meals. Follow-up assessments were made when patients attended visits at 3, 6, 9 and 12 months after randomization, and telephone follow-up was made 2–6 days after the 12-month consultation. The present article contains only data from those patients who chose to enter the extension phase (i.e. the latter 6 months).

The trial was carried out in accordance with Good Clinical Practice and the Declaration of Helsinki, and was approved by local ethics committees and health authorities according to local regulations.

Patients

Patients initiated had a history of type 1 diabetes for ≥1 year and had used basal-bolus therapy for at least 2 months prior to enrolment. All were Caucasian patients aged at least 18 years, with body mass index (BMI) ≤35 kg/m^2, HbA_{1c} ≤12% and a total daily basal insulin requirement of ≤100 IU/day. Exclusion criteria included proliferative retinopathy, impaired hepatic or renal function, severe cardiac problems, uncontrolled hypertension, recurrent major hypoglycaemia or allergy to insulin. Pregnant or breast-feeding women were also excluded. Patients completing the initial 6-month trial were invited to participate in the extension phase, with

316 of 425 accepting; written informed consent was obtained for continuation. There were no obvious demographic differences between those choosing to continue into the extension phase as compared with the original cohort at baseline.

Trial Products

Patients were injected with insulin detemir (1200 nmol/ml; 1 U = 24 nmol) or NPH insulin (Isophane human insulin 100 IU/ml, Novo Nordisk, Bagsvaerd, Denmark) subcutaneously before breakfast and bedtime, and IAsp (100 U/ml, NovoRapid, Novo Nordisk) before each main meal, using the NovoPen 3 device (Novo Nordisk). Doses of insulin detemir are expressed here in units (U) based on the to-be-marketed formulation, where 1 U of detemir is equivalent to 1 IU of insulin. Patients randomized to NPH insulin were to continue their previous total basal insulin dose. Those previously on once-daily NPH insulin were to divide that dose equally between morning and evening injections. Patients randomized to insulin detemir also commenced with an equal division of the basal dose, but their initial basal U dose was determined by halving their previous IU dose, with the expectation of titrating upwards towards glycaemic targets.

Doses were adjusted aiming at a glycaemic target of 4–7 mmol/l (72–126 mg/dl) for fasting blood glucose (FBG), preprandial and early morning blood glucose (BG) (02 : 00–04 : 00). The postprandial glycaemic target was <10 mmol/l (180 mg/dl) 90 min after a meal. During the first 2 weeks of the initial study, basal insulin was titrated with dose adjustments permitted every 2 days. In subsequent weeks, basal and bolus doses were adjusted according to investigator recommendations, based on home BG measurements.

Patients entering the extension phase maintained the insulin regimen they were taking at 6 months, with continuous dose adjustments aimed at attaining/maintaining glycaemic targets. Patients injected basal insulin in the thigh or abdomen, with IAsp injections in the abdomen only, and adhered to this throughout the trial, varying injection site within the chosen area.

Efficacy and Safety Assessments

Efficacy was evaluated using HbA_{1c}, FPG and 9-point BG profiles recorded at baseline 3, 6, 9 and 12 months. Long-term safety was assessed on the basis of the frequency, severity and nature of adverse events (AEs) and hypoglycaemic episodes. Weight was monitored throughout. Abnormalities in clinical laboratory or examination parameters were reported qualitatively.

An AE was defined as an undesirable medical incident occurring during the trial, irrespective of its relation to trial products. AEs were classified by severity as 'mild', 'moderate' or 'severe', and in addition as 'serious' if resulting in a fatal or life-threatening illness, prolonged significant disability, hospitalization or prolongation of hospitalization. Hypoglycaemic episodes were classified as major [an episode with severe central nervous system (CNS) symptoms consistent with hypoglycaemia, in which the subject was unable to treat himself/herself and which had one of the following characteristics: BG recorded as <2.8 mmol/l or symptom reversal achieved with food, glucose or glucagon], minor (BG recorded as <2.8 mmol/l, but the patient managed the episode unaided) and as symptoms only (symptomatic episodes not requiring assistance and not confirmed by a BG measurement). Hypoglycaemic episodes were recorded by the patients in booklets collected at each study visit and were classified as nocturnal if they occurred within the time interval (23 : 00–06 : 00).

Analytic Methods

HbA_{1c} (reference range of assay: 4.0–6.0%) was determined by high-performance liquid chromatography on a Biorad 'Diamat'. Fasting plasma glucose was determined by an enzymatic hexokinase method. Patients performed a total of six 9-point BG profiles using One Touch Profile BG meters (LifeScan). All analyses were performed by Central Laboratories (CRL), Belgium.

Statistical Analyses

The initial cohort size was calculated to achieve a power of 85% on the basis of non-inferiority testing at the 5% significance level and a 2 : 1 randomization.

HbA_{1c}, FPG and weight after 12 months of treatment were analysed using an analysis of variance (ANOVA) model, with treatment and country as fixed effects and baseline value as a covariate. Estimates on the final HbA1c (FPG) values based on the statistical model are hence referred to as baseline-adjusted values. Nine-point BG profiles after 12 months were analysed using repeated measures ANOVA model with treatment, time and treatment-by-time interaction as fixed effects. A claim of non-inferiority for insulin detemir could be substantiated if the upper confidence limit for the difference in HbA_{1c} between groups was <0.4%.

All hypoglycaemic episodes occurring during the maintenance period were analysed as recurrent events using a gamma frailty model. In addition, nocturnal episodes were analysed as a separate entity. Moreover,

in order to adjust for HbA_{1c} values, the analyses on hypoglycaemic episodes were repeated including the last HbA_{1c} measurement available before each episode as a covariate into the model.

AEs, vital signs, electrocardiogram (ECG), physical examination and funduscopy were evaluated by summary statistics. Clinical laboratory assessments (biochemistry and haematology lipid profile) were assessed by box plots and shift tables. Body weight was analysed using an ANOVA model with treatment and country as fixed effects and baseline weight as covariate. For all analyses, baseline refers to the start of the treatment and never to the start of the extension period.

Analyses of safety and efficacy were based on the intention-to-treat (ITT) analysis set, defined as all patients who entered the extension phase and received at least one dose of study medication. All analyses were performed using SAS version 8.0 on a Unix platform and SPLUS 2000.

Results

Patients

Of 425 patients completing the initial 6-month study, 316 (74%) chose to continue into the trial's extension phase (n = 217, i.e. 76% of those in the insulin detemir group, and n = 99, i.e. 70% of those in the NPH insulin group). One insulin detemir-treated patient was lost to follow-up before exposure; hence, 315 were included in the ITT analysis. At least 97% of patients in both groups completed the trial. Three patients withdrew from the NPH insulin group, due to 'ineffective therapy', 'non-compliance' and 'other reasons'. Five patients withdrew from the insulin detemir group, one due to non-compliance, two due to AEs and two due to 'other reasons'. The AEs leading to the two withdrawals were not believed to be related to study medication (worsening of a pre-existing skin disorder in one patient; accidental injury, pneumonia and constipation in the other).

Demographic and baseline data for the ITT analysis set are presented in table 1. Physical examination, including ECG and fundoscopy revealed similar results in both groups.

Insulin Dose

During the titration phase, the mean daily dose of insulin detemir increased more rapidly than that of NPH insulin until the unit doses were approximately equivalent. At 6 months, the mean insulin detemir dose was 29.2 U (SD, ±15), while the mean NPH insulin dose was 32.6 ± 14.9 IU. The respective total IAsp doses were 30.2 ± 15.3 IU and 27.1 ± 13.6 IU. During the extension period, basal insulin dose remained stable in both groups. At 12 months, the basal doses were 30.4 ± 15.6 U and 33.6 ± 15.3 IU in the insulin detemir and NPH insulin arms, respectively, while the IAsp doses were 31.7 ± 15.3 IU and 27.3 ± 13.0 IU. Thus, the total unit doses of insulin detemir and NPH insulin were similar implying that 1 U of insulin detemir is indeed equivalent to 1 IU of NPH insulin in terms of overall BG-lowering effect. A slightly higher ratio of bolus : basal insulin was, however, observed in the insulin detemir arm.

Efficacy

HbA_{1c}

Similar changes in HbA_{1c} occurred in both groups (figure 1). Following 12 months' treatment, mean HbA_{1c} had decreased by 0.64 and 0.56% point in the insulin detemir and NPH insulin groups, reaching baseline-adjusted final values of 7.53 ± 0.10% and 7.59 ± 0.13%, respectively. The non-inferiority criterion for insulin

Table 1 Baseline demographic characteristics of the intention-to-treat analysis set (n = 315).

	Insulin detemir (n = 216)	NPH insulin (n = 99)
Men (n, %)	116 (53.7)	52 (52.5)
Age (years)	40.1 (12.8)	40.8 (13.2)
Weight (kg)	71.3 (10.7)	71.7 (12.4)
BMI (kg/m^2)	24.4 (2.9)	24.6 (3.5)
Duration of diabetes (years)	17.8 ± 9.7	16.6 ± 10.2
HbA_{1c} (%)	8.18 ± 1.14	8.03 ± 1.11
FPG (mmol/l)	11.85 ± 5.28	11.51 ± 5.16
Pre-trial basal insulin dose (IU/day)	26.3 ± 12.1	26.2 ± 14.0
Pre-trial bolus insulin dose (IU/day)	31.3 ± 14.3	30.6 ± 15.1

Data are means ± standard deviation. FPG, fasting plasma glucose.

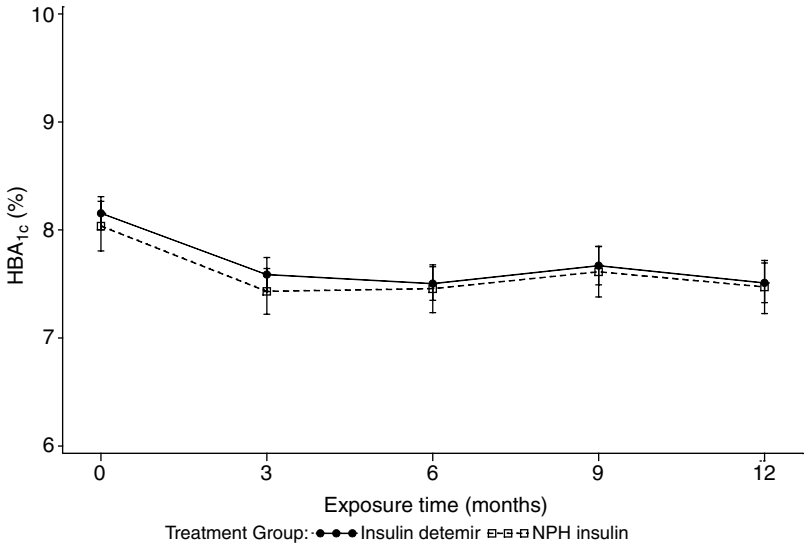

Fig. 1 Mean (SE) HbA_{1c} over time.

detemir was met demonstrating that metabolic control as measured by HbA_{1c} was comparable between the two groups.

FPG

Mean FPG values were similar between groups after 12 months' treatment (10.7 and 10.8 mmol/l in the insulin detemir and NPH insulin groups, respectively), and were slightly reduced (by 0.58 and 0.42 mmol/l, respectively) compared to baseline.

Nine-point BG profiles

After 12 months, the targets for postprandial glycaemic control had been met in both groups, but targets for time points during the night and for FBG were not met in the average profile for either group. The 9-point BG profiles were similar in overall shape for the two groups ($p = 0.24$) and showed improvement from baseline, with FBG notably decreased (figure 2).

Safety

Hypoglycaemia

Insulin detemir was associated with fewer hypoglycaemic episodes during each of the 12 months (figure 3). The relative risk for insulin detemir was 0.78, although this did not reach statistical significance (95% CI: 0.56–1.08). Approximately, 96% of patients in both groups experienced one or more hypoglycaemic episodes, but only 14% of the insulin detemir group and 21% of the NPH insulin group had 'major' events ($p = 0.90$). Insulin detemir showed a trend for a lower risk of minor hypoglycaemia than NPH insulin during the maintenance period (last 11 months of study), although this did not reach statistical significance ($p = 0.068$). In both groups, hypoglycaemic episodes reduced in frequency during the initial 6 months and remained stable thereafter.

The risk of nocturnal hypoglycaemia during the maintenance phase was 32% lower in the detemir group (1378 episodes in 180 patients) than in the NPH group (926 episodes in 87 patients; $p = 0.016$), and lower in every month (figure 3). Following correction for HbA_{1c}, the observed differences in hypoglycaemic risk remained statistically significant. The relative risk of major nocturnal hypoglycaemia for insulin detemir vs. NPH was 0.65 (CI: 0.21; 1.99).

Body Weight

At endpoint, mean body weight was 71.2 kg (SD, 11.4) in the insulin detemir group and 72.7 kg (SD, 13.1) in the NPH insulin group. Baseline-adjustment showed body weight to be significantly lower in the insulin detemir group after 12 months of treatment [between-group difference of 1.34 kg; CI: (−2.12; −0.56); $p < 0.001$]. Patients in the insulin detemir group remained stable at their pretrial weight, losing an average of 0.1 kg during 12 months, whereas those receiving NPH insulin gained a mean of 1.2 kg (figure 4). When weight data were additionally adjusted for change in HbA_{1c}, the between-group difference increased to 1.44 kg ($p = 0.0002$).

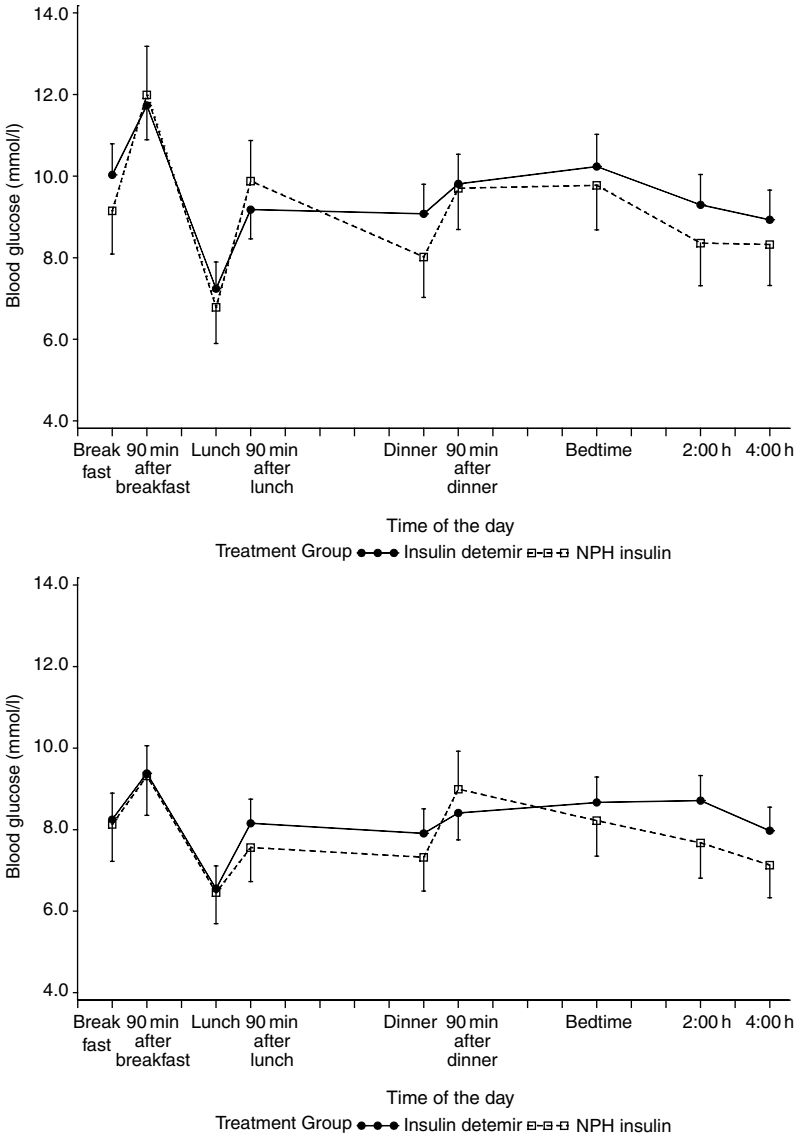

Fig. 2 Estimated means (SE) of 9-point blood glucose profiles. Top, at baseline; below, after 12 months.

Adverse Events

No formal statistical analyses were performed on AEs, and there appeared to be no overall difference between treatment groups. The proportion of patients with AEs in the two groups declined over time (72.7 and 76.8% of insulin detemir- and NPH-treated patients, respectively, in the initial 6 months vs. 60.2 and 69.7% during the final 6 months). More than 85% of AEs in each group were considered unrelated to study medication. Of AEs recorded as probably/possibly related to trial product, CNS complaints (including migraine) were the most frequent with insulin detemir (2.8%), while vision disturbances (4%) were the most frequent with NPH insulin.

Most AEs were classified 'mild' or 'moderate'. Of eight and 10% of AEs considered 'severe' in the insulin detemir and NPH insulin groups, respectively, four cases were considered probably/possibly related to trial medication, two in each group (retinal oedema and macula lutea degeneration in association with insulin detemir; major hypoglycaemia and retinal disorder with NPH insulin). Twelve insulin detemir- and seven NPH insulin-treated patients experienced 'serious' AEs, but only five events (retinal oedema, hypoglycaemia and hyperglycaemia with insulin detemir and hypoglycaemia and retinal disorder with NPH insulin) were considered probably/possibly related to study medication. There were no fatalities.

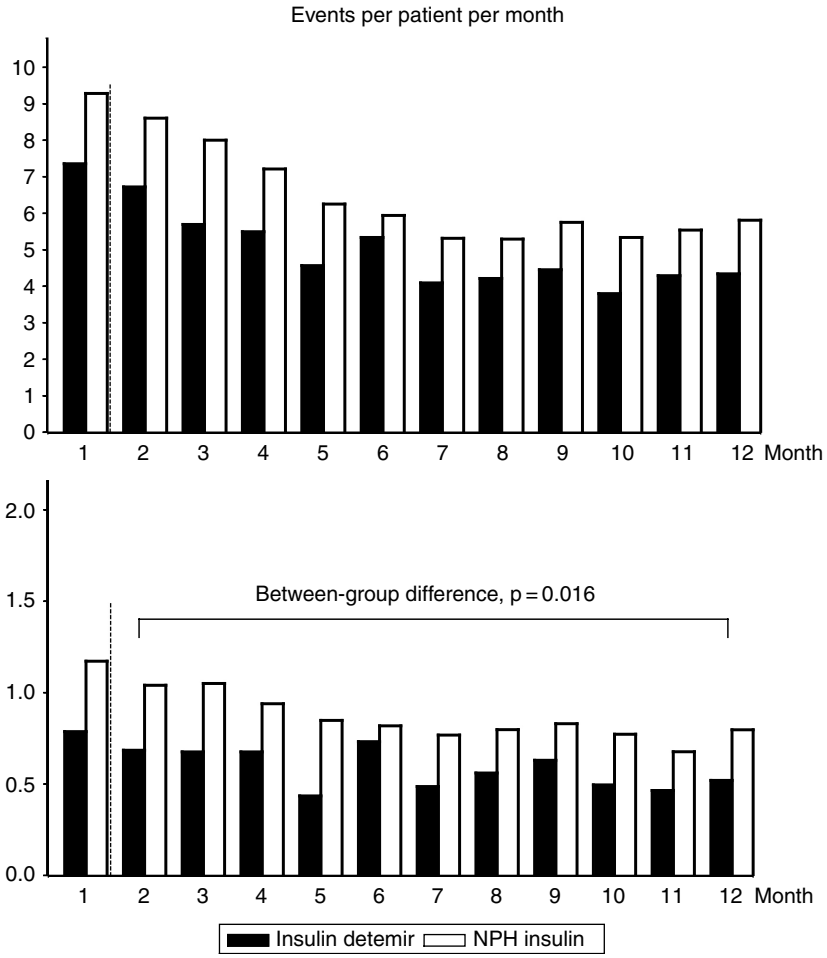

Fig. 3 Month-by-month comparison of hypoglycaemic episodes per person in insulin detemir and NPH insulin groups during 1 year of basal bolus therapy with mealtime insulin aspart. Above, all episodes; below, all nocturnal (23:00–06:00) episodes.

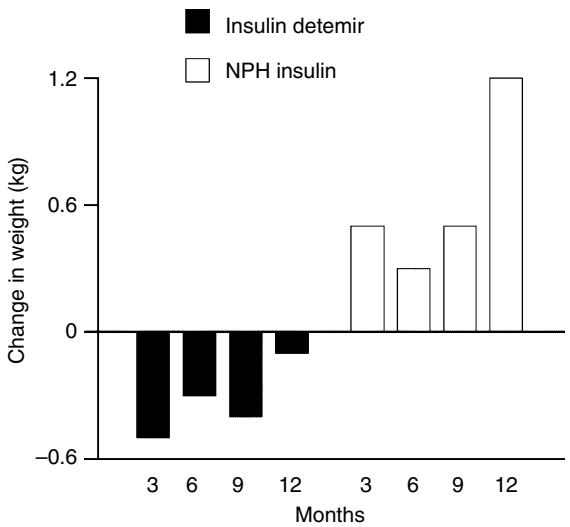

Fig. 4 Mean weight change during 1 year of basal-bolus therapy with insulin detemir or NPH insulin plus mealtime insulin aspart.

Particular attention was paid to visual and metabolic disturbances and injection site reactions due to their relevance in diabetes. The overall frequency of vision disorders was 11.1 and 14.1% in association with insulin detemir and NPH insulin, respectively. While the frequency decreased from the initial 6-month period to the second 6-month period in the insulin detemir group, it increased in the NPH insulin group. Retinal disorders were reported for 7.9% in the insulin detemir group and 10.1% in the NPH insulin group.

The proportion of patients experiencing metabolic disturbance was 3.7% in the insulin detemir group (including three 'moderate' episodes of hyperglycaemia and one 'moderate' episode of hypoglycaemia) and 7.1% in the NPH insulin group (including one 'severe' case of hypoglycaemic coma). Two patients in each group experienced ketosis.

Injection site reactions were recorded in 1.9 and 1.0% of insulin detemir- and NPH insulin-treated patients, respectively. All cases occurred in the initial 6 months,

none were classified 'severe', and no action was taken in any case. Application site disorders reported in the insulin detemir group were: myalgia and pain after injection of moderate severity, and lipodystrophy, redness around the injection site and pain at the injection site of mild severity. One person in the NPH insulin group experienced mild itching around the injection site. All patients recovered completely, except for one case of lipodystrophy (insulin detemir), where the condition was stabilized at trial end.

No clinically relevant findings were made from the laboratory assessments (haematology, biochemistry and blood lipid profile), vital signs nor ECG.

Discussion

This study provides reassurance that the efficacy and safety profile of insulin detemir, determined over a 1-year period, compares favourably with that of the widely used basal insulin preparation, NPH insulin. At equivalent efficacy, insulin detemir was well tolerated and carried a reduced risk of nocturnal hypoglycaemia. In addition, there was an intriguing weight advantage in association with insulin detemir; patients receiving insulin detemir maintained a stable body weight over time while NPH insulin-treated patients gained weight.

Tolerability

Insulin detemir and NPH insulin showed similar overall safety profiles, with equivalent incidences of AEs and a tendency for these to decline in frequency over time. The majority of AEs were 'mild' or 'moderate' in severity. AEs with relation to diabetes or their treatment were slightly less frequent in the insulin detemir group, with a lower incidence of visual disorders and metabolic disturbances being reported. The incidence of injection site reactions was low in both groups (insulin detemir 1.9%, NPH insulin 1.0%), and all such reactions occurred early in the study.

Hypoglycaemia

Although a slightly higher ratio of bolus : basal insulin is observed in the insulin detemir arm, the evidence of the present study suggests that insulin detemir offers a clinically meaningful hypoglycaemia advantage over NPH insulin. Indeed, regardless of any discrepancy in dosing, the reduction in nocturnal hypoglycaemia must be viewed in the context of similar metabolic control as determined by HbA_{1c} and FPG values. Conversely, however, the relatively increased bolus dose in the insulin detemir group might have undermined a potential advantage in daytime hypoglycaemia. In fact, 6-month data from the original randomized cohort show a 22% lower overall risk for hypoglycaemia in association with insulin detemir [25]. The overall risk of hypoglycaemia in the present study was not statistically significant between treatments, but the statistical discrepancy between the 6- and 12-month data is likely due to the reduced cohort entering the extension phase of the trial. It could also derive from a study effect, i.e. patients tend to receive extra-ordinary levels of medical attention during a clinical trial such that the incidence of hypoglycaemic events tends to be lower than anticipated from empirical experience. This may be a progressive effect, as the frequency of hypoglycaemic events declined over the initial 6 months and remained lower during the extension phase (figure 3). The rate of daytime hypoglycaemia was not relatively increased in the insulin detemir group, as is also evident from figure 3. Indeed, hypoglycaemia occurred with a lower overall incidence in association with insulin detemir in every month during the 12-month study. The present trial therefore corroborates results from other clinical trials that have shown relative risk reductions for hypoglycaemia when comparing insulin detemir with NPH insulin [24–27]. The between-group difference over 12 months was only statistically significant for nocturnal hypoglycaemia, but this is not unexpected with basal-bolus therapy. This is because nocturnal hypoglycaemia is supposedly more indicative of treatment differences between the basal insulin components due to the negligible influence of bolus insulin during the nocturnal hours. This is particularly so when rapid-acting analogues are used. After correction for change in HbA_{1c}, there was a statistically significant 31% risk reduction in nocturnal hypoglycaemia. The risk reduction for major nocturnal hypoglycaemia for insulin detemir vs. NPH was 35%, but this did not reach statistical significance, probably because too few events occurred to provide conclusive evidence (insulin detemir, 20 events in 5.1% of patients; NPH insulin, 14 events in 9.1% of patients).

Nocturnal hypoglycaemic episodes are unpredictable in their occurrence and so are likely to occur in individuals when the insulin absorption profile (and consequently the glycaemic profile) departs from the mean for that individual. Thus, a reduced incidence of nocturnal hypoglycaemia is more likely to reflect differences in the within-person variability of different insulin preparations than differences in their mean profiles within populations. Although variability was not assessed in the extension phase of the present study, an analysis of 6-month data from the initially randomized cohort con-

firmed that variability in FBG was indeed lower with insulin detemir (SD, 3.37 mmol/l vs. 3.78 mmol/l, $p < 0.001$) [25]. This observation is consistent with previous clinical research that has shown insulin detemir to be associated with significantly less variability in FBG in comparison to NPH insulin [24–27], as well as pharmacological research demonstrating greater within-person consistency in pharmacokinetic and pharmacodynamic endpoints than NPH insulin and insulin glargine [20].

Weight Development

Weight gain is a well-documented consequence of insulin treatment [4,28–30], and one with important implications for compliance, although this may be a greater concern in patients with type 2 diabetes, many of whom are already significantly overweight when they begin insulin therapy. Nevertheless, for a number of patients with type 1 diabetes, especially adolescents, body weight and image have greater immediacy than concerns about diabetic complications in later life. Thus, weight gain or the prospect of weight gain can become a barrier to the effective implementation of multiple injection therapy. Furthermore, when weight gain does occur as a result of intensified insulin therapy, it may be associated with increases in cardiovascular risk factors including hip : waist ratio and blood pressure, as well as unfavourable changes in the plasma lipid profile.

Comparative studies have consistently demonstrated a statistically significant relative weight gain in patients treated with NPH insulin compared with those treated with insulin detemir, whose weight tends to remain more stable [25–27]. The present study is the first to show that this apparent advantage endures and may even increase over a 1-year period. The mechanism underlying this advantage has yet to be determined. A possible contributory factor may be a reduction in defensive eating made possible by the lower risk of nocturnal hypoglycaemia arising from insulin detemir's more stable and predictable action profile. However, a causal relationship between hypoglycaemia and weight gain is difficult to identify and may not be revealed by a simple correlation of hypoglycaemic risk and weight gain if patients are successful in eliminating their excess hypoglycaemic risk through modification of their eating patterns. Weight gain may therefore effectively become a surrogate for hypoglycaemic risk. Thus, the observation of a concomitant relative reduction in both nocturnal hypoglycaemia and weight may be regarded as a benefit of major clinical significance.

Design Limitations

It must be considered that the cohort that continued into the extension phase cannot be considered randomized, as their inclusion was voluntary. An open design was chosen as the products are easily distinguishable, insulin detemir being a solution and NPH a suspension. The doses were not fully optimized, possibly due to undue investigator caution in titration. It is also possible that as risk estimates of hypoglycaemia were based on self-recording by patients, those receiving insulin detemir were more diligent in their reporting.

Conclusions

In conclusion, this study has shown that insulin detemir is well tolerated in long-term use with insulin aspart in basal-bolus therapy, and that reduced nocturnal hypoglycaemia and a relative stability of weight are attainable at equivalent levels of glycaemic control when compared to NPH insulin. Future studies may determine whether more aggressive, optimized dose titration with insulin detemir can harness these advantages to target improved levels of glycaemic control.

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