Proportional Dose – Response Relationship and Lower Within-Patient Variability of Insulin Detemir and NPH Insulin in Subjects With Type 1 Diabetes Mellitus


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Summary of this original article:

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Short summary of the content and keywords:

This study was conducted to evaluate the dose ratio of insulin detemir and NPH insulin over a range of therapeutically relevant subcutaneous doses.

→ TYPE 1 Diabetes Mellitus
→ HbA1c-Wert
→ insulin detemir
→ NPH Insulin

Keywords of the study: Glucose uptake, glucose production, glucose clamp, tracer infusion technique
The question of the study:

P (Problem) \rightarrow Type 1 Diabetes Mellitus
I (Intervention) \rightarrow Insulin detemir
C (Control) \rightarrow NPH insulin
O (Outcome) \rightarrow The data indicate that insulin detemir has a lower degree of within-subject variability.

Is there a proportional dose-response relationship and a lower within-patient variability with insulin detemir or NPH insulin in patients with Type 1 Diabetes Mellitus?
Overall Clinical Trial Procedure:

12 patients (4f, 8m) with type 1 Diabetes Mellitus (C-peptide-negative)

Day 1 / Screening

Day 2 / Dosing day 1
Wash out period 5-10 days

Day 3 / Dosing day 2
Wash out period 5-10 days

Day 4 / Dosing day 3
Wash out period 5-10 days

Day 5 / Dosing day 4

Day 6 / Follow up

Arrival at the clinic – run in period, 4 p.m.
Continuous infusion of the labeled D-5,6-3H2Glucose, 6 p.m.
Blood glucose steady state conditions at 7.2 ±/ at approx. dosing 9 p.m.
1 hour Dosing

24-h-iso-euglycemic clamp
Medication:

subcutaneous injection of **insulin detemir** (0.15, 0.3, 0.6 U / kg)
and **NPH insulin** (0.15, 0.3, 0.6 IU / kg)
Are the results valid? Randomization & Blinding

single-center randomized
crossover design
incomplete block design (2 of 3 possible doses were given)

How was the randomization done?
→ Not described in the publication

double blind
Are the results valid? **Comparability (Begin.)**

yes →

C-peptide-negative (< 0.03 nmol / l) type 1 Diabetes Mellitus
age 40 ± 13 years
BMI 23.3 ± 2.9 kg/m²
HbA1c 7.5 ± 1.0 %
diabetes duration 19 ± 10 years

**Exclusion criteria:**
impaired renal or hepatic function, or a history of significant cardiac disease

Patients using a basal insulin other than NPH where placed on NPH treatment for the entire trial period.
Are the results valid? **Comparability of treatment**

Each patient got 2 doses of the two insulines. There were 4 days of intervention.

“At 21:00 hours, or later if steady state conditions were not achieved for at least 1 hour, the trial drug was administered s.c. [...]”

“The trial ended 24 hours after trial drug administration, or earlier if plasma glucose levels exceeded 11.1 mmol/l in the absence of glucose infusion.”
Are the results valid? **Analysis**

All in all the patients were at evaluation interpretation considered adequately,

**BUT:**

“**Pharmacokinetic data from one patient were excluded** due to unexpectedly high insulin serum concentrations.”

“Furthermore, **data from one patient at one visit were excluded** (0.3 IU / kg NPH insulin) because the pharmacokinetic data suggested i.v. rather than s.c. administration.”
Are the results valid? Graphic

Fig. 1 Time profiles for intravenous plasma glucose levels (A), and glucose infusion rates (B) 1 h before and after subcutaneous injection of NPH insulin and insulin detemir of 0.15, 0.3 and 0.6 (l)U/kg. Data are mean ± SEM.
Are the results clinically relevant? **Endpoints**

**Primary Endpoints:** Pharmacodynamics, **Secondary Endpoints:** Pharmacokinetics

In our opinion not mentioned and differed clearly enough!
Are the results clinically relevant? **Efficacy of treatment**

**Fig. 4** Individual time profiles for glucose infusion rates after subcutaneous injection of 0.6 (I)U NPH insulin (A) and insulin detemir (B), mean profiles (bold line).
Statistical analysis:

Based on previously published variability of this parameter (Plank et al., 2005), 12 patients would be required in order to estimate the 90% confidence interval (CI) for the dose ratio to be between 0.8 and 1.25 if no difference was observed.

The statistical analysis of $\text{AUC}_{\text{GIR} \, 0-24 \, h}$ was performed after transformation with the natural logarithm, by an analysis of variance (ANOVA):

- treatment period und insulin type: fixed effects
- log-transformed dose und quadratic log-transformed dose: covariates
- subject: random effect

The dose ratio between the insulin types with 95% CI was estimated, based on the log-linear model.

RR: not described
Conclusion:

Looking at the article over all, there might be an indication of an effect of insulin detemir described as: The data indicate that insulin detemir has a lower degree of within-subject variability.