Pharmacokinetics and Pharmacodynamics of Therapeutic Doses of Basal Insulins NPH, Glargine, and Detemir After 1 Week of Daily Administration at Bedtime in Type 2 Diabetes

A randomized cross-over study

OBJECTIVE—To compare the pharmacokinetics and pharmacodynamics of NPH, glargine, and detemir insulins in type 2 diabetes.

RESEARCH DESIGN AND METHODS—This study used a single-blind, three-way, cross-over design. A total of 18 type 2 diabetic subjects underwent a euglycemic clamp for 32 h after a subcutaneous injection of 0.4 units/kg at 2200 h of either NPH, glargine, or detemir after 1 week of bedtime treatment with each insulin.

RESULTS—The glucose infusion rate area under the curve from 0 to 32 h was greater for glargine than for detemir and NPH (1,538 ± 688, 1,081 ± 785, and 1,170 ± 703 mg/kg, respectively, P < 0.05). Glargine suppressed endogenous glucose production more than detemir (P < 0.05) and similarly to NPH (P = 0.16). Glucagon, C-peptide, free fatty acids, and β-hydroxybutyrate were more suppressed with glargine than detemir. All 18 subjects completed the glargine study, but two subjects on NPH and three on detemir interrupted the study because of plasma glucose >150 mg/dL.

CONCLUSIONS—Compared with NPH and detemir, glargine provided greater metabolic activity and superior glucose control for up to 32 h.

Very few studies have investigated the pharmacokinetics and pharmacodynamics of NPH insulin in type 2 diabetes (1,2). These studies have provided valuable information that is limited, however, by a short period of observation (12–16 h) and by the comparison of NPH with only one long-acting insulin analog, either glargine or detemir. The present randomized cross-over study was undertaken to establish the pharmacokinetics and pharmacodynamics of the basal insulins NPH, glargine, and detemir in subjects with type 2 diabetes who need insulin.
-third basal insulin and studied for the third and last time.

The primary end point was the glucose infusion rate (GIR) over 0–32 h (area under the curve [AUC]₀–₃₂ h). Secondary outcomes are shown in the Supplementary Data. Duration of action was defined as the minimal duration of action and end of insulin action (calculated as the time at which plasma glucose was >118 and 136 mg/dL, respectively). The study ended at the time at which plasma glucose was, for at least 30 min, >150 mg/dL (all definitions in the absence of glucose infusion). Plasma glucose, C-peptide, insulin, glucagon, and nonglucose substrates (free fatty acids, β-hydroxy-butyrate, and glycerol), as well as glucose fluxes, were measured as previously described (4) (Supplementary Analytical Methods). During the clamp, glucose flux calculations were based on a non–steady-state assumption (5).

Data analysis was carried out by using ANOVA for cross-over design (6) and is

Figure 1—Plasma glucose, GIR, rates of EGP and glucose utilization, and plasma concentrations of free fatty acids (FFAs) and β-hydroxybutyrate after a subcutaneous injection of NPH, detemir, and glargine insulin in type 2 diabetic subjects.
described in Supplementary Statistical Analysis.

RESULTS—All 18 subjects performed the three clamp studies. However, two and three of the 18 subjects treated with NPH and detemir, respectively, discontinued the clamp study earlier than 32 h because of plasma glucose >150 mg/dL. Glycemic control and insulin doses in the week prior to the studies, as well as plasma glucose concentration and rates of intravenous insulin infusion prior to the subcutaneous insulin injection at the beginning of the clamp study, are given online (Supplementary Results), likewise for plasma insulin, plasma C-peptide, glucagon, and plasma glycerol (Supplementary Fig. 1 and Supplementary Tables 2 and 3).

The mean GIR for the 32-h study period (AUC₀₋₃₂ h) was greater with glargine than NPH by 31% and detemir by 42% (Fig. 1; Supplementary Table 2). Endogenous glucose production (EGP) decreased after the subcutaneous insulin injection in all three treatments but to a greater extent with glargine (Fig. 1). Glucose utilization decreased in all treatments and overall was no different among insulin treatments (P = 0.268) (Fig. 1). Plasma free fatty acid concentrations were higher with detemir compared with NPH (+15%, P = 0.003) and glargine (+26%, P < 0.001) throughout the study, as was plasma β-hydroxy-butyrate (Fig. 1).

The median time of minimal duration of action (plasma glucose >118 mg/dL) and duration of action (plasma glucose >136 mg/dL) differed among the three treatments. Glargine exhibited a smaller interquartile range in time of duration of action than NPH and detemir, although the statistical significance was achieved only versus detemir (Supplementary Table 2).

Results of the 0- to 32-h period and of the 0- to 16-h and 16- to 32-h periods are given online (Supplementary Tables 2 and 3, respectively).

CONCLUSIONS—The results of the current study indicate that the main outcome pharmacodynamic parameter GIR₀₋₃₂ h, taken as a surrogate measure of insulin metabolic activity, was greater for glargine compared with NPH and detemir. GIR with NPH increased shortly after the subcutaneous injection at 0400 h, as a result of a rapid suppression of EGP by ~50%, followed by a sensible reduction after 10–11 h because of increased EGP, which resulted in a significant increase in plasma glucose. This most likely accounts for the greater risk for nocturnal hypoglycemia reported in clinical studies with NPH versus glargine and detemir (7), as well as for the abnormal early morning increase in blood glucose known as the “dawn phenomenon” (8). In the second half of the study, from 1400 h, GIR requirements for NPH and glargine were greater than those for detemir up to the end of the study. Likely, this was the result of the interplay of greater activity of NPH and glargine compared with detemir and the afternoon increased insulin sensitivity in type 2 diabetes (9). This finding is in line with the observation of more frequent predinner hyperglycemia and/or need for twice-daily detemir dosing in clinical studies compared with glargine (10). Finally, glargine had greater effects on suppression of lipolysis than NPH and detemir. Compared with detemir only, glargine suppressed more C-peptide and glucagon concentrations. In addition, it had a longer duration of action with lower variability across subjects, as suggested by the smaller interquartile range.

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P.L. performed clamps and glucose turn-over measurements, analyzed data, and reviewed and edited the manuscript. F.P. wrote the study protocol, performed clamps, researched data, and reviewed and edited the manuscript. P.R. enrolled patients, performed clamps, researched data, and reviewed and edited the manuscript. C.G.F. performed clamps and laboratory assays. P.C., S.M., A.M.A., and R.F. performed clamps and reviewed and edited the manuscript. G.B.B. provided the study concept and design, supervised the protocol development and the research, contributed to discussion, and reviewed and edited the manuscript. C.G.F. performed clamps, analyzed data, performed statistical analysis, and wrote the manuscript.

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References


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