

# Time-Action Profile of the Long-Acting Insulin Analog Insulin Glargine (HOE901) in Comparison With Those of NPH Insulin and Placebo

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**OBJECTIVE** — To study the pharmacodynamic properties of the subcutaneously injected long-acting insulin analog HOE901 (30 µg/ml zinc) in comparison with those of NPH insulin and placebo.

**RESEARCH DESIGN AND METHODS** — In this single-center double-blind euglycemic glucose clamp study, 15 healthy male volunteers (aged  $27 \pm 4$  years, BMI  $22.2 \pm 1.8$  kg/m<sup>2</sup>) received single subcutaneous injections of 0.4 U/kg body wt of HOE901, NPH insulin, or placebo on 3 study days in a randomized order. The necessary glucose infusion rates (GIRs) to keep blood glucose concentrations constant at 5.0 mmol/l were determined over a 30-h period after administration.

**RESULTS** — The injection of HOE901 did not induce the pronounced peak in metabolic activity observed with NPH insulin ( $GIR_{max}$   $5.3 \pm 1.1$  vs.  $7.7 \pm 1.3$  mg · kg<sup>-1</sup> · min<sup>-1</sup>) ( $P < 0.05$ ); after an initial rise, metabolic activity was rather constant over the study period. This lack of peak was confirmed by a lower glucose consumption in the first 4 h after injection (area under the curve from 0 to 4 h [ $AUC_{0-4h}$ ]  $1.02 \pm 0.34$  vs.  $1.48 \pm 0.34$  g/kg) ( $P < 0.001$ ) with HOE901, as compared with NPH insulin. In this single-dose study, the metabolic effect measured over a period of 30 h was lower with HOE901 than with NPH insulin ( $AUC_{0-30h}$   $7.93 \pm 1.82$  vs.  $9.24 \pm 1.29$  g/kg) ( $P < 0.05$ ).

**CONCLUSIONS** — This study shows that the soluble long-acting insulin analog HOE901 induces a smoother metabolic effect than NPH insulin, from which a better substitution of basal insulin requirements may follow.

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The long-acting insulin analog insulin glargine (HOE901) is produced by substituting asparagine with glycine in position A21 of the A-chain of the human insulin molecule and by adding 2 arginine-molecules on positions B31 and B32 of the B-chain of the human insulin molecule. These modifications of the

insulin molecule led to a shift of the isoelectric point from pH 5.4 in native insulin to  $6.7 \pm 0.2$ , making HOE901 a soluble insulin preparation at a slightly acidic pH and a less soluble insulin preparation at physiological pH levels. After subcutaneous injection, HOE901 precipitates in the subcutaneous tissue, which delays its absorp-

tion and thereby prolongs its duration of action. Moreover, HOE901 forms hexamers that are more stable and more dense than those of human insulin (1).

Up to now, the protracted time-action profile of HOE901 in comparison with that of NPH insulin has never been described in published clinical pharmacology studies. Only abstracts or review articles describing investigations of the time-action profile are available (2–4). Furthermore, these studies investigated HOE901 with the addition of 15 and 80 µg/ml zinc, which is different than the zinc content of HOE901 that is used in phase II and phase III clinical trials (30 µg/ml). Even more importantly, one of these studies (2) conducted in healthy volunteers suffers from a problematic study design that uses somatostatin for suppression of the endogenous insulin production. Somatostatin is well known to influence subcutaneous blood flow and insulin clearance (5), which makes pharmacodynamic results difficult to interpret.

A continuous intravenous insulin infusion allows the establishment of comparable baseline insulin levels and suppression of endogenous insulin secretion. Nevertheless, the infused insulin induces a metabolic effect on its own, which might vary over time, especially over a study duration of >12 h. To correct for this metabolic effect of the intravenous insulin infusion and the prolonged fasting, a control experiment with application of placebo must be included.

The aim of our study was to evaluate the pharmacodynamic properties of HOE901 (with a zinc concentration of 30 µg/ml) in comparison with those of NPH insulin after subcutaneous injection in healthy volunteers, taking into account the metabolic effect of the continuous intravenous insulin infusion.

**RESEARCH DESIGN AND METHODS** — This euglycemic glucose clamp study was designed as a single-dose randomized double-blind placebo-con-

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**Abbreviations:** AUC, area under the curve;  $C_{max}$ , maximal serum insulin concentration;  $C_{min}$ , minimal serum insulin concentration; CV, coefficient of variation; GIR, glucose infusion rate;  $GIR_{max}$ , maximal GIR;  $t_{max}$ , maximal time to GIR;  $t_{min}$ , minimal time to GIR.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

trolled 3-way crossover trial. The protocol was approved by the local ethics committee, and the study was carried out according to the Declaration of Helsinki and the principles of Good Clinical Practice. A total of 15 healthy male volunteers (aged  $27 \pm 4$  years, BMI,  $22.2 \pm 1.8$  kg/m<sup>2</sup>, and insulin antibody-negative) received a single injection of either HOE901, human NPH insulin (Aventis, Bridgewater, NJ), or placebo (0.9% saline solution) on 1 of 3 study days in random order. All subjects had been nonsmokers for at least 3 months, were free of concomitant illnesses, were not taking concomitant medication, and had no family history of diabetes.

After an overnight fast, subjects were connected to a Biostator (Life Science Instruments, Elkhart, IN), and a euglycemic glucose clamp was established (constant intravenous insulin infusion of  $0.15$  mU · kg<sup>-1</sup> · min<sup>-1</sup>). After a baseline period of 2 h, the subjects received a subcutaneous injection of  $0.4$  U/kg body wt of either insulin preparation or placebo into a paraumbilical skinfold by means of a syringe ( $1.0$  ml) (Micro-Fine IV+; Becton Dickinson, Heidelberg, Germany). The long-acting insulin analog was available in a clear and colorless preparation with a pH of 4.0 containing  $600$  nmol insulin/l (or  $4$  mg/ml), which was equimolar to the NPH insulin preparation used. To maintain the double-blind character of the study, the administration of the study medication was performed by an independent person who was otherwise not involved in the study. Glucose infusion rates (GIRs) necessary to keep blood glucose levels at  $5.0$  mmol/l were monitored for the subsequent 30 h. The volunteers remained in a supine position and, except for water intake, fasted during the study days. The washout period between the 3 study days was at least 7 days.

Blood samples were collected at 30-min intervals throughout the study to estimate plasma glucose levels (APEC-Glucose Analyser; Ruhrtal Labortechnik, Delecke, Germany). Samples for the determination of serum insulin and serum C-peptide levels were collected in 60-min intervals. Both parameters were determined by a commercial radioimmunoassay kit (Biodata Insulin and C-Peptide Kit; BioChem Immunosystems, Montréal, PQ). Determinations were performed by the FARMOVS Research Centre (University of the Orange Free State, Bloemfontein, South Africa). The insulin detection limit was  $15$  pmol/l (inter- and intra-assay coefficients of varia-

tion [CVs] for insulin  $8.0$  and  $7.4\%$  at  $54$  pmol/l,  $4.1$  and  $4.2\%$  at  $180$  pmol/l, and  $4.5$  and  $4.5\%$  at  $390$  pmol/l). The C-peptide detection limit was  $0.05$  nmol/l (inter- and intra-assay CVs  $3.5$  and  $3.6\%$  at  $0.2$  nmol/l,  $3.2$  and  $3.3\%$  at  $1.1$  nmol/l, and  $6.2$  and  $7.0\%$  at  $2.6$  nmol/l). However, it must be noted that the insulin assay has a cross-reactivity to HOE901 and its metabolites of only  $50\%$ , which leads to a systematic underestimation of these components.

### Statistical analysis

Results are given as means  $\pm$  SD throughout the text and as means  $\pm$  SEM in Figs. 1 and 2. Areas under the GIR profiles (AUC) were calculated by means of the trapezoidal rule. A polynomial function (6th order) was fitted to the individual GIRs to allow for graphical estimation of the pharmacodynamic summary measures (maximal GIR [GIR<sub>max</sub>] and time to GIR<sub>max</sub> [t<sub>max</sub>]). Summary measures were analyzed by analysis of variance with subject, treatment, and period as the main effects. To correct for the metabolic effect of the continuous intravenous insulin infusion, GIR values obtained on the control study day were subtracted individually from those obtained with HOE901 and NPH insulin. Subsequently, the summary measures for these profiles were estimated. For serum insulin and serum C-peptide, descriptive statistics for pharmacokinetic summary measures (maximal serum insulin concentration [C<sub>max</sub>], time to C<sub>max</sub> [t<sub>max</sub>], and AUC; minimal serum C-peptide concentrations [C<sub>min</sub>], time to C<sub>min</sub> [t<sub>min</sub>], percentage suppression, and AUC) are given. The pharmacokinetic summary measures were not subject to statistical analysis because the radioimmunoassay used for quantifying insulin has a cross-reactivity of only  $50\%$  to HOE901 and its metabolites, which results in underestimation of these components.

Due to the differences between the calculation of mean summary measures (calculation of individual values for every experiment initially, then calculation of mean values per treatment) and mean curves (which are mean values per treatment for every minute), the summary measures given in Table 1 are not identical to the mean values in Figs. 1 and 2 (6).

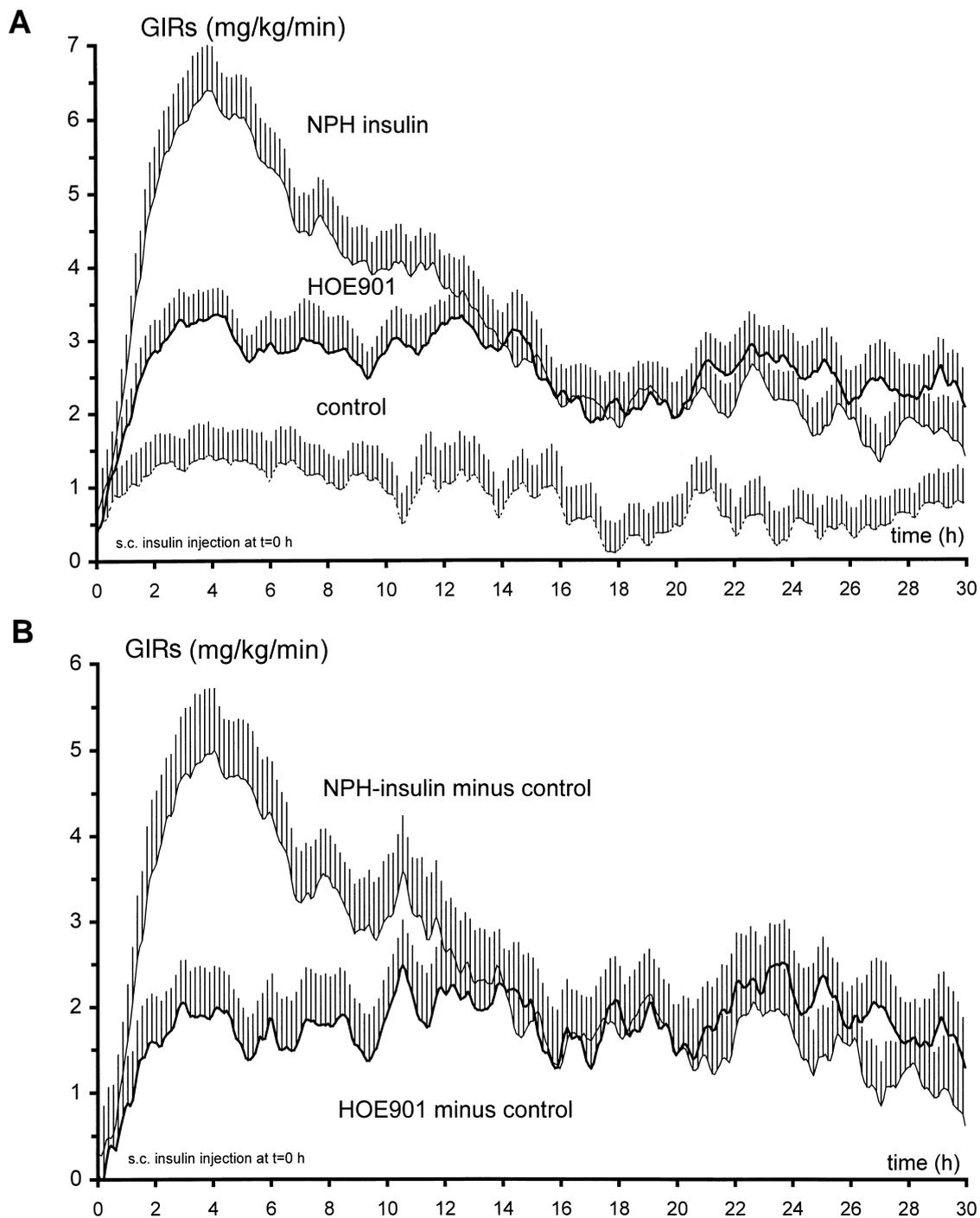
Due to the exploratory nature of this study, no formal study-size calculation was performed. Based on the results of previous studies with long-acting insulin preparations, we decided to include 15 subjects.

**RESULTS** — After subcutaneous injection of HOE901, the metabolic activity increased to a plateau within 4 h and remained rather constant thereafter and during the entire study period (Fig. 1A and Table 1). In contrast, the time-action profile of NPH insulin showed a pronounced peak after 4–6 h. Thereafter, the metabolic activity declined constantly until the end of the experiments, but it did not return to baseline values. Such differences were observed in 12 of the 15 subjects ( $80\%$ ). In the control experiment with application of placebo, the metabolic activity increased to a level of  $3$  mg · kg<sup>-1</sup> · min<sup>-1</sup> for 16 h and declined thereafter to  $2$  mg · kg<sup>-1</sup> · min<sup>-1</sup>. The maximal metabolic activity observed with HOE901 was lower and was reached later than with NPH (Table 1). The metabolic activity (AUC<sub>0–30 h</sub>) of HOE901 was lower than that of NPH insulin. The between-subject variability of AUC<sub>0–30 h</sub> was  $23\%$  for HOE901 and  $14\%$  for NPH insulin. Correction for the metabolic effect of the continuous intravenous insulin infusion led to absolute GIR levels of HOE901 and NPH insulin that were  $2$ – $3$  mg · kg<sup>-1</sup> · min<sup>-1</sup> lower, but they did not alter the shape of the profiles (Fig. 1B and Table 1).

Subcutaneous injection of HOE901 led to an increase in serum insulin concentrations within 2 h to a level remaining more or less constant for the next 20 h (Fig. 1B and Table 1). Thereafter, the levels slowly declined. In contrast, injection of NPH insulin resulted in a remarkable peak in serum insulin within 4 h. Thereafter, serum insulin levels slowly declined, but, in accordance with the metabolic effect observed, they did not return to baseline levels within the study period. In the control experiments with application of placebo, serum insulin remained rather stable at baseline levels. The changes in serum C-peptide levels were similar for all 3 treatments, indicating that the endogenous insulin secretion was comparably suppressed ( $>30\%$ ) during the clamp procedure on all of the study days (Table 1).

Neither type of insulin caused any side effects. In particular, no local reactions at the injection sites were observed.

**CONCLUSIONS** — This study shows that subcutaneous injection of HOE901 leads to an even metabolic effect that lasts for at least 24 h. In other words, its time-action profile does not show the typical peak observed within 4–7 h after injection of NPH insulin (7,8). In the experiments,



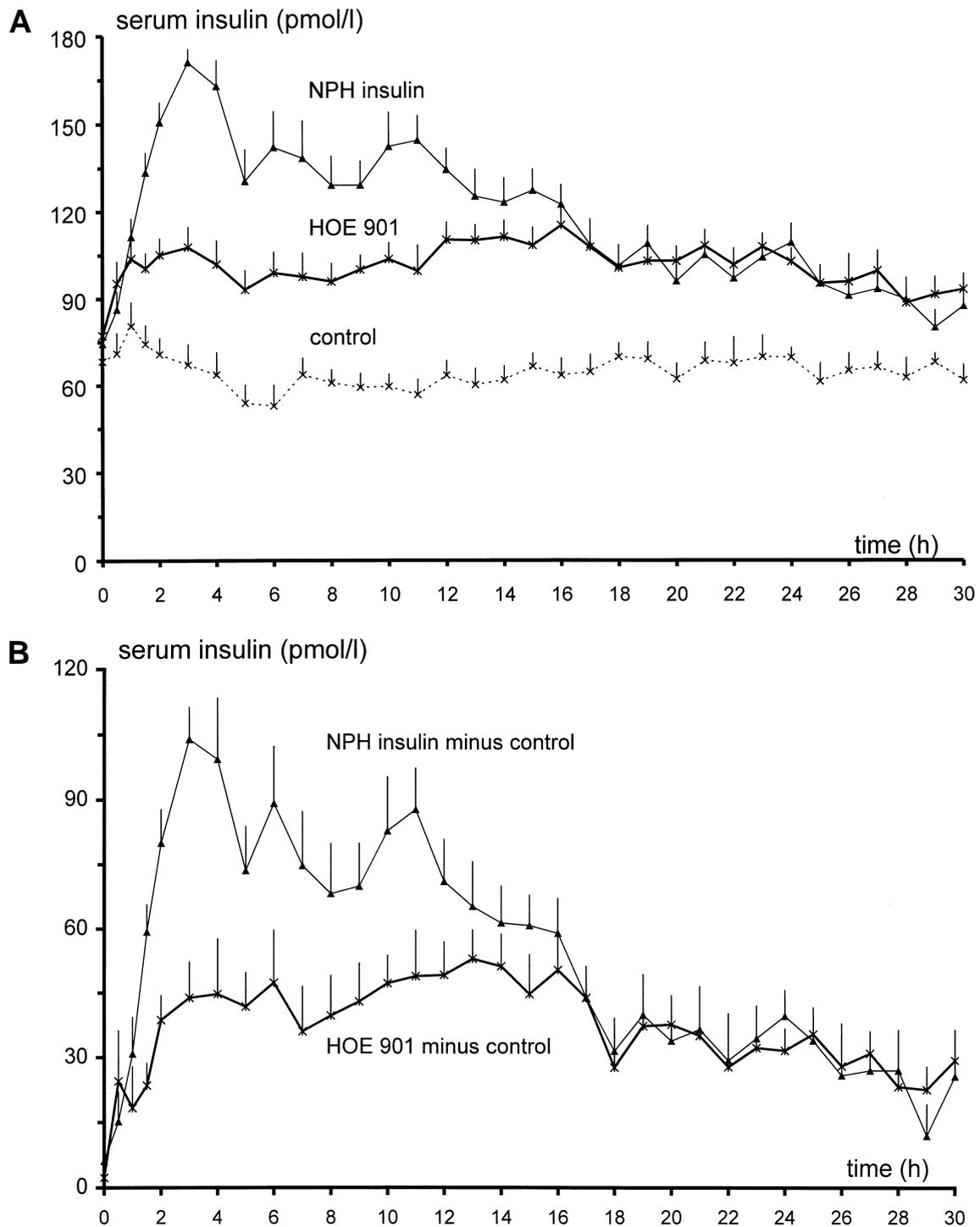
**Figure 1**—A: GIRs after subcutaneous injection of 0.4 U/kg body wt (mean dose  $29.4 \pm 3.3$  U) of HOE901, NPH insulin, and placebo on 3 different study days in 15 healthy volunteers. Data are means + SEM. B: GIRs with HOE901 and NPH insulin after subtraction of the metabolic effect observed in the control experiments with placebo.

the metabolic effect of HOE901 did not return to baseline values, indicating a duration of action of at least 30 h. Similar results were obtained in a glucose clamp study with type 1 diabetic patients, in which the end of the metabolic activity was >24 h in 16 of 20 patients (9). It remains to be stud-

ied whether this long duration of action leads to an accumulation of the metabolic effect over time.

In clinical practice, the metabolic effect of an injection of NPH insulin usually vanishes within 12–18 h. In our study, it may have been due to the high dose

administered (mean dose 29.4 U) that the duration of action of NPH insulin registered seems to be much longer. This explanation seems to be the most probable, given that the serum insulin levels also remained above baseline levels until the end of the experiments.



**Figure 2**—A: Serum insulin concentrations after subcutaneous injection of 0.4 U/kg body wt of HOE901, NPH insulin, and placebo on 3 different study days in 15 healthy volunteers. Data are means + SEM. B: Serum insulin concentrations with HOE901 and NPH insulin after correction for the serum insulin levels observed in the control experiments with placebo.

We cannot exclude the possibility that the peak observed with NPH insulin would have been less pronounced after injection in the thigh. Nevertheless, from clinical practice, it is well known that NPH

insulin does show a peak effect even after injection in the thigh, and it has been shown that changes in the injection site do not alter the time-action profile of HOE901 (10).

In principle, one would assume higher serum concentrations of HOE901 in comparison with those of NPH insulin in the second half of the experimental period in view of the 50% cross-reactivity. However,

**Table 1—Pharmacodynamic and pharmacokinetic summary measures of the long-acting insulin analog HOE901, NPH insulin, and placebo after subcutaneous injection in 15 healthy volunteers**

Parameter	Unit	HOE901	NPH insulin	Placebo	P*
Pharmacodynamics					
GIRs					
Baseline GIR	mg · kg <sup>-1</sup> · min <sup>-1</sup>	1.7 ± 1.2	2.2 ± 1.1	1.9 ± 1.1	NS
GIR <sub>max</sub>	mg · kg <sup>-1</sup> · min <sup>-1</sup>	5.3 ± 1.1 (2.6 ± 1.2)	7.7 ± 1.3 (4.5 ± 1.9)	3.6 ± 1.2	<0.05 (<0.01)
t <sub>max</sub>	h	8.6 ± 4.4 (16.4 ± 8.4)	5.4 ± 1.0 (5.6 ± 2.0)	6.1 ± 4.6	<0.01 (<0.001)
AUC <sub>0-4 h</sub>	g/kg	1.02 ± 0.34 (0.31 ± 0.27)	1.48 ± 0.34 (0.77 ± 0.45)	0.71 ± 0.30	<0.001 (<0.01)
AUC <sub>0-16 h</sub>	g/kg	4.42 ± 1.03 (1.60 ± 1.00)	5.90 ± 0.90 (3.08 ± 1.41)	2.81 ± 1.07	<0.001 (<0.01)
AUC <sub>0-24 h</sub>	g/kg	6.41 ± 1.50 (2.48 ± 1.51)	7.89 ± 1.14 (3.96 ± 1.90)	3.92 ± 1.41	<0.01 (<0.05)
AUC <sub>0-30 h</sub>	g/kg	7.92 ± 1.82 (3.12 ± 1.74)	9.24 ± 1.29 (4.46 ± 2.16)	4.89 ± 1.72	<0.05 (<0.05)
Pharmacokinetics					
Serum insulin levels					
Basal insulin	pmol/l	77 ± 21	74 ± 26	68 ± 21	NS
C <sub>max</sub>	pmol/l	143 ± 26 (91 ± 30)	197 ± 36 (141 ± 35)	110 ± 26	—
t <sub>max</sub>	h	16.7 ± 8.8 (13.7 ± 8.7)	5.1 ± 3.2 (6.6 ± 4.4)	9.8 ± 9.6	—
AUC <sub>0-30 h</sub>	nmol · l <sup>-1</sup> · h	3.05 ± 0.48 (1.13 ± 0.50)	3.54 ± 0.61 (1.61 ± 0.61)	1.92 ± 0.40	—
Serum C-peptide levels					
Basal values	nmol/l	0.58 ± 0.18	0.54 ± 0.25	0.56 ± 0.26	NS
C <sub>min</sub>	nmol/l	0.25 ± 0.10	0.24 ± 0.09	0.26 ± 0.09	NS
t <sub>min</sub>	h	18.3 ± 7.2	16.1 ± 8.2	15.6 ± 11.0	NS
AUC <sub>0-30 h</sub>	nmol · l <sup>-1</sup> · h	13.7 ± 4.5	13.2 ± 4.5	14.2 ± 4.3	NS

Data are means ± SD. Pharmacodynamic values for HOE901 and NPH insulin minus the metabolic effect of control experiment are given in parentheses. \*P values for the comparison of HOE901 with NPH insulin are from analysis of variance of treatment, subject, and period effect and from paired Student's *t* test. C<sub>max</sub>, maximal concentration; C<sub>min</sub>, minimal concentration; GIR<sub>max</sub>, maximal GIR; NS, not significant; t<sub>max</sub>, time to maximal concentration; t<sub>min</sub>, time to minimal concentration.

insulin receptor binding of HOE901 is also only 50% of that of human insulin. As described previously, such a difference in receptor binding leads to higher circulating levels (11). We regard this as the most plausible explanation for the serum insulin concentration observed. Unfortunately, there has been no information published about the clearance rate of HOE901.

It may be a profound advantage in daily clinical life that HOE901 is a clear solution; it has been shown that suspensions like NPH insulin are often not sufficiently shaken by the patients before administration (12). Because it is not necessary to mix HOE901 before injection, it may have a lower intraindividual variability of the metabolic effect induced. Furthermore, it can be speculated that a clear solution may show a more even distribution in the subcutaneous tissue before it precipitates and thereby reduces also the variability in effect. The only study available addressing the issue of variability of the metabolic effect did not find significant differences between HOE901 and NPH insulin when the latter was thoroughly shaken (13). In recent clinical trials, however, HOE901 insulin, as compared with NPH insulin, led to a reduced variability of

fasting blood glucose and a lower risk of hypoglycemic episodes (14,15).

It must be pointed out that determination of the time-action profile of long-acting insulin preparations is difficult, because the onset of action is rather slow and the overall metabolic action is considerably lower than that with rapid-acting insulin preparations. In healthy volunteers, it must be ensured that the metabolic action measured is not influenced by endogenous insulin secretion. The methods used up to now all show several disadvantages (i.e., infusion of somatostatin suppresses endogenous glucagon secretion and influences subcutaneous blood flow and insulin clearance) (5). A continuous intravenous insulin infusion leads to the desired suppression of endogenous insulin secretion; however, the metabolic effect of this infusion cannot be extrapolated from a baseline period of 2 h to the entire 30-h duration of the experiment. Changes might occur due to, for example, variations in the suppression of endogenous insulin secretion and/or insulin sensitivity over time. Therefore, we chose to include a control experiment with the administration of placebo to measure the actual glucose requirements elicited by

a constant insulin infusion during prolonged glucose clamp studies.

Therefore, our study allows for correction of the metabolic effect of the long-acting insulin preparations studied on the basis of the metabolic effect of the low-dose continuous intravenous insulin infusion. Under these conditions, it is reasonable to assume that the time-action profiles of HOE901 and NPH insulin registered in healthy subjects are predictive of the insulin activity in diabetic patients, just as it was observed with other long-acting insulin formulations (16,17). It may be argued that it is more reasonable to study the time-action profiles of insulin preparations in the target population (e.g., type 1 diabetic patients) to avoid the problem of suppression of endogenous insulin secretion. This procedure, however, bears other difficulties. For instance, one must ensure that the overall metabolic control and, especially, the blood glucose control immediately before injection are comparable between the patients to reduce inter- and intraindividual differences in insulin sensitivity.

For the description of the time-action profiles studied, summary measures were given. However, in the case of long-acting

insulin preparations, estimation of such pharmacodynamic properties is associated with a considerable error. In case the time-action profile has a real square-wave profile, estimation of  $GIR_{max}$  and  $t_{max}$  is impossible, and statistical comparison is meaningless. Thus, pharmacodynamic summary measures describing the maximal metabolic effect—with the exception of the AUC—are of limited value with long-acting insulin preparations. This parameter is not influenced by the shape of the time-action profile, but it reflects the sum of the metabolic effect elicited over the entire study duration or certain time intervals. The difference between  $t_{max}$  for serum insulin and  $t_{max}$  for  $GIR_{max}$  ( $16.7 \pm 8.8$  vs.  $8.6 \pm 4.4$  h) obtained with HOE901 has to be interpreted in view of the considerations previously described. The serum insulin levels observed with HOE901 did not show a marked peak. Thus, maximal GIR values were mainly influenced by random changes in serum insulin levels and in metabolic action rather than by the time-action profile itself. This high between-subject variability can also be depicted by the fairly large standard deviations.

In our study, HOE901 induced a lower metabolic effect than NPH insulin over a period of 24 h. It might be argued that this effect is too small to sufficiently lower blood glucose levels. However, long-acting insulin preparations are usually applied to avoid an increase in blood glucose levels over time and not to lower glycemia. Thus, an ideal long-acting insulin should have a metabolic effect that only substitutes basal insulin requirements. Furthermore, one has to take into account that, in our study, HOE901 was injected only once so that no steady-state conditions were established. Repeated injections of HOE901 may induce a higher metabolic effect.

In some European countries, patients are accustomed to twice-a-day injections of NPH insulin. Therefore, it would be interesting to compare the effects of a once-a-day injection of HOE901 with those of twice-a-day injections of NPH insulin in accordingly lower doses.

In summary, subcutaneous injection of the long-acting insulin analog HOE901

leads to a smooth time-action profile without pronounced peaks. This profile and the duration of action observed suggest that HOE901 is a promising candidate for a once-a-day basal insulin substitution. This hypothesis, however, has to be confirmed in clinical studies.

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