ORIGINAL ARTICLE doi: 10.1111/j.1463-1326.2006.00643.x

Time-action profile of insulin detemir and NPH insulin in patients with type 2 diabetes from different ethnic groups*

M. Hompesch,[1] B. Troupin,[1] T. Heise,[2] B. Elbroend,[3] L. Endahl,[3] H. Haahr[3] and L. Heinemann[2]

[1]Profil Institute for Clinical Research, San Diego, CA, USA
[2]Profil Institut für Stoffwechselforschung, Neuss, Germany
[3]Novo Nordisk, A/S, Bagsvaerd, Denmark

Aim: To evaluate the time-action profiles and the dose–response relationship of the long-acting insulin analogues insulin detemir (IDet) and NPH insulin (NPH) in type 2 diabetic patients belonging to different ethnic groups.
Methods: Forty-eight type 2 diabetic patients belonging to different ethnic groups (three groups of 16 African Americans (AA), 16 Hispanics/Latinos (HL) and 16 Caucasians) participated in this double-blind crossover trial. Each patient took part in six 16-h isoglycaemic glucose clamps (clamp target 7.2 mmol/l) and was randomly allocated to three doses (0.3, 0.6 and 1.2 (I)U/kg) of IDet and NPH, respectively.
Results: IDet and NPH showed comparable pharmacodynamic effects [the area under the glucose infusion rate curve ($AUC_{GIR\ 0\text{-}16\ h}$) (mg/kg)] in the investigated dose range: IDet, 0.3 U/kg, 207 AA, 535 HL, 285 Caucasians; 0.6 U/kg, 1203 AA, 824 HL and 1126 Caucasians; 1.2 U/kg, 1502 AA, 1977 HL and 2269 Caucasians; NPH, 0.3 IU/kg, 733 AA, 1148 HL and 1148 Caucasians; 0.6 IU/kg, 1395 AA, 1976 HL and 1077 Caucasians; 1.2 IU/kg, 2452 AA, 3296 HL and 2455 Caucasians. Both IDet and NPH showed a linear dose–response relationship in all three groups ($p = 0.31$), without any significant differences in slope ($p = 0.71$) or intercept ($p = 0.51$). Comparable results were obtained for pharmacokinetics.
Conclusions: These results confirm a linear dose–response relationship of IDet, without any relevant differences between ethnic groups. This suggests that similar dosing recommendation can be used for IDet in type 2 diabetic patients belonging to different ethnic group.

Keywords: basal insulin, ethnicity, glucodynamics, pharmacokinetics, variability
Received 10 May 2006; returned for revision 30 May 2006; revised version accepted 1 June 2006

Introduction

Differences in responsiveness to medicinal products have frequently been observed across racial and ethnicity groups. In diabetes, such differences may be attributable to intrinsic factors (e.g. genetics, metabolism, elimination), extrinsic factors (e.g. lifestyle, environmental exposure, sociocultural issues) or interactions between these factors.

For instance, in a recent publication, it was found that the Hispanics on average were less insulin sensitive than non-Hispanic Caucasians, despite a higher average energy and fat intake among the latter [1]. Obviously, differences in insulin sensitivity across ethnic groups may affect recommendations on treatment type/dosage. Even for insulin therapy, where the dose is individually titrated according to patients' needs and wishes, the recommended starting dose may vary across ethnic/racial

Correspondence:
Prof. Dr. Lutz Heinemann, Profil Institut für Stoffwechselforschung GmbH, Hellersbergstr. 9, 41460 Neuss, Germany.
Email:
lutz.heinemann@profil-research.de
*A preliminary report of this study was presented at the 65th Scientific Sessions of the American Diabetes Association.

groups. During the registration process of insulin detemir (IDet; Levemir®), Food and Drug Administration (FDA) recommended that a trial investigating potential differences in responsiveness to IDet by racial/ethnic group was initiated. IDet represents a new class of soluble long-acting human insulin analogues, which differ from human insulin in the attachment of a 14-C fatty acid chain at position B29 and removal of the amino acid residue at position B30. The protracted action of IDet results from self-association of IDet molecules at the injection site and via fatty acid side chain binding to albumin in the subcutis. In the blood stream, more than 98% of IDet is bound to albumin, which slows its delivery to peripheral target tissues [1,2]. IDet shows a more reproducible insulin absorption and time-action profile than NPH insulin (NPH) and insulin glargine, resulting in improved day-to-day, within-subject variability in fasting blood glucose in both type 1 and type 2 diabetes [3–15].

The aim of this study was to investigate the pharmacodynamic (PD) and pharmacokinetic (PK) properties of IDet and NPH over a range of therapeutically relevant doses in type 2 diabetic patients belonging to different ethnic group.

Research Design and Methods

Patients

Forty-eight patients with type 2 diabetes (33 men and 15 women) were exposed to trial drug in this randomized, double-blind, single-dose, six-period, crossover isoglycaemic glucose clamp study (table 1): 16 African Americans (AA), 16 Caucasians of Hispanic or Latino origin (HL) and 16 Caucasians not of Hispanic or Latino origin. The study was carried out in accordance with the principles of the Declaration of Helsinki and of Good Clinical Practice, and was approved by a central ethics committee.

Table 1 Demographic characteristics of the 48 patients with type 2 diabetes studied (33 men and 15 women) from three different ethnic groups

	African Americans	Caucasians of Hispanic or Latino origin	Caucasians not of Hispanic or Latino origin
Sex (men/women)	10/6	11/5	11/5
Smokers/Non-smokers	4/12	4/12	1/15
Age (years)	52 ± 10	51 ± 8	54 ± 13
Body mass index (kg/m)	30.2 ± 4.5	28.9 ± 3.9	28.9 ± 3.5
Haemoglobin A1c (%)	7.6 ± 1.3	8.3 ± 1.4	8.1 ± 0.9
Duration of diabetes (years)	9 ± 6	11 ± 7	12 ± 7
Fasting serum C-peptide (nmol/l)	0.65 ± 0.30	0.88 ± 0.58	0.58 ± 0.30

Out of the 48 patients, 27 patients (nine AA, six HL and 12 Caucasians) were treated with insulin in combination with one or two oral antidiabetics (OADs). Those patients discontinued all OADs before entering the trial. Forty-three patients (14 AA, 15 HL, 14 Caucasians) completed all six dosing visits. Data from one patient were excluded from the statistical analyses due to implausibly high serum insulin concentrations.

Study Procedure

All patients were instructed to have their usual dinner the evening before trial product administration, to have a light lunch and then not to take any other food after 14:00 hours on the day of study drug administration. The patients were instructed to take their usual insulin (other than insulin glargine) the evening before study drug administration. Patients treated with insulin glargine were asked to have their last insulin glargine injection the evening 2 days before study drug administration, and to have an injection of NPH the evening before study drug administration.

On the first dosing day, each patient was randomized to three subcutaneous (s.c.) doses of IDet [0.3, 0.6 and 1.2 U/kg, Levemir®; 100 U/ml (2400 nmol/ml); Novo Nordisk, Bagsvaerd, Denmark] and three s.c. doses of NPH [0.3, 0.6 and 1.2 (I)U/kg, Novolin® N; 100 U/ml (600 nmol/ml); Novo Nordisk]. The six days on which different doses and types were applied were separated by 4–14 days. Between 16:00 and 17:00 hours, patients were connected to a Biostator (Life Science Instruments, Elkhart, IN, USA) for intravenous glucose infusion to maintain blood glucose at 7.2 mmol/l (130 mg/dl). The patients were still fasting and in supine position, and they were allowed to take only water during the entire clamp. Immediately after connecting the patients to the Biostator, an intravenous insulin infusion (regular human insulin, at a rate of at least 0.15 mU/kg/min) was established. One hour before the study drug administration, the infusion rate was fixed at 0.2 mU/kg/min until the end of the experiments. The different insulin formulation/doses were injected s.c. by syringe (Becton Dickinson BD Ultra Fine, Heidelberg, Germany) into a lifted skinfold in the thigh. NPH was resuspended appropriately prior to drawing up the insulin dose. After trial drug administration at around 21:00 hours (time point zero), intravenous glucose infusion rates (GIR) necessary to keep blood glucose constant were adjusted every minute by the Biostator for 16 h.

PK and PD Evaluations

Blood samples were drawn hourly for the measurement of blood glucose, serum IDet, serum human insulin and serum C-peptide concentrations. Blood glucose was

Table 2 Pharmacodynamic and plasma cokinetic summary measures of the 48 type 2 diabetic patients of different ethnic groups treated with different doses of insulin detemir and NPH insulin

		Insulin detemir (U/kg)			NPH insulin (U/kg)		
		0.3	0.6	1.2	0.3	0.6	1.2
Pharmacodynamic summary measures							
$AUC_{GIR\ 0\text{-}16\ h}$ (mg/kg) least	AA	207 (103–419)	1203 (583–2481)	1502 (743–3033)	733 (453– 1187)	1395 (874–2227)	2452 (1536–3916)
square mean (95% CI)	HL	535 (259–1108)	824 (407–1667)	1977 (955–4092)	1148 (684–1926)	1976 (1215–3214)	3296 (2027–5361)
	Caucasians	285 (138–590)	1126 (556–2277)	2269 (1096–4696)	942 (582–1526)	1077 (675–1720)	2455 (1538–3920)
GIR_{max} (mg/kg/min) least	AA	0.9 (0.6–1.4)	2.1 (1.4–3.2)	2.5 (1.7–3.8)	1.7 (1.2–2.5)	2.6 (1.9–3.7)	3.8 (2.7–5.4)
square mean (95% CI)	HL	1.3 (0.8–2.0)	1.7 (1.1–2.6)	3.5 (2.3–5.3)	2.3 (1.6–3.4)	3.3 (2.3–4.8)	5.1 (3.6–7.3)
	Caucasians	1.0 (0.6–1.5)	2.2 (1.5–3.4)	3.7 (2.4–5.7)	2.1 (1.5–3.0)	2.1 (1.5–2.9)	4.0 (2.8–5.6)
t_{max} (min) arithmetic	AA	536 ± 341	639 ± 274	551 ± 203	519 ± 284	550 ± 263	643 ± 237
mean ± s.d.	HL	508 ± 289	535 ± 236	558 ± 126	629 ± 226	545 ± 193	564 ± 266
	Caucasians	574 ± 245	493 ± 238	743 ± 191	521 ± 211	485 ± 200	531 ± 241
Pharmacokinetic summary measures							
$AUC_{0\text{-}16\ h}$	AA	1312 (1141–1510)	2782 (2419–3199)	5382 (4678–6191)	45 (32–64)	115 (80–163)	237 (168–334)
(nmol × min/l) least	HL	1355 (1172–1566)	2595 (2254–2987)	4973 (4301–5749)	53 (37–75)	114 (80–163)	192 (134–274)
square mean (95% CI)	Caucasians	1481 (1281–1712)	3100 (2693–3569)	5263 (4553–6085)	75 (52–108)	77 (55–109)	222 (157–313)
C_{max} (pmol/l) least square	AA	2318 (1967–2730)	4803 (4078–5658)	8024 (6812–9452)	129 (98–170)	230 (175–304)	403 (309–527)
mean (95% CI)	HL	2555 (2156–3027)	4574 (3882–5388)	7415 (6259–8785)	109 (83–144)	207 (157–273)	335 (254–442)
	Caucasians	2408 (2032–2853)	5082 (4314–5987)	7471 (6306–8851)	169 (127–225)	157 (120–205)	354 (271–462)
t_{max} (min) arithmetic	AA	304 ± 125	368 ± 115	348 ± 161	369 ± 210	476 ± 284	516 ± 280
mean ± s.d.	HL	369 ± 168	340 ± 124	373 ± 158	476 ± 251	467 ± 277	441 ± 275
	Caucasians	424 ± 136	404 ± 181	476 ± 132	355 ± 241	496 ± 272	612 ± 280

AUC, area under the curve; GIR, glucose infusion rate; AA, African Americans; HL, Hispanics/Latinos.

measured using a glucose oxidase method (Glucose Analyzer, Analox GM9, Analox Instruments, London, UK). Serum IDet concentrations were measured using a specific enzyme-linked immunosorbent assay (ELISA) not cross-reacting with human insulin. Total serum IDet concentrations (free and albumin bound) were measured. Lower limit of quantification (LLOQ) was 25 pmol/l. Serum insulin concentrations were measured using the DAKO insulin ELISA (DAKO, Glostrup, Denmark). LLOQ was 5 pmol/l.

Statistical Methods

The overall significance level was set to 5%, and accordingly, 95% confidence intervals were calculated for the relevant parameter estimates. The GIR curves were smoothed using LOESS (SAS, version 7) with first-degree local polynomials and a smoothing parameter of 0.25 after baseline adjustment (subtraction of the average GIR from −1 to 0 h before trial product administration). The primary endpoint, the area under the GIR curve (AUC_{GIR}), was calculated using the trapezoidal technique on interpolated points. GIR_{max} and t_{GIRmax} were derived as the maximum of the smoothed GIR curve for each isoglycaemic clamp and the corresponding time. The PK endpoints were derived from the PK curves using a similar approach. The dose–response relationship within the three ethnic groups was evaluated in an analysis of variance (ANOVA) approach using log-transformed values for $AUC_{GIR\ 0\text{-}16\ h}$ (primary endpoint), GIR_{max} or the PK parameters $AUC_{0\text{-}16\ h}$ and C_{max}. The ANOVA fitted to these data (as the dependent variables) was a repeated measures set-up with ethnicity × insulin preparation × dose as fixed effect and subject as a random effect to account for the within-subject variation and an error term, both with variances depending on drug. The model was fitted using Proc Mixed in SAS(R) v7.0 using the restricted maximum likelihood method.

The linearity of the dose–response relationship was tested. In addition, it was tested whether the slopes and intercepts depended on ethnic group within each insulin preparation.

Results

PD Results

Mean $AUC_{GIR\ 0\text{-}16\ h}$ increased with increasing dose for IDet and NPH in all three ethnic groups (table 2, figure 1), with the exception of NPH in Caucasians.

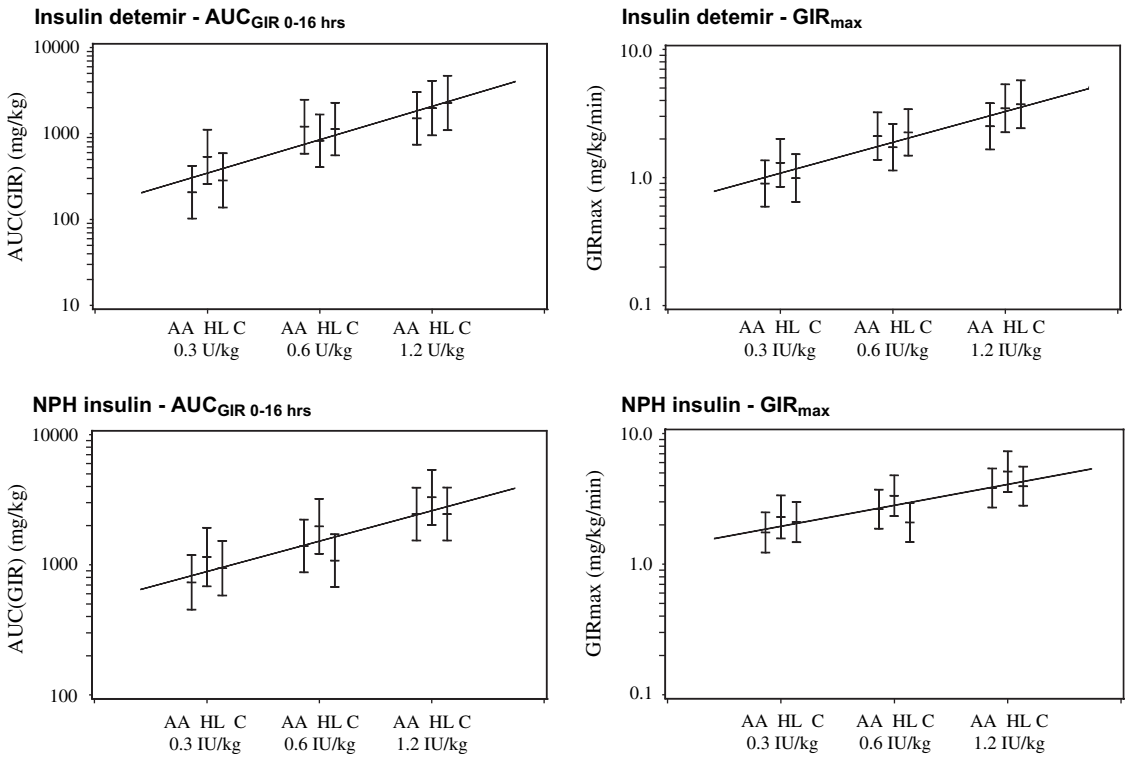

Fig. 1 The log($AUC_{GIR\ 0\text{-}16\ h}$) vs. log(dose) for insulin detemir (IDet) and for NPH insulin (NPH), and log(GIR_{max}) vs. log(dose) for IDet and for NPH. AUC, area under the curve; GIR, glucose infusion rate.

However, the total metabolic activity was higher with NPH than with IDet. The log($AUC_{GIR\ 0\text{-}16\ h}$) increased linearly with log(dose) ($p = 0.31$), with similar slopes ($p = 0.71$) and intercepts ($p = 0.51$) for the three ethnic groups for both IDet and NPH. Similar results were obtained for GIR_{max} ($p = 0.24$, 0.80 and 0.51, respectively) (table 2).

PK Results

Mean $AUC_{0\text{-}16\ h}$ and mean C_{max} increased with increasing dose for both IDet and NPH in all three ethnic groups, without significant differences (table 2). There was no noteworthy difference between AA, HL and Caucasians. Dose proportionality was demonstrated for $AUC_{0\text{-}16\ h}$ vs. dose for both IDet and NPH (figure 2). Mean t_{max} ranged from 304 to 476 min for IDet and from 355 to 612 min for NPH, but it did not vary markedly between ethnic groups or between doses.

Serum C-peptide concentrations were slightly suppressed after dosing with IDet and NPH, with no marked increase towards the end of the clamp (data not shown). There was no indication of a difference between IDet and NPH or between AA, HL and Caucasians.

Safety Results

There was no apparent difference between AA, HL and Caucasians with regard to the safety profiles of IDet and NPH. The observed adverse events were mainly related to the clamp procedure and were similar to those seen in previous clamp trials.

Discussion

In view of the request by the FDA to provide more data on whether specific dosing recommendations must be given for different ethnic groups or not, the need to perform more studies in the future in which potential differences in response to other insulin formulations (or routes of insulin application, such as inhaled insulin) in patients with diabetes from different ethnic groups are investigated can be foreseen. To our knowledge, no such comparative studies have been performed in the three different ethnic groups studied. It appears as if this aspect has to date been neglected.

On comparison, the results obtained in this study involving patients with type 2 diabetes and those obtained in patients with type 1 diabetes were similar [6].

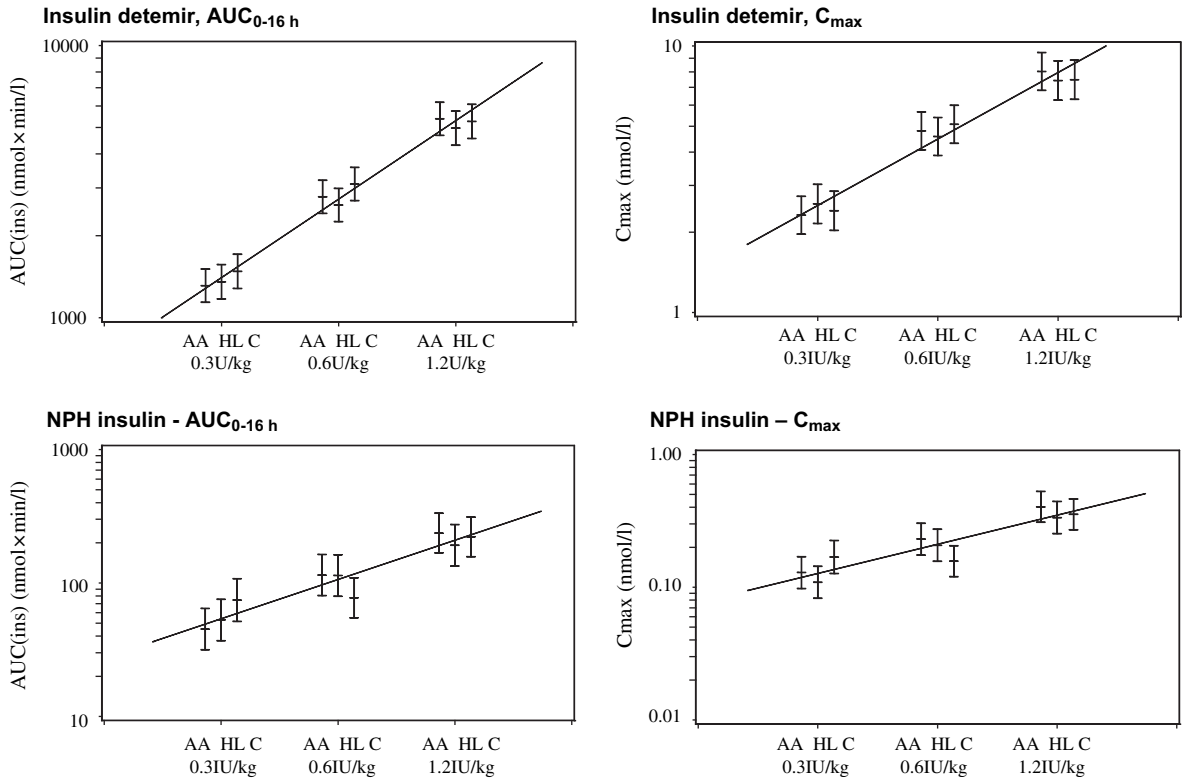

Fig. 2 The log($AUC_{0\text{-}16\ h}$) vs. log(dose) for insulin detemir (IDet) and for NPH insulin (NPH) and log(C_{max}) vs. log(dose) for IDet and for NPH. AUC, area under the curve.

The observed differences in the maximal metabolic action (GIR_{max}) between IDet and NPH underline the different time-action profile of these two basal insulins, that is IDet has a flatter profile and a longer duration of action than NPH, with its marked peak in the time-action profile [5,6]. The higher metabolic activity observed with NPH can be explained by the fact that nominally identical insulin doses (in terms of units per kilogram body weight) were applied; however, both insulin formulations differ in their molar concentration (600 nmol/l with NPH and 2400 nmol/l with IDet). This increase in insulin strength was necessary to take into account the lower affinity to the insulin receptor of IDet in comparison with human insulin.

In conclusion, the PD dose–response relationship observed with IDet and NPH was linear, and there was no difference between the three ethnic groups (AA, HL and Caucasians) in the investigated dose range from 0.3 to 1.2 (I)U/kg. Thus, there is no indication of a need for different titration guidelines for different ethnic groups when using IDet and as with any other insulin, patients should be individually titrated.

Acknowledgement

The study was supported by Novo Nordisk (Princeton, NJ, USA).

References

1 Diaz VA, Mainous AG, Koopman RJ, Geesey ME. Are ethnic differences in insulin sensitivity explained by variation in carbohydrate intake? Diabetologia 2005; **48:** 1264–1268.
2 Markussen J, Havelund S, Kurtzhals P *et al.* Soluble, fatty acid acylated insulins bind to albumin and show protracted action in pigs. Diabetologia 1996; **39:** 281–288.
3 Kurtzhals P, Havelund S, Jonassen I *et al.* Albumin binding of insulins acylated with fatty acids: characterization of the ligand-protein interaction and correlation between affinity and timing of the insulin effect in vivo. Biochem J 1995; **321:** 725–731.
4 Heise T, Nosek L, Stender A *et al.* Lower within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in people with type 1 diabetes. Diabetes 2004; **53:** 1614–1620.
5 Heinemann L, Sinha K, Weyer C, Loftager M, Hirschberger S, Heise T. Time-action profile of the soluble, fatty acid acylated long-acting insulin analogue NN304. Diabet Med 1999; **16:** 332–338.
6 Plank J, Bodenlenz M, Sinner F *et al.* A double-blind, randomized, dose-response study investigating the pharmacodynamic and pharmacokinetic properties of the long-acting insulin analog detemir. Diabetes Care 2005; **28:** 1107–1112.
7 Hermansen K, Madsbad S, Perrild H, Kristensen A, Axelsen M. Comparison of the soluble basal insulin analog insulin detemir with NPH insulin: a randomized open crossover trial in type 1 diabetic subjects on basal-bolus therapy. Diabetes Care 2001; **24:** 296–301.
8 Vague P, Selam J-L, Skeie S *et al.* Insulin detemir is associated with more predictable glycaemic control and lower risk of hypoglycaemia compared to NPH insulin in subjects with type 1 diabetes. Diabetes Care 2003; **26:** 590–596.
9 Russell-Jones D, Simpson R, Hylleberg B, Draeger E, Bolinder J. Effects of once-daily insulin detemir or NPH insulin on blood glucose control in patients with type 1 diabetes mellitus using a basal-bolus regimen. Clin Ther 2004; **26:** 724–736.
10 Pieber T, Draeger E, Kristensen A, Grill V. Comparison of three multiple regimens for type 1 diabetes: morning plus dinner or bedtime administration of insulin detemir vs. morning plus bedtime NPH insulin. Diabet Med 2005; **22:** 850–860.
11 Home P, Bartley P, Russell-Jones D *et al.* Insulin detemir offers improved glycemic control compared with NPH insulin in people with type 1 diabetes: a randomised clinical trial. Diabetes Care 2004; **27:** 1081–1087.
12 Haak T, Tiengo A, Draeger E, Suntum M, Waldhausl W. Lower within-subject variability of fasting blood glucose and reduced weight gain with insulin detemir compared to NPH insulin in patients with type 2 diabetes. Diabetes Obes Metab 2005; **7:** 56–64.
13 Standl E, Lang H, Roberts A. The 12-month efficacy and safety of insulin detemir and NPH insulin in basal-bolus therapy for the treatment of type 1 diabetes. Diabetes Technol Ther 2004; **6:** 579–588.
14 Jhee SS, Lyness WH, Rojas PB, Leibowitz MT, Zarotsky V, Jacobsen LV. Similarity of insulin detemir pharmacokinetics, safety, and tolerability profiles in healthy Caucasian and Japanese American subjects. J Clin Pharmacol 2004; **44:** 258–264.
15 Hermansen K, Derezinski T, Kim H, Gall M-A. Treatment with insulin detemir in combination with oral agents is associated with less risk of hypoglycaemia and less weight gain than NPH insulin at comparable levels of glycaemic improvement in people with type 2 diabetes (abstract). Diabetologia 2004; **47** (Suppl. 1): A273.