A Single Center, Open-Labeled Trial to Investigate the Pharmacokinetics of Insulin Detemir in Healthy Taiwanese Subjects

Ching Fai Kwok[1], and Low Tone Ho[2],*

[1]Division of Endocrine and Metabolism, Department of Medicine, Cheng Hsin General Hospital and Taipei Veterans General Hospital, Taipei, Taiwan

[2]Department of Medical Education and Internal Medicine, Taipei Veterans General Hospital and School of Medicine, National Yang-Ming-Chao-Tung University School of Medicine, Taipei, Taiwan

***Corresponding author:** Low Tone Ho, MD, Department of Medical Education and Internal Medicine, Taipei Veterans General Hospital and School of Medicine, National Yang-Ming-Chao-Tung University School of Medicine, Taipei, Taiwan, E-mail: ltho@vghtpe.gov.tw

Abstract

Backgrounds: Insulin detemir (NN304) is a long-acting insulin analogue reported to provide more predictable blood glucose level throughout the day, leading to a lower within-subject variability compared to NPH insulin. Pharmacokinetic profiles of insulin detemir had not been investigated in Taiwanese. This study was to determine whether there is a difference between Taiwanese subjects in pharmacokinetic profile of insulin detemir compared to Caucasian subjects.

Methods: Pharmacokinetic profile of insulin detemir was measured in twenty male Taiwanese (NN304-3023). Eligible subjects were given insulin detemir as a single dose subcutaneous injection at 0.5 U/kg body weight in the mid-thigh using NovoPen® 3 device. 32-hour serum insulin detemir concentrations were measured. Hypoglycemia and other adverse events were recorded. The results were compared to data obtained from a previous trial in Caucasian subjects (NN304-1451).

Results: There was no significant difference between Taiwanese (NN304-3023) and Caucasian (NN304-1451) in the primary endpoint, $AUC_{(0-\infty)}$, and the secondary endpoints, $AUC_{(0-24h)}$, and $t_{1/2}$. However, the secondary endpoints, C_{max} was 40% higher, t_{max} was shorter (270.0 *vs* 420.0 min) and $AUC_{(0-5h)}$ was 2-fold more in Taiwanese. When only male subjects were included in the comparator trial (NN304-1451), the $t_{1/2}$ was significantly shorter in Taiwanese (348 min *vs* 404 min). There was no significant difference in the mean blood glucose concentrations between Taiwanese and Caucasian subjects. A single episode of hypoglycemia (53 mg/dL) was reported in a 24-year-old male approximately 2.5 hours after the administration of insulin detemir. He was able to treat himself for the episode.

Conclusion: In this pharmacokinetic evaluation of a single dose administration of insulin detemir in Taiwanese male subjects, the $AUC_{(0-\infty)}$, and $AUC_{(0-24h)}$ were not different from that of Caucasians in the comparator trial. However, insulin detemir appeared to be more rapidly absorbed in Taiwanese males. Further studies are warranted to elucidate its pharmacodynamic response and mechanisms. Finally, there was no clinically relevant safety concern raised in this study (Funded by research grant from Novo Nordisk, Taiwan, first registration (22/12/2011) ClinicalTrials.gov number, NCT01497587).

Keywords: Insulin detemir; Pharmacokinetics; Taiwanese; Males

Introduction

Insulin detemir (NN304) is a derivative of human insulin [Lys^B29(Ne-tetradecanoyl) des(^B30) human insulin], in which the threonine residue at position B30 of the human insulin molecule has been removed and a C14 fatty acid side-chain has been attached to position B29 [1]. The fatty acid side- chain contributes to an increased self-association of hexamers, which delays hexamer dissociation and consequently absorption [2]. Upon dissociation of the hexamers into dimers and monomers, the fatty acid residue associates with the free fatty acid binding sites on the albumin molecule in the interstitial

fluid and in the plasma and prolongs the absorption of insulin detemir further. The free and biologically active fraction of insulin detemir permeates the capillary wall and enters the bloodstream, where it binds to albumin again. To reach the muscle and fat target tissues, insulin detemir dissociates from albumin and passes the capillary wall once more. Hence, the protracted action of insulin detemir is mediated by the strong self-association of insulin detemir molecules at the injection site and albumin binding (98-99% bound to albumin in plasma) [2-4] *via* the fatty acid side-chain. The rate of absorption is slow due to the low concentration of insulin detemir available

for diffusion through the tissue and passage across the capillary wall. In combination, the two mechanisms of protraction provide a more reproducible absorption and action profile of insulin detemir compared to NPH insulin [5]. Insulin detemir is a clear and colourless solution, and provides a homogenous concentration of insulin detemir, which increases the dosing accuracy. The more reproducible action profile leads to a more predictable blood glucose level throughout the day, leading to lower within-subject variability than that reported with NPH insulin [6]. At equivalent dosing levels, insulin detemir has a longer duration of action than NPH insulin. No safety concerns have been raised during the preclinical and clinical phase 1, 2 and 3 trials. Clinical trials have confirmed a delayed but sustained blood glucose lowering effect with insulin detemir in both healthy subjects, and subjects with type 1 and type 2 diabetes. To date, clinical trials with insulin detemir in healthy subjects as well as in subjects with type 1 and type 2 diabetes have been conducted in Europe, USA, Japan and Australia. The latest results from clinical phase 3 trials have suggested that subjects with type 1 and 2 diabetes can be successfully treated with insulin detemir once or twice daily to cover basal insulin needs in combination with human soluble insulin or the rapid-acting insulin analogue administered at meals [5,6].

The purpose of this study was to determine whether there was a difference between Taiwanese subjects in pharmacokinetic profile of insulin detemir compared to Caucasian subjects.

Materials and Methods

The trial design was based on trial NN304-1451 in order to compare with the Caucasian subjects in that trial [7]. Twenty Taiwanese male subjects were included based on the inclusion and exclusion criteria. The inclusion criteria were: healthy male Taiwanese subjects aged between 18 and 55 years (inclusive), Body Mass Index (BMI) between 18 and 27 kg/m² (inclusive); fasting plasma glucose ≤ 6.1 mmol/L and non-smoker or smoking ≤ 5 cigarettes per day or the equivalent. Exclusion criteria were: participation in any other clinical trial involving other investigational products within the last 3 months, previous participation in this trial, clinically significant abnormal hematology or biochemistry screening tests, any serious systemic infectious disease that occurred during the four weeks prior to the first dose of test drug, any intercurrent illness that may affect blood glucose, subject with a history of alcohol or drug dependence, any positive reaction of drug of abuse or alcohol screen, positive Hepatitis B or C or HIV screens, use of prescription drugs within 3 weeks preceding the first dosing of insulin detemir, mental incapacity, unwillingness or language barriers precluding adequate understanding or cooperation, subject with a first-degree relative with diabetes mellitus, history of, or presence of diabetes, cancer or any clinically significant cardiac, respiratory, metabolic, renal, hepatic, gastrointestinal, endocrinological, dermatological, venereal, hematological, neurological, or psychiatric disease or disorder as judged by the investigator, previous history of anaphylactic reaction, known or suspected allergy to trial product or related products.

An overview of the trial flow is provided in figure 1. The procedures for the relevant visit were conducted according to the trial flow chart. Before screening, subjects received a screening number in ascending order and were asked to attend the screening visit in a fasting state, having consumed only water since midnight. Blood samples were collected for the analysis of virology, hematology and clinical chemistry. Subjects were advised to abstain from strenuous activity 48h prior to visit 1.
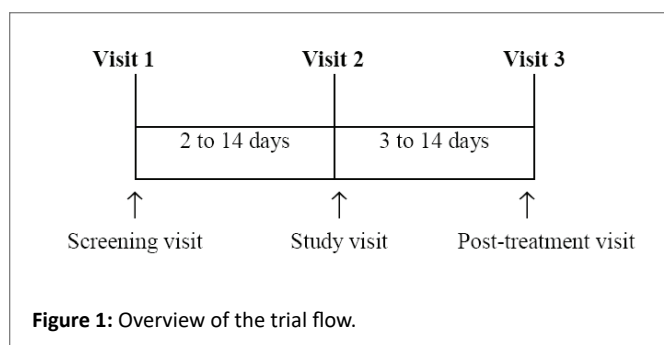

Figure 1: Overview of the trial flow.

On visit 2, subjects were admitted to the Clinical Research Centre of Taipei Veterans General Hospital approximately at 1900h in the evening of Day-1 and stayed until 32 hours after the subcutaneous dose. All subjects were given a carbohydrate-rich meal between 20h and 22h in the evening of Day-1. In the morning of Day 0, Insulin detemir was administered subcutaneously in the thigh region at time-point zero, using a NovoPen® 3 device at a dose of 0.5 U/kg body weight. Serial blood sampling for the assessment of insulin detemir concentrations were performed at 30-minute intervals for 6 hours and then at 1-h intervals until 32 h post-dosing. A cannula was inserted antegradely into a vein for blood sampling. The cannula was kept open and free from coagulated blood by using a heparinized saline flush post sampling. One mL of blood was drawn and discarded. Thereafter, 4 mL of blood was drawn and 3.5 mL of blood was handled according to the laboratory manual from Capio Diagnostik. The remaining 0.5 mL of blood was taken for bedside glucose measurement using a glucometer. The total amount of blood drawn for this trial did not exceed 120 mL per subject. Insulin detemir concentration was measured by Capio Diagnostik Clinical Trials Lab, Copenhagen using the insulin detemir-specific enzyme-linked immunosorbent assay.

Subjects were required to remain in a supine or semi-supine position for at least 6h after the administration of the trial product. Thereafter, they were allowed to walk around. Meals were served at 30 minutes prior to dose administration, and approximately 3, 22, and 26 hours post dosing. Snacks were given on 5 and 7 hours post dosing.

All adverse events were recorded by the investigator and evaluated. Adverse events [5] included hypoglycemia and any other undesirable medical event occurring to the subject, whether or not related to trial product. The subjects were also asked at each contact with the site if they had any adverse events.

The protocol was approved by the independent Ethics Committee of Taipei Veterans General Hospital prior to study initiation. The study was performed in accordance with the Declaration of Helsinki (1964) [8] and the local Good Clinical Practice regulations. Informed consent was obtained in writing prior to any study-related activities.

Statistical methods: statistical analysis was performed using SAS version 8.2 on a Microsoft Windows platform and pharmacokinetic parameters were calculated [9]. The primary endpoint was the area under the insulin detemir concentration curve from zero to infinity($AUC_{(0-\infty)}$). The null hypothesis was that there was no difference in ($AUC_{(0-\infty)}$) in Taiwanese subjects compared to Caucasian subjects in trial NN304-1451 with thigh administration of insulin detemir. The log- transformed primary endpoint, ($AUC_{(0-\infty)}$)was analyzed using an ANOVA model with ethnic group as fixed effect. The ratio of the geometric means for the two ethnic groups was obtained, together with the 95% Confidence Interval (CI). The secondary endpoints were the maximum insulin detemir concentration (C_{max}), time to maximum

Citation: Kwok CF, Ho LT (2021) A Single Center, Open-Labeled Trial to Investigate the Pharmacokinetics of Insulin Detemir in Healthy Taiwanese Subjects. J Drug Res Dev 7(3): dx.doi.org/10.16966/2470-1009.168

2

insulin detemir concentration (t_{max}), Mean Residence Time of insulin detemir (MRT), the area under the insulin detemir concentration curve in the time interval 0-5h ($AUC_{(0-5h)}$), the area under the insulin detemir concentration curve in the time interval 0-24h ($AUC_{(0-24h)}$), and insulin detemir half-life ($t_{1/2}$). The safety endpoints were: incidence of hypoglycemic episodes, adverse events and serious adverse events, laboratory assessments, weight, vital signs and physical examination. All summary tables described for hypoglycemia and adverse events were based on treatment emergent events only, that is, events starting after the time of first administration of the trial product and within 7 days after the last treatment day.

Subjects were excluded from the analysis if they did not fulfill any of inclusion or exclusion criteria, or had any protocol violation such that the assessment of pharmacokinetic endpoints was likely to be biased or had unacceptable data quality. For comparison, data from Caucasian subjects in a previously published trial NN304-1451 [7] were used. A significance level of 5% was used throughout the analyses, unless stated otherwise.

Results

Twenty Taiwanese subjects completed the study. Their demographic data were shown in table 1. Two of them were excluded from the pharmacokinetic analysis due to violation of protocol. There was no significant difference between Taiwanese and Caucasian in the primary endpoint, $AUC_{(0-\infty)}$. The ratio was 0.9 (95% CI: 0.83; 1.07, p=0.327) (Table 2).

For the secondary endpoints, there was no significant difference between Taiwanese and Caucasian in the $AUC_{(0-24h)}$ and $t_{1/2}$ (Table 2, Figure 2). However, the C_{max} was 40% higher (ratio was 1.4, 9% CI 1.19; 1.60, p<0.0001) and $AUC_{(0-5h)}$ was doubled (ratio was 2, 95% CI 1.56; 2.62, p<0.0001)in Taiwanese compared to Caucasians (Table 2, Figure 2). Furthermore, the t_{max} (270.0 *vs* 420.0 min, p=0.0005) and MRT (ratio was 0.7, 95% CI: 0.62; 0.76, p<0.0001) were significantly shorter in Taiwanese (Table 2, Figure 2).

As Taiwanese subjects were lighter in weight and only male subjects were included, we decided to explore if the results of pharmacokinetic analysis could have been influenced by factors such as BMI and gender. Exploratory analysis was carried out by including BMI as a covariate

in the ANOVA model. The results were similar to the analysis without any adjustments for BMI (data not shown). Hence, BMI was not found to be a confounding factor on pharmacokinetic endpoints. When only male subjects were included in the comparator trial (NN304-1451) [7], the results showed no significant difference between Taiwanese and Caucasian in the primary endpoint, $AUC_{(0-\infty)}$ with a ratio of 0.9 (95% CI: 0.75; 1.01, p=0.062). For the secondary endpoints, there was

Table 1: Baseline demographic data in Taiwanese subjects (NN304-3023) and Caucasians (NN304-1451).

	NN304-1451*	NN304-3023
Number of Subjects Exposed	28	20
Age, years		
N	28	20
Mean (SD)	32.6 (9.9)	23.8 (4.2)
Median	32.7	23.4
Min-Max	18.3-51.4	19.2-36.6
Sex, N (%)		
Female	14 (50.0%)	0 (0.0%)
Male	14 (50.0%)	20 (100%)
Weight, kg		
N	28	18
Mean (SD)	72.8 (10.2)	65.1 (6.4)
Median	70.0	63.7
Min-Max	61.0-102.0	54.6-78.5
Height, m		
N	28	18
Mean (SD)	174 (9.52)	172 (4.39)
Median	173	172
Min-Max	154-196	165-180
BMI, kg/mA²		
N	28	18
Mean (SD)	24.1 (1.9)	21.9 (1.9)
Median	24.3	22.2
Min-Max	19.8-27.0	18.7-25.9

*Data for NN304-1451 is obtained from a previous study on Caucasian subjects.
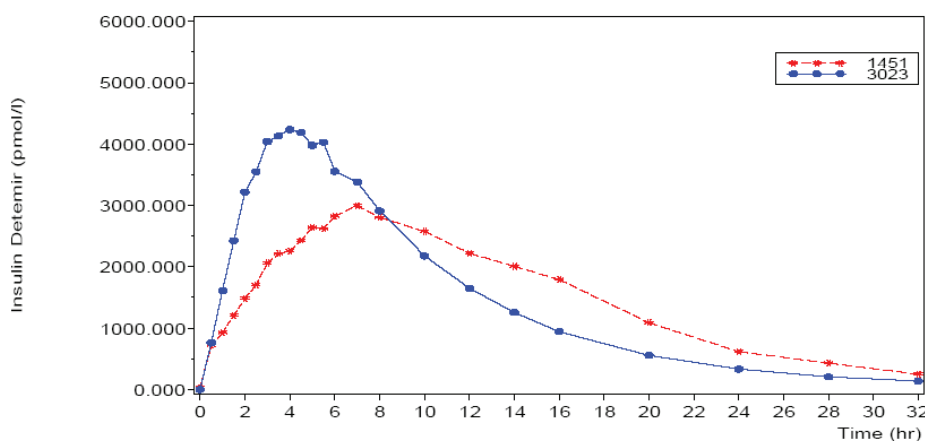

Figure 2: Mean Insulin Detemir Concentration (pmol/L) over 32 h in Taiwanese (3023) and Caucasians (1451) after a single injection of insulin detemir.

Citation: Kwok CF, Ho LT (2021) A Single Center, Open-Labeled Trial to Investigate the Pharmacokinetics of Insulin Detemir in Healthy Taiwanese Subjects. J Drug Res Dev 7(3): dx.doi.org/10.16966/2470-1009.168

3

Table 2: Pharmacokinetic parameters in Taiwanese subjects (NN304-3023) compared to Caucasians (NN304-1451).

	NN304-1451*	NN304-3023	3023 *vs* 1451*^
Number of Subjects Exposed	26	18	
AUC(0-q), pmol/L*min			
Mean (SD)	2987516.0 (545452.6)	2831626.2 (660003.3)	
Median	29813144	27630756	
Min-Max	2050718.6-3838962.2	1836563.8-4250225.7	
Estimate	2939007.1	2761852.0	0.9
95.0% C.I.	[2710720.1; 3186519.7]	[2506087.7; 3043718.8]	[0.83; 1.07]
p-value			0.327
AUC(0-5h), pmol/L*min			
Mean (SD)	489814.6 (219857.8)	904128.3 (191784.2)	
Median	458685.0	906465.0	
Min-Max	126165.0-944475.0	524520.0-1264800.0	
Estimate	437269.7	883303.4	2.0
95.0% C.I.	[369946.0; 516845.1]	[722507.4;1079885.0]	[1.56; 2.62]*
p-value			<0.0001*
AUC(0-24h), pmol/L*min			
Mean (SD)	2639841.9 (479433.7)	2660035.0 (640198.0)	
Median	2626890.0	2612805.0	
Min-Max	1842300.0-3500325.0	1707510.0-3931680.0	
Estimate	25975925	2589531.7	1.0
95.0% C.I.	[2392600.9; 2820147.3]	[2345925.7; 2858434.3]	[0.88; 1.13]
p-value			0.961
Cmax, pmol/L			
Mean (SD)	3577.3 (861.3)	4917.2 (1122.0)	
Median	3735.0	4785.0	
Min-Max	2000.0-5280.0	3020.0-7240.0	
Estimate	3474.4	4798.9	1.4
95.0% C.I.	[3157.9; 3822.6]	[4278.5; 5382.7]	[1.19; 1.60]*
p-value			<0.0001*
Tmax, min			
Mean (SD)	443.1 (213.4)	275.0 (75.1)	
Median	420.0	270.0	
Min-Max	30.0-960.0	180.0-420.0	
p-value, Kruskal Wallis Test			0.0005*
t1/2, min			
Mean (SD)	366.4 (68.4)	348.2 (52.8)	
Median	365.7	360.9	
Min-Max	253.9-518.9	259.0-407.4	
Estimate	360.4	344.2	1.0
95.0% C.I.	[336.2; 386.3]	[316.7; 374.1]	[0.86; 1.06]
p-value			0.398
MRT, min			
Mean (SD)	785.6 (156.2)	577.0 (72.2)	
Median	794.0	562.3	
Min-Max	568.7-1149.5	414.6-722.2	
Estimate	771.2	527.3	0.7
95.0% C.I.	[722.4; 823.3]	[487.5; 570.4]	[0.62; 0.76]*
p-value			<0.0001*

*Data for NN304-1451 is obtained from a previous study on Caucasian subjects.
^Ratio of treatment estimates are presented (except T_{max}).
All PK endpoints (except T_{max}) are analyzed by ANOVA model on log scale.

Citation: Kwok CF, Ho LT (2021) A Single Center, Open-Labeled Trial to Investigate the Pharmacokinetics of Insulin Detemir in Healthy Taiwanese Subjects. J Drug Res Dev 7(3): dx.doi.org/10.16966/2470-1009.168

4

no significant difference between Taiwanese and Caucasian in the $AUC_{(0-24h)}$, with a ratio of 1(95% CI: 0.82;1.12, p=0.587). But the $t_{1/2}$ was significantly shorter with a ratio of 0.9 (95% CI: 0.76; 0.97, p=0.016). The C_{max} was 50% higher (ratio was 1.5, 95% CI: 1.28; 1.81, p<0.0001) and $AUC_{(0-5h)}$ was 1.5-fold more(ratio was 2.5, 95% CI: 2.02; 3.16, p<0.0001) in Taiwanese compared to Caucasians.

Furthermore, t_{max} (270.0 *vs* 420.0 min, p=0.0005) and MRT (ratio was 0.7, 95% CI: 0.62; 0.76) were significantly shorter in Taiwanese subjects.

The mean blood glucose concentration is shown in figure 3. Over 32h, there was no significant difference in the mean blood glucose concentrations between Taiwanese and Caucasian subjects.

Adverse Events: only two non-serious events were reported by two subjects, both of which were mild in severity and assessed as unlikely to be related to administration of trial product. A single episode of hypoglycemia was reported in a 24-year-old male, reported experiencing symptom of hypoglycemia approximately 2.5h after the administration of insulin detemir. Blood glucose level was 53 mg/dL and he was able to treat himself for the episode.

Discussion and Conclusion

In the present study, the pharmacokinetic profile of insulin detemir after a single dose administration to the thigh in healthy male Taiwanese subjects was compared to healthy male/female Caucasian subjects in an earlier similar study (NN304-1451) [7]. Except for gender the inclusion criteria were similar in both trials with regard to age range and BMI. The demography showed that Taiwanese subjects were younger (23.8 ± 4.2 *vs* 32.6 ± 9.9 years) than Caucasians and had lower BMI (21.9 ± 1.9 *vs* 24.1 ± 1.9 kg/m²). Equal gender distribution was observed among the Caucasian subjects. The dose of insulin detemir (0.5 U/kg) administered to Taiwanese was equivalent to the dose (12 nmol/L) administered to Caucasian. Due to their lower body weight, Taiwanese subjects received a lower total dose of insulin detemir than Caucasians (32.6 U *vs* 36.8 U). There were no apparent differences between Taiwanese and Caucasian with regard to physical examination, concomitant illnesses/medication or medical history.

Although we found no difference between Taiwanese and Caucasian in the $AUC_{(0-\infty)}$, $AUC_{(0-24h)}$ and $t_{1/2}$, there was a left shift of the curve for serum concentration of insulin detemir (Figure 2) suggesting a faster absorption of the insulin detemir in Taiwanese male subjects. This hypothesis is further supported by the finding of a significantly shorter $t_{1/2}$ in Taiwanese when the comparison was done between Taiwanese and Caucasian including male-only. The observation of comparable $t_{1/2}$ compared to Caucasian in the main analysis was possibly confounded by female gender. Although the mean blood glucose levels showed no difference between Taiwanese and Caucasian subjects, the consequence of the left shift for insulin detemir concentration was not clear since it was not investigated in this study. Further study with the effects of meals and endogenous insulin secretion controlled involving techniques such as glucose clamp may be needed.

The action of insulin detemir is reported to be prolonged by association of the fatty acid residue to binding sites on albumin in the subcutaneous extracellular fluid and blood [3,10]. With more than 98% of insulin detemir bound to albumin, the rate of absorption is limited by the low concentration of available insulin detemir for diffusion. In comparing anthropometric measurements between Asians and Caucasians, Wang J, et al. [11] found that fat for the same BMI category Asians have higher % body fat and thicker subcutaneous fat, except for the thigh. The skin fold fat area of the mid- thigh in Caucasian males tended to be thicker than Asian males. It could be hypothesized that the lower mid-thigh subcutaneous space of Taiwanese may result in more rapidly diffusion of insulin detemir molecule than in Caucasian in the first 5h after subcutaneous injection into the thigh.

Ethnic differences in the pharmacokinetics of insulin detemir had been explored and found to be similar between healthy Japanese American and Caucasian subjects [12]. However, we are unable to make comparison with that of healthy Japanese [12] due to different dosages used in this study.

The limitation of this study was that healthy Caucasian male subjects were not recruited at the same period and put through similar protocols under the same conditions as healthy Taiwanese male subjects. Although we did observe consistently higher mean blood glucose concentrations in Taiwanese than Caucasian subjects regardless of insulin detemir concentration (Figure 3), the pharmacodynamic effect of insulin detemir cannot be inferred because several factors could have influenced the blood glucose concentration curve. For example, the glycemic index and the calorie count of the carbohydrate-rich meal served in both trials may not be similar. As no baseline 24h blood glucose values were collected in this trial, any inference on the
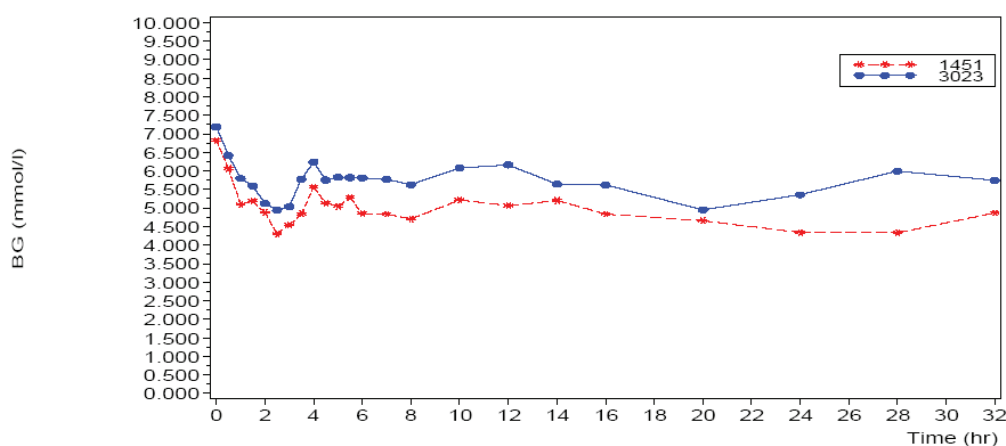

Figure 3: Mean blood glucose concentrations (mmol/L) over 32 hours in Taiwanese (3023) and Caucasians (1451) after a single injection of insulin detemir.

Citation: Kwok CF, Ho LT (2021) A Single Center, Open-Labeled Trial to Investigate the Pharmacokinetics of Insulin Detemir in Healthy Taiwanese Subjects. J Drug Res Dev 7(3): dx.doi.org/10.16966/2470-1009.168

5

blood glucose lowering effect of insulin detemir is inconclusive based on the results of this trial. Including pharmacodynamic response would enable us to determine if the difference in pharmacokinetic profiles between the two ethnic groups will translate into significant differences in pharmacodynamic endpoints.

In conclusion, in this pharmacokinetic evaluation of a single dose administration of insulin detemir in Taiwanese male subjects, the $AUC_{(0-\infty)}$, and $AUC_{(0-24h)}$ were not different from that of Caucasians in the comparator trial. However, insulin detemir appeared to be more rapidly absorbed in Taiwanese males. Further studies are warranted to elucidate its pharmacodynamic response and mechanisms. Finally, there was no clinically relevant safety concern raised in this study (Funded by research grant from Novo Nordisk, Taiwan, first registration (22/12/2011) ClinicalTrials.gov number, NCT01497587).

Declaration

Ethics approval and consent to participate

The protocol, the protocol amendments, the consent form, and the subject information sheet were reviewed and approved by an independent Ethics Committee, Taipei Veterans General Hospital and submitted to the appropriate health authority, according to local regulations prior to trial initiation. The approval date was 19/04/2005(NN304-3203). The trial was performed in accordance with the "Declaration of Helsinki" and local Good Clinical Practice regulations. The subjects were informed of the risks and benefits of the trial and that they could withdraw from the trial at any time for any reason. Consent was obtained in writing prior to any trial-related activities and the Investigators retained the consent forms; the consent forms were available to Novo Nordisk for inspection.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Funding

Funded by research grant from Novo Nordisk, Taiwan, 19/04/2005, NN304-3203.

Authors' contribution

C.F.K. wrote the manuscript. All authors reviewed the manuscript.

Acknowledgements

We thank the staff of GCRC of Taipei Veterans General Hospital for their support for this study.

Competing interests

The authors declare that they have no competing interests.

References

1. Kurtzhals P, Havelund S, Jonassen I, Kiehr B, Larsen UD, et al. (1995) Albumin binding of insulins acylated with fatty acids: characterizations of the ligand-protein interaction and correlation between binding affinity and timing of the insulin effect *in vivo*. Biochem J 312: 725-731.

2. Whittingham JL, Havelund S, Jonassen I (1997) Crystal structure of a prolonged-acting insulin with albumin binding properties. Biochemistry 36: 2826-2831.

3. Markussen J, Havelund S, Kurtzhals P, Andersen AS, Halstrøm J, et al. (1996) Soluble, fatty acid acylated insulins bind to albumin and show protracted action in pigs. Diabetologia 39: 281-288.

4. Jehle PM, Micheler C, Jehle DR, Breitig D, Boehm BO (1999) Inadequate suspension of Neutral Protamine Hagedorn (NPH) insulin in pens. Lancet 354: 1604-1607.

5. Vague P, Selam JL, Skeie S, De Leeuw I, Elte JW, et al. (2003) Insulin detemir is associated with more predictable glycemic control and reduced risk of hypoglycemia than NPH insulin in patients in type 1 diabetes on a basal-bolus regimen with premeal insulin aspart. Diabetes Care 26: 590-596.

6. Haak T, Tiengo A, Draeger E, Suntum M, Waldhäusl W (2005) 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 7: 56-64.

7. Internal Novo Nordisk A/S Clinical Trial Report, NN304-1451. An open, randomized, cross-over trial in healthy subjects comparing the pharmacokinetics of insulin detemir when administered subcutaneously at different injection sites (abdomen, thigh, deltoid) investigating the absolute bioavailability.

8. Declaration of Helsinki Website (1997) World Medical Association declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. JAMA 277: 925-926.

9. Shargel L, Yu ABC (1999) Applied Biopharmaceutics and Pharmacokinetics. 4th edition, Appleton & Lange, Spain 643-652.

10. Kurtzhals P, Havelund S, Jonassen I, Kiehr B, Ribel U, et al. (1996) Albumin binding and time action of acylated insulins in various species. J Pharm Sci 85: 304-308.

11. Wang J, Thornton JC, Russell M, Burastero S, Heymsfield S, et al. (1994) Asians have lower body mass index (BMI) but higher percent body fat than do whites: comparisons of anthropometric measurements. Am J Clin Nutr 60: 23-28.

12. Jhee SS, Lyness WH, Rojas PB, Leibowitz MT, Zarotsky V, et al. (2004) Similarity of insulin detemir pharmacokinetics, safety, and tolerability profiles in healthy Caucasian and Japanese American subjects. J Clin Pharmacol 44: 258-264.

Citation: Kwok CF, Ho LT (2021) A Single Center, Open-Labeled Trial to Investigate the Pharmacokinetics of Insulin Detemir in Healthy Taiwanese Subjects. J Drug Res Dev 7(3): dx.doi.org/10.16966/2470-1009.168

6