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Research Article

COMPARISON OF ONCE-DAILY WITH TWICE-DAILY ADMINISTRATION OF LONG-ACTING INSULIN ANALOGUE, DETEMIR, IN BASAL-BOLUS INSULIN THERAPY IN JAPANESE PATIENTS WITH DIABETES

TARO HAYAKAWA*[1,3], MEGUMI WATANABE[1], HIDEO NAKAYAMA[1], ASAKO NISHIMURA[3], HIROYA IWASE[2], MICHIYO ISHII[2], KENJI KAMIUCHI[2], MOTOHIDE ISONO[2], AND NOBUHITO SHIBATA[3]

[1] Department of Pharmacy, Otsu Municipal Hospital, 9-9 2-cho-me, Motomiya, Otsu, Shiga, 520-0804, Japan, [2] Department of Internal Medicine, Otsu Municipal Hospital, 9-9 2-cho-me, Motomiya, Otsu, Shiga, 520-0804, Japan, [3] Department of Biopharmaceutics, Faculty of Pharmaceutical Sciences, Doshisha Women's College of Liberal Arts, Kodo Kyotanabe, Kyoto, 610-0395, Japan
Email: nshibata@dwc.doshisha.ac.jp

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ABSTRACT

The aim of this study is to evaluate whether dosage regimen of long-acting insulin analogue, detemir, at twice-daily administration offers any clinical advantages over once-daily administration in basal-bolus insulin therapy in Japanese patients with diabetes. To compare outcomes of once-daily administration of detemir with those of twice-daily, a retrospective study was conducted. Fourteen patients were enrolled into the study and changes in hemoglobin A1c (HbA1c), bodyweight, blood glucose level (BG) before meals, within-patient day-to-day variability in BG before meals, prevalence of hypoglycemia and insulin dose were compared. Significant improvements of HbA1c with twice-daily administration were found compared with that in the once-daily period. Fasting BG and within-patient day-to-day variability in BG before meals were lower with twice-daily than once-daily detemir. Hypoglycemic attacks decreased significantly in the twice-daily period compared with those in the once-daily period. Despite total insulin dose remaining unchanged, basal insulin dose tended to increase and bolus insulin dose decreased significantly with twice-daily administration of detemir. Bodyweight was unchanged throughout the study periods. These observations demonstrate that changing the dosage regimen of detemir from once-daily to twice-daily administration have the advantages of reduced the risk of hypoglycemia without increasing HbA1c level in Japanese insulin-dependent patients with diabetes who receive basal-bolus insulin therapy with detemir as basal insulin.

Keywords: Insulin detemir, Dosage regimen, Basal-bolus insulin therapy, Japanese diabetes patients, Hypoglycemia

INTRODUCTION

A number of studies have demonstrated that strict glycemic control reduces the incidence and delays the progression of long-term complications associated with diabetes.[1-5] Diabetic patients with deficient insulin secretion are routinely treated with basal-bolus insulin therapy to reproduce endogenous insulin secretion, where the goals of basal-bolus insulin therapy are to achieve glycemic control and to minimize the risk of hypoglycemia and weight gain. Long-acting insulin has been developed to reproduce the physiological and basal insulin profile more accurately. Insulin detemir is one such long-acting insulin analogue, which was released in Japan in December 2007. The protracted action of detemir is attributable to a combination of increased self-association and albumin binding due to acylation of the amino acid lysine in position B29 with myristic acid.[6, 7]

Recent pharmacokinetic studies have shown that the maximum effect of detemir occurs later than that of glargine or neutral protamine Hagedorn insulin (NPH), and the duration of action of detemir is less than 24 hours. Porcellati *et al.* reported that detemir had a peak effect around 7 to 11 hours after injection, the mean value of the end of action was 19.4 hours, and the median was 17.5 hours.[8] In a study by Plank *et al.*, detemir had a peak action between 8 and 12 hours, and the duration of action was dose-dependent and varied from 12.1, 19.9, 22.7 and 23.2 hours for 0.2, 0.4, 0.8 and 1.6 IU/kg, respectively. Only at the highest dose (1.6 IU/kg) did the mean duration of action continue for 24 hours.[9] Indeed, insulin detemir is approved for once-daily or twice-daily administration, and some studies have been performed with a twice-daily injection schedule in patients with type 1 or type 2 diabetes.[10-16] Once-daily administration of detemir has not always shown adequate efficacy in insulin-dependent diabetes patients. In a previous study, we reported that replacement of NPH with detemir resulted in a significant increase in the frequency of hypoglycemic attacks. Here we described that the effects of detemir in Japanese subjects were similar to those in Caucasian subjects in many respects.[17] Moreover, we encountered some cases that showed a more extreme rise in fasting blood glucose levels (BG) when treated with a once-daily dose of detemir in basal-bolus insulin therapy in clinical practice. Jhee *et al*. reported that the pharmacokinetics of detemir in ascending doses is similar in healthy Japanese and Caucasian subjects.[18] Therefore, we hypothesized that changing the dosage regimen of detemir from once-daily to twice-daily improves glycemic control or reduces hypoglycemia if detemir has a peak action or its duration of action is less than 24 hours. A potential benefit may exist for the twice-daily administration of detemir as is often the case with insulin therapy using NPH as basal insulin. However, there are no previously published reports of changing dosage regimen from once-daily to twice-daily detemir in Japanese patients with diabetes in clinical practice. In order to clarify the clinical properties of the pharmacokinetics and pharmacodynamics of detemir in Japanese patients with diabetes, we carried out a retrospective study to compare the effects of once-daily with twice-daily administration in basal-bolus insulin therapy using the long-acting insulin analogue detemir.

SUBJECTS AND METHODS

Patients

Eighty adult outpatients with diabetes received basal-bolus therapy that involved regular insulin or ultra-rapid insulin (bolus insulin) in combination with detemir (basal insulin) at Otsu Municipal Hospital (Otsu, Shiga) between January 2008 and June 2010. Of these patients, 16 patients underwent a change in dosage regimen from once-daily to twice-daily detemir without a change in the bolus insulin preparations during the study period. The main aims for changing the dosage regimen were to improve glycemic control and to reduce variability in BG and prevalence of hypoglycemia. Two patients were excluded because of a lack of detailed self-measured blood glucose (SMBG) records and discontinuation of treatment with twice-daily detemir within 60 days. This left 14 patients (11 males and 3 females) to be analyzed. All patients were initially treated with once-daily injections of detemir and underwent a change of dosage regimen from once-daily to twice-daily detemir. In changing the dosage regimen of detemir, basal dose was divided into similar doses at morning and night. Both before and after the change

of the dose regimen, the periods of observation were set at 60 days. Throughout the study period, doses of bolus and basal insulin were adjusted by a physician according to the blood glucose profiles recorded at each hospital visit. If necessary, insulin dose was increased or reduced by 1-2 units to meet the target BG. The dosage of oral anti-diabetic drugs was unchanged throughout the study period in all patients. Residual β-cell function in the pancreas was evaluated by fasting plasma C-peptide (CPR) levels in patients. Retinopathy was classified as either no diabetic retinopathy (NDR), simple diabetic retinopathy (SDR), pre-proliferative diabetic retinopathy (PPDR) or proliferative diabetic retinopathy (PDR). Nephropathy stage was classified into three stages as normoalbuminuria, microalbuminuria or macroalbuminuria. This study was conducted in accordance with the Declaration of Helsinki and its amendments, and the Japanese government's "Ethical Standards for Clinical Research". The Ethics Committee of Otsu Municipal Hospital gave its approval for this study.

Insulin products administered to the patients

For bolus insulin injection, the patients received regular insulin (Novorin-R Flex pen™, NovoNordisk, Bagsvaerd, Denmark), ultra-rapid insulin including insulin lispro (HumalogTM, Eli Lilly, Indianapolis, USA) or insulin aspart (Novo Rapid Flex pen™, NovoNordisk, Bagsvaerd, Denmark), and received detemir (Revemir Flex pen™, NovoNordisk, Bagsvaerd, Denmark) for basal insulin.

Biochemical tests and monitoring indexes

HbA1c was measured by a latex agglutination immunoassay using the Determiner HbA1c kit (Kyowa Medex Co., Ltd., Tokyo, Japan) and an automatic analyzer (DM-JACK; Kyowa Medex Co., Ltd., Tokyo, Japan). The inter- and intra-assay coefficients of variation in HbA1c determination ranged from 0.37 to 0.47% and 0.57 to 0.83%, respectively. Self-measured blood glucose (SMBG) was measured using a glucose meter (Glutest Ace, Sanwa Kagaku, Nagoya, Japan). Fasting plasma CPR concentration was determined by chemiluminescent enzyme immunoassay using the laboratory testing services provided by SRL Inc. (Tokyo, Japan). The lower detection limit of plasma CPR level was 0.03 ng/mL and values below the detection limit of plasma CPR level were treated as 0.03 ng/mL. Bodyweight was measured at the hospital using a calibrated scale. Basic clinical information on the patients was collected by reviewing medical records and included medical history, clinical progress, laboratory tests, concurrent drugs and time-dependent changes in insulin dose. BG before meals and incidence of hypoglycemia were collected from patients' SMBG records. Hypoglycemia was defined as a confirmed blood glucose level <70 mg/dL. Hypoglycemia that occurred during sleep from bedtime to getting up in the morning was defined as nocturnal. Severe hypoglycemia was defined by impaired consciousness or convulsions requiring assistance from other persons and the need for an intramuscular injection of glucagon or intravenous glucose. Using these data, changes in HbA1c values, bodyweight, BG before meals, within-patient variability in BG before meals, frequency of hypoglycemia and insulin dose were compared for once-daily and twice-daily detemir.

Calculations and statistics

The mean values for each parameter were calculated for each period and the results are expressed with standard error of the mean (SEM) unless otherwise stated. Within-patient day-to-day variability in BG before meals was calculated as the standard deviation of BG before meals. Japan Diabetes Society (JDS), National Glycohemoglobin Standardization Program (NGSP) and International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) values of HbA1c were calculated according to Consensus and Statement on International Standardization of HbA1c in Japan.[19]

The percentage of basal insulin dose was obtained by calculating the ratio of basal insulin dose against total insulin dose. Statistical testing was performed using Wilcoxon's signed rank test. A *P*-value of < 0.05 was considered statistically significant. All analyses were performed with the statistical software Statview ver 5.0 (SAS Institute Inc., Cary, NC, U.S.A.).

RESULTS

Patient characteristics

Table 1 shows the clinical characteristics of the subjects at baseline during once-daily detemir. Most of patients had little β-cell function left. There were no patients with proliferative retinopathy requiring acute treatment, impaired renal or hepatic function, severe cardiac problems, uncontrolled hypertension, recurrent major hypoglycemia, allergy to insulin, pregnancy or who worked night shifts during the study. Twelve patients received once-daily detemir at night and 2 patients received it in the morning. Twice-daily detemir was injected before breakfast and at night. No patient was prescribed additional oral anti-diabetic drugs during the study.

Results of HbA1c, bodyweight, BG and within-patient day-to-day variability in BG before meals

Table 2 shows the mean values of HbA1c, bodyweight, BG and variability in BG before meals for each period. Significant ($P < 0.05$) improvements in the values of HbA1c in the twice-daily period were found compared with those of the once-daily period. Despite the fact that the mean values of BG before breakfast and lunch tended to improve in the twice-daily period compared with those in the once-daily period, the differences were not significant. In contrast, the mean value of BG before dinner in the twice-daily period was similar to that in the once-daily period.

Within-patient day-to-day variability in BG before meals was lower in the twice-daily than in the once-daily period. No significant difference was observed in bodyweight between once-daily and twice-daily periods.

Table 1: Characteristics of the patients at baseline, once-daily detemir

Parameter	*n* = 14
Male/female (*n*)	11/3
Age (years)	50.1 (13.2)
Classification of diabetes (type 1/ type 2/ pancreatic diabetes), *n*	9/4/1
Duration of diabetes (years)	13.9 (11.4)
Bodyweight (kg)	61.3 (10.7)
Body mass index (kg/㎡)	21.9 (2.8)
JDS HbA1c (%)	7.8 (0.8)
NGSP HbA1c (%)	8.2 (0.8)
IFCC HbA1c (mmol/mol)	64.2 (8.3)
Fasting plasma C-peptide (ng/mL)	0.18 (0.27)
Retinopathy (NDR/SDR/PPDR/PDR), *n*	10/1/2/1
Nephropathy stage (normoalbuminuric/microalbuminuric/macroalbuminuric), *n*	7/7/0

Each value represents the mean (SD) of the 14 patients in the study.
JDS HbA1c, Japan Diabetes Society values.
NGSP HbA1c, National Glycohemoglobin Standardization Program.
IFCC HbA1c, International Federation of Clinical Chemistry and Laboratory Medicine values.
NDR, no diabetic retinopathy; SDR, simple diabetic retinopathy; PPDR, pre-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

Table 2: Changes in mean HbA1c, BG and variability in BG before meals, and bodyweight at once-daily versus twice-daily detemir

	Once-daily	Twice-daily	*P* value
JDS HbA1c (%)	7.8 (0.2)	7.5 (0.2)	$P < 0.05$
NGSP HbA1c (%)	8.2 (0.2)	8.0 (0.2)	$P < 0.05$
IFCC HbA1c (mmol/mol)	64.2 (2.2)	61.6 (2.5)	$P < 0.05$
BG before breakfast (mg/dL)	159.1 (17.2)	154.1 (9.3)	NS
BG before lunch (mg/dL)	129.5 (12.2)	126.7 (9.3)	NS
BG before dinner (mg/dL)	143.2 (11.2)	143.2 (10.8)	NS
Variability in BG before meals (mg/dL)	57.3	53.7	NS
Bodyweight (kg)	61.3 (2.9)	61.1 (2.9)	NS

Each value represents the mean (SEM) of the 14 patients in the study.
JDS HbA1c, Japan Diabetes Society values.
NGSP HbA1c, National Glycohemoglobin Standardization Program.
IFCC HbA1c, International Federation of Clinical Chemistry and Laboratory Medicine values.
BG represents blood glucose levels.
Variability in BG before meals was calculated as the standard deviation of BG before meals.
P value vs once-daily detemir (Wilcoxon's signed rank test).

Frequency of hypoglycemia and other side effects

Fig. 1 shows the mean values of the frequency of hypoglycemic episodes in once-daily and twice-daily periods. Significant decreases ($P < 0.05$) were found in the frequency of overall and daytime hypoglycemia in the twice-daily period compared with those in the once-daily period. Nocturnal hypoglycemia was confirmed one patient. Nocturnal hypoglycemia also tended to decrease, but the differences were not significant. There was no severe hypoglycemic episode that required external help during the study period. No other adverse events were caused by the change in the number of injections of detemir.

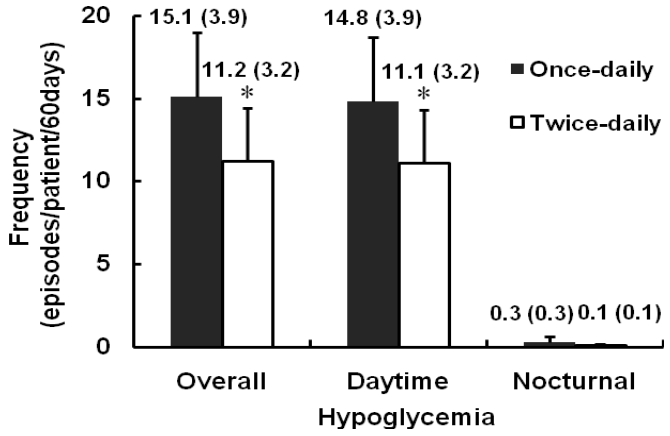

Fig. 1: Changes in the mean frequency of hypoglycemia for once-daily versus twice-daily detemir

Each column with a bar represents the mean (SEM) of the 14 patients in the study; *) $P < 0.05$ vs once-daily detemir (Wilcoxon's signed rank test)

Results of insulin dose adjustment

Table 3 shows the mean insulin dose in the once-daily and twice-daily periods. Although the mean total insulin dose decreased a little in the twice-daily period, the mean basal insulin dose tended to increase in the twice-daily period. The dose of twice-daily detemir was similar in morning and night. The mean total dose of bolus insulin decreased significantly ($P < 0.01$) in the twice-daily period. In particular, the mean dose of bolus insulin at lunch and dinner decreased significantly ($P < 0.05$) in the twice-daily period. The ratio of basal insulin dose to total insulin dose was increased in the twice-daily period ($P = 0.054$) compared with that in the once-daily period.

Table 3: Changes in the mean dose of daily basal and bolus insulin at once-daily versus twice-daily detemir

	Once-daily	Twice-daily	*P* value
Total dose (IU/kg/day)	0.69 (0.05)	0.66 (0.05)	NS
Basal dose (IU/kg/day)	0.25 (0.02)	0.27 (0.03)	NS
Morning dose (IU/kg/day)	0.04 (0.03)	0.13 (0.01)	-
Night dose (IU/kg/day)	0.21 (0.03)	0.14 (0.01)	-
Bolus dose (IU/kg/day)	0.44 (0.03)	0.39 (0.03)	$P < 0.01$
Morning dose (IU/kg/day)	0.12 (0.02)	0.11 (0.02)	NS
Lunch dose (IU/kg/day)	0.15 (0.01)	0.13 (0.01)	$P < 0.05$
Dinner dose (IU/kg/day)	0.17 (0.01)	0.15 (0.01)	$P < 0.05$
Proportion of basal insulin (%)	36.3 (2.4)	40.8 (1.8)	$P = 0.054$

Each value represents the mean (SEM) of the 14 patients in the study.
The proportion of basal insulin represents the ratio of basal insulin dose divided by total insulin dose.
P value vs once-daily detemir (Wilcoxon's signed rank test).

DISCUSSION

The results obtained in this study revealed that HbA1c levels were slight improved and frequency of hypoglycemia was reduced after changing the dosage regimen from once-daily to twice-daily detemir in basal-bolus insulin therapy. As shown in Table 2, the values of BG before breakfast and lunch, and variability in BG before meals were not improved significantly; however, these values were lower in the twice-daily than in the once-daily period. In general, HbA1c is highly correlated with fasting BG, postprandial glucose and mean BG in particular.[20, 21] In comparison with once-daily administration, split dosing might result in a relatively steady basal insulin level in all days, and might reduce around injection hyperglycemia by overlapping basal insulin profiles. The stabilizing effect of twice-daily detemir was likely to reduce overall BG and fluctuations of BG, and thereby lead to improved HbA1c levels slightly.

In this study, the frequency of overall and daytime hypoglycemic attacks decreased significantly, but that of nocturnal attacks did not change significantly after the change from once-daily to twice-daily detemir (Fig. 1). The reason for this was assumed to be the low number of events of nocturnal attack. Thus, splitting of the basal insulin dose might also reduce variability of effects and decrease the prevalence of hypoglycemia.

As shown in Table 3, the mean basal insulin dose increased a little with twice-daily detemir, whereas the mean bolus insulin dose in the twice-daily regimen was significantly decreased. The overall BG profile and insulin levels are flatter in the case of twice-daily detemir; therefore, BG can be controlled by reducing bolus insulin dose. In particular, the bolus insulin dose at lunch- and dinnertime decreased significantly with twice-daily detemir. These results indicated that the increase in bolus insulin dose was not necessary to compensate for an insufficient duration of action with once-daily detemir. In contrast, as shown in Table 2, the mean values of BG before dinner were not improved by twice-daily detemir, despite most of the patients receiving once-daily detemir at night. The BG before dinner may be improved without increasing hypoglycemia if the bolus insulin dose at lunchtime is titrated according to BG before dinner. Hence, these results indicate that dividing the basal insulin dose would provide dose adjustment of bolus insulin more easily.

Recently it has been reported that the mean duration of action of detemir falls slightly short of 24 hours at clinically relevant doses.[8, 9] Fewer studies have examined the pharmacodynamic profile of detemir, which showed that the duration of action exceeds that of NPH insulin and is dose-dependent, with means of 12.1 and 19.9 hours at doses of 0.2 and 0.4 IU/kg, respectively.[9] Our data show that the mean doses of detemir were about 0.25 IU/kg at once-daily and 0.27 IU/kg at twice-daily detemir. These observations suggest that some Japanese patients with insulin-dependent diabetes may require twice-daily dosing to provide basal insulin supplementation over 24 hours at these usual doses. Therefore, the rises in fasting BG that we encountered in clinical practice upon treatment with once-daily detemir in basal-bolus insulin therapy could reflect insufficient efficacy of basal insulin. In normal subjects, basal insulin constitutes approximately half of the daily insulin requirements.[22] Yokoyama *et al.* reported that basal–bolus therapy using the long-acting insulin analogue glargine as basal insulin might result in good fasting BG control when the proportion of basal glargine is increased to 48% of the total insulin dose.[23] In the present study, change to twice-daily dosing made it possible to increase the proportion of basal detemir up to 41%. The slight peak of action caused by once-daily detemir must prevent an increase in the ratio of basal insulin dose up to half of the daily insulin requirement. Twice-daily administration of detemir proved to mimic physiologic basal insulin secretion better than once-daily administration. The results in this study are consistent with those of previous studies implying that some patients with insulin-dependent diabetes may ideally require twice-daily administration of detemir to achieve full basal insulin replacement.[8, 9, 24]

Insulin detemir has been assessed in comparison with glargine. A study in patients with type 1 diabetes by Lepore *et al.* showed that a mean duration of action for glargin was 20.5 hours following a dose of 0.3 IU/kg.[25] We recognize that changing the dosage regimen from once-daily to twice-daily glargin has clinical advantages in terms of improvements of BG and decline in the prevalence of hypoglycemia. However, Garg *et al.* reported that the weight gain was significantly higher in the group that received twice-daily glargine.[26] Therefore they concluded that twice-daily glargine did not offer any advantages in glycemic control. The increase in insulin dose causes bodyweight gain, which worsens glucose tolerance, and also adversely affects blood pressure or lipid profile.[27, 28] In this study, it was proved that bodyweight did not increase after a change to twice-daily detemir, regardless of a slight increase in detemir dose (Table 2, 3). We previously reported that patients treated with detemir in basal-bolus therapy exhibited less weight gain than those with NPH.[17] These observations suggest that detemir is associated with less weight gain.

Thus, once-daily dosing may not always be adequate, especially in patients with little endogenous insulin secretion. There is no evidence indicating that twice-daily detemir have the advantages in Asian patients with diabetes. According to our results, we consider that administration of once-daily detemir in Japanese patients with diabetes does not maximize the drug's potential. Better glycemic control may be obtained in clinical practice if patients are not always restricted to once-daily dosing of detemir. In a previous study, it was reported that injection-related problems of insulin, for example, interference with daily activities and injection pain, cause a decrease in adherence to insulin therapy.[29, 30] However, in this study, the adherence upon a change in dosage regimen from once-daily to twice-daily detemir remained unchanged. Therefore, in patients with poor BG control who showed a higher incidence of hypoglycemia, a change in the dosage regimen from once-daily to twice-daily detemir is worth considering. The fact that mean total dose of bolus insulin decreased significantly with twice-daily detemir indicates that the frequency of hypoglycemia could increase without dose adjustment of bolus insulin, since the split dosing of detemir could increase the ratio of basal insulin and minimize the fluctuation of BG.

Since the size of the study population was small and observation periods were short owing to the very limited clinical setting, the subjects include those with three different types of diabetes: type 1, type 2 and pancreatic diabetes. There were limitations in explaining the detailed relationship between the efficacy of twice-daily dosage of detemir and disease type. Further studies for each disease type are required in a large population to establish an optimal dosage regimen for twice-daily administration of detemir. In addition, the insulin dose was adjusted according to the results of HbA1c values and patient SMBG recordings in this study. Use of a new technology, such as a continuous glucose monitoring system, is currently the best medical approach for monitoring BG.[31-34] Using this apparatus would make it possible to reveal pharmacokinetic and pharmacodynamic profiles of twice-daily detemir in Japanese subjects. Nevertheless, the results of this study should provide useful information for patients with diabetes who have been treated with insulin therapy using detemir as basal insulin.

CONCLUSION

The results in this study demonstrated that changing the dosage regimen of detemir from once-daily to twice-daily administration have the advantages of reduced the risk of hypoglycemia without increasing HbA1c level in Japanese patients with insulin-dependent diabetes who received basal-bolus insulin therapy with detemir as basal insulin.

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