ORIGINAL ARTICLE

Effects of dosage and dosing frequency on the efficacy and safety of high-dose metformin in Japanese patients with type 2 diabetes mellitus

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ABSTRACT

Aims/Introduction: Differences in the efficacy and safety of antidiabetic drugs among different ethnic groups are well documented. Metformin is widely used in the treatment of type 2 diabetes in Western countries, but high doses of metformin have been approved only recently for clinical use in Japan. The aim of the present study was to investigate the effects of dosage and dosing frequency on the efficacy and safety of high-dose metformin in Japanese patients.

Materials and Methods: A total of 71 Japanese patients with type 2 diabetes were prospectively studied for the effects of dosage and dosing frequency on the efficacy and safety of metformin during hospitalization. Dose effects were studied in 27 patients treated with 0, 500, 1,000, 1,500 and 2,250 mg/day of metformin. The effect of dosing frequency was compared in 56 patients with 1,500 mg/day of metformin administered either two or three times per day.

Results: Significant dose-dependent improvement in daily profiles of blood glucose was observed with metformin dosages up to 1,500 mg/day, with a trend towards further improvement observed at 2,250 mg/day. The efficacy of 1,500 mg of metformin was comparable when the drug was administered either two or three times per day. The most frequently reported side-effects were gastrointestinal symptoms, which were not affected by the dosage or dosing frequency of metformin.

Conclusions: These results show that the efficacy of high-dose metformin is dose-dependent in Japanese patients. The efficacy and safety of metformin were similar when the drug was administered either two or three times per day.

INTRODUCTION

Differences in the efficacy and safety of antidiabetic drugs among different ethnic groups are well documented[1], leading to differences in recommendations and guidelines for the treatment of type 2 diabetes between East Asian and Western countries[2,3]. Metformin has been used as an oral antidiabetic drug for more than 50 years. The guidelines for the treatment of type 2 diabetes mellitus – consensus statements established by the American Diabetes Association and European Association of the Study of Diabetes – recommend the use of metformin as an initial treatment[2]. Prospective studies, such as the Multicenter Metformin Study[4] and the United Kingdom Prospective

Diabetes Study[5], have provided evidence for beneficial effects of metformin, including cardiovascular protection and safety, in the treatment of type 2 diabetes mellitus, leading to an increase in the use of metformin not only in Europe and the USA but also in Japan. Although the usual dosage of metformin is >2,000 mg/day in Europe and the USA[6], the maximum dose allowed for clinical use in Japan has long been limited to 750 mg/day, which is less than half that of Western countries. In addition, the recommended prescription of the maximum dose of metformin in Japan (750 mg/day) has been through 250-mg tablets administered three times per day. In contrast, treatment with metformin in the United Kingdom Prospective Diabetes Study[5] started with one 850-mg tablet per day, then 850 mg twice daily, and ultimately 1,700 mg in the morning

and 850 mg with the evening meal. These differences in dosage and dosing frequency of metformin between Japan and Western countries have made it difficult to translate the results of clinical trials in Western countries to Japanese patients. Recently, the maximum allowed dose of metformin in Japan was increased to 2,250 mg/day, a comparable dose with those in Western countries. It is still unknown, however, whether high-dose metformin shows the same efficacy and safety in Japanese patients as in European and USA patients. To address these questions, we studied the dose dependence of the efficacy and safety of high-dose metformin for the treatment of type 2 diabetes in Japanese patients. We also compared the efficacy and safety of the same daily dose of metformin when the drug was administered either two or three times per day.

METHODS

Participants and study design

This was a prospective open-label, non-randomized study carried out in a single hospital. The study design is summarized in Figures S1 and S2. Participants were recruited between August 2011 and October 2016. A total of 71 patients with type 2 diabetes were studied (Table 1). To minimize confounding factors, such as diet and exercise, all studies were carried out during hospitalization at the Department of Endocrinology, Metabolism and Diabetes of Kindai University Hospital. All patients were provided standard meals for patients with diabetes as recommended by the Japan Diabetes Society (25–30 kcal/ideal body-weight kg, 50–60% carbohydrate, 15–20% protein and 20–25% fat). Treatment with metformin was not started until fasting

plasma glucose reached at least ≤11.0 mmol/L to minimize the confounding effect of initial improvement in glycemic control as a result of hospitalization. To study potential dose-dependent changes in the efficacy and safety of metformin, 27 patients who were newly prescribed metformin were selected (study 1; Figure S1). To study the effects of dosing frequency on the efficacy and safety of metformin, 56 patients who were prescribed 1,500 mg/day of metformin were selected (study 2; Figure S2). Among 56 patients in study 2, 12 patients were studied in both study 1 and study 2. These patients were included in study 2 because they did not agree to increase doses from 1,500 mg to 2,250 mg in study 1, but agreed to change dosing frequency.

Inclusion criteria was no contraindications for metformin, age ≥20 years, fasting plasma C-peptide immunoreactivity >0.20 nmol/L and no acute illness or serious conditions other than diabetes. Patients were excluded if they had contraindications for metformin, including impaired renal function (serum creatinine >114.9 μmol/L for men, >106.1 μmol/L for women); impaired liver function (serum transaminases >100 IU/L); congestive heart failure; respiratory diseases with hypoxia; history of lactic acidosis; presence of acute or chronic metabolic acidosis, including diabetic ketoacidosis with or without coma; or a known hypersensitivity to metformin. A total of 14 patients were treated with metformin only, whereas the others were administered metformin as an add-on therapy to other antidiabetic medications (Table S1). During both study periods, doses of concomitant medications were not changed (Tables S1, S2). Insulin doses were also fixed, except for a minimal reduction of insulin dose when the patients suffered from hypoglycemia.

Table 1 | Clinical characteristics of patients at baseline

	Study 1 (dose dependence) (*n* = 27)	Study 2 (dosing frequency) (*n* = 56)	Total[†] (*n* = 71)
Sex (male/female)	16/11	31/25	39/32
Age (years)	57.9 ± 13.4	60.8 ± 12.0	60.6 ± 12.0
Median	64	64	64
Range	21–77	21–84	21–84
BMI (kg/m^2)	25.6 ± 4.4	27.2 ± 6.4	27.0 ± 5.9
Duration of diabetes (years)	6.5 ± 8.7	8.4 ± 7.4	8.4 ± 8.0
Family history (–/+)	14/13	29/27	36/35
Diabetic retinopathy (NDR, SDR, PrePDR, PDR)	21/3/3/0	44/9/1/2	55/10/4/2
Diabetic nephropathy (stage 1,2,3,4,5)	24/3/0/0/0	47/7/2/0/0	59/10/2/0/0
Fasting plasma glucose (mmol/L)	8.6 ± 3.0	7.2 ± 2.3	7.5 ± 2.4
Glycated hemoglobin (%)	10.5 ± 2.4	9.7 ± 2.0	9.9 ± 2.1
Creatinine (μmol/L)	64.9 ± 17.8	66.1 ± 18.2	65.3 ± 17.9
eGFR (mL/min/1.73 m^2)	80.9 ± 20.3	77.3 ± 19.3	78.3 ± 19.5
Aspartate amino transferase (IU/L)	28.6 ± 15.3	25.7 ± 12.9	26.4 ± 14.0
Alanine amino transferase (IU/L)	35.8 ± 23.6	31.7 ± 21.8	32.3 ± 21.8
Fasting C-peptide (nmol/L)	0.7 ± 0.4	0.7 ± 0.3	0.7 ± 0.3
Lactic acid (mmol/L)	1.1 ± 0.3	1.2 ± 0.5	1.2 ± 0.4

Data are expressed as the mean ± standard deviation or number. Median and range are also shown for age. [†]A total of 12 participants were studied in both study 1 and study 2, resulting in a total of 71 patients. BMI, body mass index; eGFR, estimated glomerular filtration rate; NDR, no diabetic retinopathy; PDR, proliferative diabetic retinopathy; PrePDR, pre-proliferative diabetic retinopathy; SDR, simple diabetic retinopathy.

This study was approved by the institutional ethics committee of Kindai University Faculty of Medicine, and was registered with the University Hospital Medical Information Network Clinical Trial Registry (registration no. UMIN000011626). All participants provided written informed consent to participate in this study, which was carried out in accordance with the Declaration of Helsinki.

Study 1: dose-dependent effects

The effect of metformin dosage on the efficacy of glycemic control was studied in 27 patients with type 2 diabetes with increasing doses of metformin, including 0, 500, 1,000, 1,500 and 2,250 mg daily (Figure S1). To normalize dosing frequency, metformin was taken twice daily after breakfast and dinner for all doses up to 1,500 mg/day. A subset of the patients ($n = 11$) who did not reach optimal glycemic control (blood glucose <6.7 mmol/L before each meal and at bedtime) with 1,500 mg/day and agreed to further increases in dose were treated with the maximum dose of 2,250 mg/day by adding 750 mg after lunch, resulting in 750 mg of metformin three times a day. Dosages of metformin were increased after at least 3 days of treatment with the previous dosage.

The efficacy of metformin was evaluated by daily profiles of blood glucose measured by a blood glucose meter for self-monitoring of blood glucose. Daily profiles of nine-point blood glucose was monitored before and 2 h after meals, at bedtime, at 00.00 hours and at 03.00 hours by patients under the supervision of medical staff.

Study 2: dosing frequency

The effect of dosing frequency on the efficacy and safety of high-dose metformin was studied in 56 patients with type 2 diabetes who were treated with 1,500 mg of metformin daily. Two groups of patients were studied (Figure S2). One group included patients who were treated with 500 mg of metformin three times per day and switched to 750 mg twice daily. The other group included patients who were treated with 750 mg of metformin twice daily and switched to 500 mg three times per day. Efficacy regarding glycemic control was evaluated by nine-point daily profiles as described in study 1. Dosing frequency was changed after at least 3 days of treatment with the previous frequency.

To compare the differences in plasma concentrations of metformin between twice daily and three times daily administration, blood samples were collected before and 2 h after meals and at bedtime. The plasma concentrations of metformin were measured by high-performance liquid chromatography with tandem mass spectrometry analysis (Sumika Chemical Analysis Service, Osaka, Japan). The lower and upper limits of metformin concentration were 10.0 and 5,000.0 ng/mL, respectively.

Safety and tolerability

Patients were carefully monitored for adverse events. If gastrointestinal symptoms, such as diarrhea, nausea, vomiting and appetite loss, occurred after increases in dose, patients were asked whether these were within a tolerable range. If symptoms were not tolerable, then the patients were asked to reduce the dose to the previous level, and further studies with increases in dose were terminated. All 27 patients successfully increased their dosage of metformin up to 1,500 mg. All 11 patients who agreed to further increase their dosage up to the maximum of 2,250 mg also tolerated this dosage.

The plasma concentration of lactic acid was measured by chromogenic enzyme assay (Nittobo Medical Co. Ltd, Tokyo, Japan). The lower and upper limits of quantification for lactic acid were 0.02 and 17.8 mmol/L, respectively.

Among all medications concomitantly prescribed with metformin, medications shown to inhibit organic cation transporter 1 (OCT1) activity *in vitro* were evaluated because of the possible contribution of these drugs to adverse effects[7]. OCT1-inhibiting medications included tricyclic antidepressants, proton pump inhibitors, diltiazem, doxazosin, spironolactone and clopidogrel[7]. There were no prescriptions for other OCT1-inhibiting drugs.

Statistical analysis

The data are presented as the mean ± standard deviation unless otherwise stated. A paired *t*-test was used to analyze differences in daily profiles of blood glucose levels and plasma levels of lactic acid. Categorical variables were compared using χ^2-tests or Fisher's exact probability tests (as in the case where a number in a category was <5).

RESULTS

Clinical characteristics

The baseline characteristics of the participants are summarized in Table 1. The anti-glutamic acid decarboxylase antibody was negative and fasting plasma C-peptide levels were >0.20 nmol/L in all participants.

Dose-dependent effects

Figures 1a and S3 show daily profiles of glucose levels when treated with different doses of metformin. Significant decreases in blood glucose were observed with increasing doses of metformin (Figures 1a, S3). Areas under the curve of nine-point daily profiles of blood glucose also significantly decreased with increasing doses of metformin up to 1,500 mg/day (Figure 1b), and tended to decrease with further increases in metformin from 1,500 to 2,250 mg/day (Figure S4). Dose-dependent improvement in glycemic control was similarly observed in the metformin monotherapy group (Figure S5), metformin add-on groups with insulin (Figure S6) and without insulin (Figure S7).

Dosing frequency

Figure 2 shows the nine-point blood glucose levels in the twice-daily and the three times-daily treatment groups. Blood glucose levels were comparable between the two groups, except for a slightly higher blood glucose level before dinner in the twice-daily group than in the three times-daily group (6.9 ± 1.7 vs 6.3 ± 1.3 mmol/L, $P = 0.02$). A similar tendency was observed
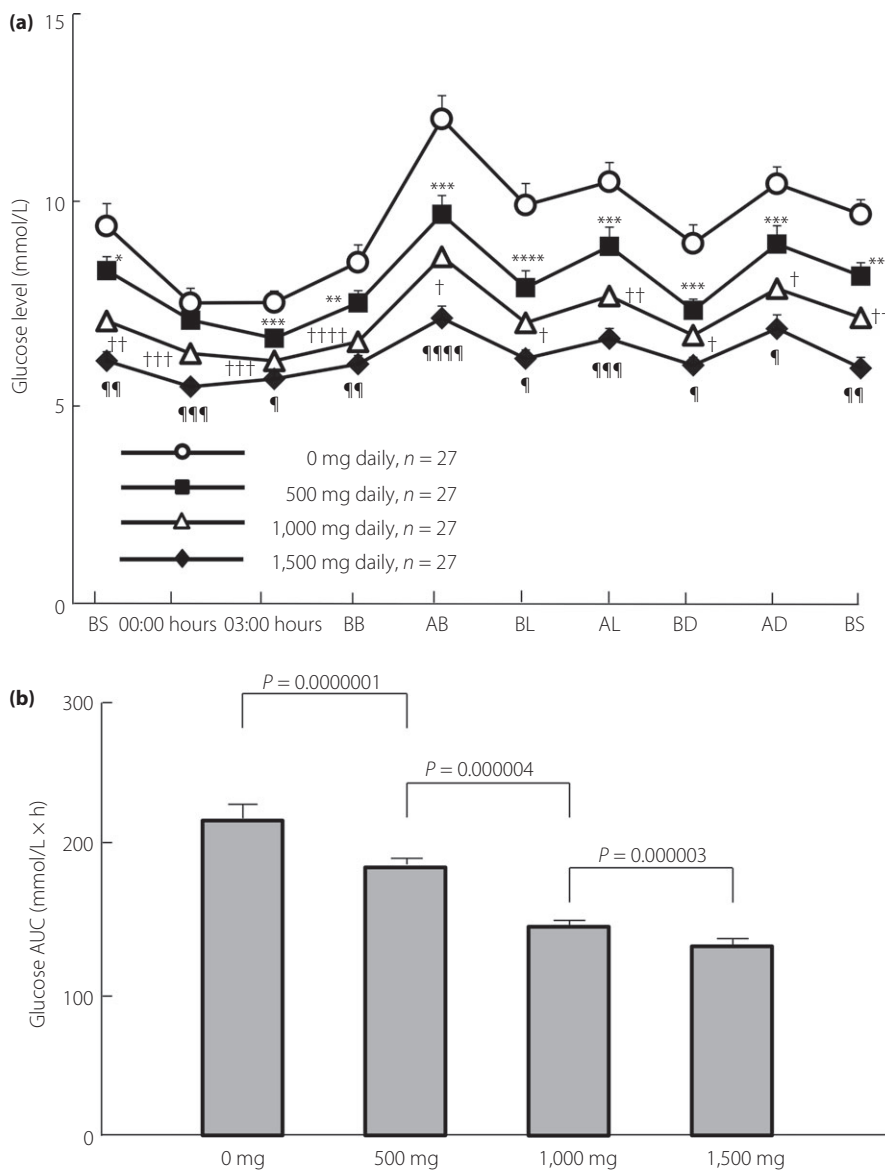
Figure 1 | Effect of increasing dosages of metformin on (a) daily profiles of blood glucose and (b) areas under the curve (AUC) in patients with type 2 diabetes mellitus. Nine-point daily profiles of blood glucose in 27 patients with type 2 diabetes mellitus treated with metformin: 0 mg (open circle), 500 mg (closed square), 1,000 mg (open triangle) and 1,500 mg (closed diamond) daily doses are shown. Data are presented as the mean ± standard error of the mean. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$, $****P < 0.0001$: 0 mg vs 500 mg; $^{\dagger}P < 0.05$, $^{\dagger\dagger}P < 0.01$, $^{\dagger\dagger\dagger}P < 0.001$, $^{\dagger\dagger\dagger\dagger}P < 0.0001$: 500 mg vs 1,000 mg; $^{\P}P < 0.05$, $^{\P\P}P < 0.01$, $^{\P\P\P}P < 0.001$, $^{\P\P\P\P}P < 0.0001$: 1,000 mg vs 1,500 mg. AB, after breakfast; AD, after dinner; AL, after lunch; BB, before breakfast; BD, before dinner; BL, before lunch; BS, before sleep.

in the metformin monotherapy group (Figure S8), and metformin add-on groups with and without insulin (Figure S9).

To clarify the possible contribution of plasma concentrations of metformin to the differences in blood glucose profiles between the twice and three times-daily treatment groups, the plasma concentrations of metformin were measured in eight patients (Figure 3). Plasma concentrations of metformin were significantly lower after lunch ($1,010.5 \pm 420.6$ vs $1,440.9 \pm 371.2$ ng/mL, $P = 0.04$) and before dinner

(823.6 ± 350.8 vs $1,255.6 \pm 584.0$ ng/mL, $P = 0.009$) in the twice-daily group than in the three times-daily group.

Safety and tolerability

The most common treatment-related adverse events were gastrointestinal symptoms, such as diarrhea, nausea and appetite loss. No serious adverse events occurred during the study. The frequencies of adverse events are shown in Table S3. Gastrointestinal symptoms were observed in 29.6% (8/27) and 30.3%
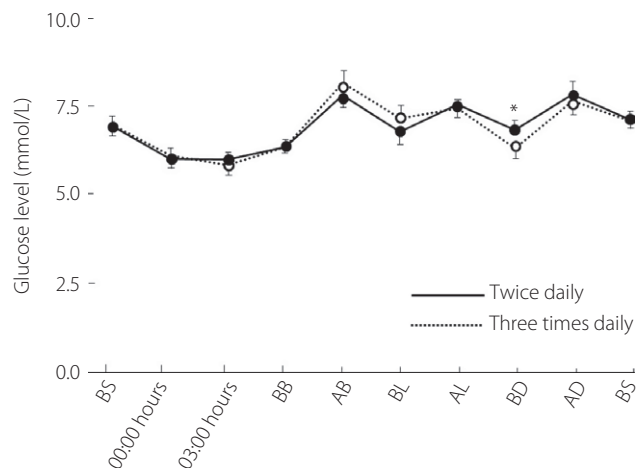
Figure 2 | Effect of dosing frequency on daily profile of blood glucose in patients with type 2 diabetes. Data are presented as the mean ± standard error of the mean. *$P < 0.05$. AB, after breakfast; AD, after dinner; AL, after lunch; BB, before breakfast; BD, before dinner; BL, before lunch; BS, before sleep.
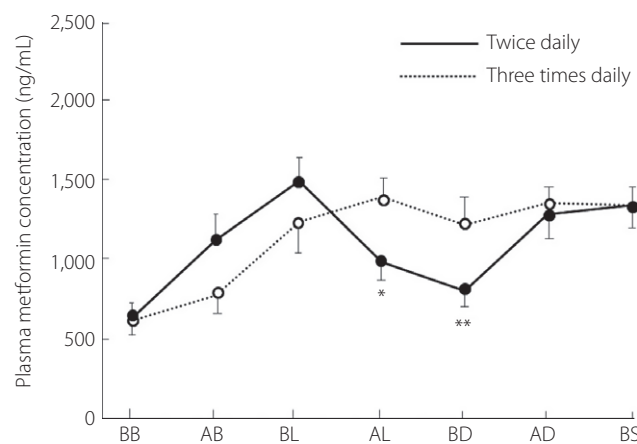

Figure 3 | Plasma concentration of metformin in patients treated with 1,500 mg metformin daily, administered either twice per day (solid line) or three times per day (broken line). Data are presented as the mean ± standard error of the mean. *$P < 0.05$, **$P < 0.01$. AB, after breakfast; AD, after dinner; AL, after lunch; BB, before breakfast; BD, before dinner; BL, before lunch; BS, before sleep.

(17/56) of patients in study 1 and study 2, respectively. Frequencies of gastrointestinal symptoms were not significantly different between the different dosage groups or between the twice-daily and the three times-daily treatment groups. No significant difference between patients with and without gastrointestinal symptoms was observed with the concomitant use of OCT1-inhibiting drugs (Table S4). The plasma concentration of lactic acid was not significantly different between the different dosage groups or between the twice- and three times-daily treatment groups (Table S5).

DISCUSSION

Metformin is widely used as an oral antidiabetic drug in Western countries, as well as in East Asian countries, including Japan. Marked differences, however, in maximum dosage, dosing frequency and dose of each tablet exist in Japan compared with Western countries. The maximum daily dose has long been limited to 750 mg, the dose of the most commonly used tablet has been 250 mg and the usual dosing frequency for a maximum daily dose of 750 mg has been three times per day in Japan. The maximum maintenance dose of metformin in Japan was recently increased to 1,500 mg, and further increases up to 2,250 mg are now permissible if required, making the dosage of metformin in Japan comparable with Western countries. We have previously reported the efficacy and safety of metformin within the lower dose range allowed for use in Japan[8]. The efficacy and safety of high doses of metformin, however, are largely unknown in Japanese patients with type 2 diabetes. We therefore studied the effects of dosage and dosing frequency on the efficacy and safety of high doses of metformin in Japanese patients with type 2 diabetes.

Dose-dependent effects were clearly observed in the efficacy of metformin up to 1,500 mg per day, as shown by significant improvement in glycemic control in both blood glucose levels and areas under the curve of 24-h daily profiles (Figure 1). A tendency towards further improvement was also observed with a maximum dose of metformin of 2,250 mg per day (Figures S3 and S4). A previous study in the USA on the dose response of metformin efficacy reported a dose-dependent improvement in glycated hemoglobin, with the greatest decrease at doses of ≥2,000 mg[9].

Effects of dosing frequency on the efficacy and safety of metformin have not previously been studied in detail, most likely because of a limited range of dosing frequency at once or twice daily in most in Western countries. In contrast, the recommended dosing frequency of metformin in Japan is commonly three, or at least two, times per day. This is likely due to the smaller maximum dose of metformin previously allowed for clinical use in Japan, leading to more frequent administration to maintain effective plasma levels of the drug throughout the day. In the United Kingdom Prospective Diabetes Study[5], initial treatment with metformin was started with an 850-mg tablet once daily, which was more than threefold higher than the 250-mg tablet commonly used in Japan. Another reason for more frequent administration in Japan might be gastrointestinal side-effects, which might increase with increasing doses of metformin. As a higher dose is now allowed for clinical use in Japan, we compared the effects of dosing frequency on the efficacy and safety of high-dose metformin by comparing three times-daily and twice-daily administration. The daily profiles of blood glucose and their areas under the curve were comparable between the twice-daily and the three times-daily treatment groups, indicating that dosing frequency had little effect on the efficacy of 1,500-mg metformin in Japanese patients with type 2

2 diabetes. The only difference between the two groups was a slightly higher blood glucose level in the twice-daily group before dinner (Figure 2). According to pharmacokinetic data, peak concentrations of plasma metformin after oral administration are reached after approximately 2–4 h, and 90% of the absorbed metformin is eliminated in the urine, unchanged, after approximately 20 h[10]. To study the possible contribution of pharmacokinetics of metformin on the difference in blood glucose levels between the twice-daily and the three times-daily treatment groups, plasma concentrations of metformin were compared between the two groups. Plasma concentrations of metformin were significantly lower after lunch and before dinner in the twice-daily treatment group compared with the three times-daily treatment group, suggesting that the higher level of blood glucose before dinner in the twice-daily group was likely as a result of lower concentrations of metformin in the afternoon.

In addition to plasma concentration, the distribution and concentration of metformin in target organs might affect the efficacy and safety of this drug. Metformin is transported into the liver and other target organs by organic cation transporters, mainly OCT-1, to exert its metabolic effects[7,10]. Comparable effects despite significant differences in plasma concentrations of metformin between the two groups might be a result of reduced differences in metformin concentrations in the target organs compared with the blood. Altogether, the data in the present study suggest that twice-daily administration can be used as an alternative to three times-daily administration in prescribing high doses of metformin, especially in patients with poor adherence to frequent dosing of the drug.

The most common side-effects of metformin in the present study were gastrointestinal disturbances, including diarrhea, nausea and appetite loss (Table S3), as reported previously[2,7,11,12]. The frequency of gastrointestinal symptoms observed in the present study was comparable with the 20% frequencies reported previously[4,7,9,12]. No significant influence of the dosage or dosing frequency of metformin was observed on gastrointestinal symptoms (Table S3), suggesting that dosage and dosing frequency have little effect on gastrointestinal symptoms. Gastrointestinal symptoms have been suggested to be correlated with metformin concentrations in the intestine[7], which is affected by absorption of metformin from the intestinal lumen by the transporter OCT1. Concomitant use of OCT1-inhibiting drugs has been reported to increase metformin intolerance[7]. However, no significant differences were observed in the frequencies of concomitant use of OCT1-inhibiting drugs between patients with or without gastrointestinal symptoms (Table S4). The plasma concentration of lactic acid was not different with different dosages of metformin or between the twice- and three times-daily treatment groups (Table S5).

The present study had a few limitations. First, the present study was carried out as an open label, single arm and non-controlled design. Second, the effect of initial improvement as a result of hospitalization might have modified the efficacy of metformin, although we tried to minimize this by delaying metformin treatment until glycemic control reached a certain level. Third, the sample size for the treatment with the highest dose of metformin (2,250 mg) was rather small, which could have resulted in no significant difference between 1,500 mg and 2,250 mg of metformin. Further studies with larger numbers of participants are required to clarify this point.

In conclusion, the results of the present study show that the efficacy of high-dose metformin is dose-dependent in Japanese patients with type 2 diabetes. The efficacy and safety of metformin were similar when taken either twice daily or three times daily.

DISCLOSURE

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1 | Study design to evaluate dose-dependent effects (study 1).

Figure S2 | Study design of dosing frequency (study 2).

Figure S3 | Effect of increasing dosage of metformin on nine-point daily profiles of blood glucose in 11 patients with type 2 diabetes mellitus treated with up to a maximum dose of 2,250 mg metformin daily.

Figure S4 | Effect of increasing dosages of metformin on areas under the curve (AUC) of nine-point daily profiles of blood glucose in 11 patients with type 2 diabetes mellitus treated with the maximum dose of 2,250 mg metformin daily.

Figure S5 | Effect of increasing dosages of metformin on (A) daily profiles of blood glucose and (B) areas under the curve (AUC) in the metformin monotherapy group.

Figure S6 | Effect of increasing dosages of metformin on (A) daily profiles of blood glucose and (B) areas under the curve (AUC) in the add-on therapy group with insulin (insulin users).

Figure S7 | Effect of increasing dosages of metformin on (A) daily profiles of blood glucose and (B) areas under the curve (AUC) in the add-on therapy group without insulin (non-insulin users).

Figure S8 | Effect of dosing frequency on daily profile of blood glucose in 10 patients with type 2 diabetes mellitus treated with metformin monotherapy.

Figure S9 | Effect of dosing frequency on daily profile of blood glucose in patients with type 2 diabetes mellitus treated with metformin add-on to other antidiabetic medications. (A) insulin users ($n = 35$); (B) non-insulin users ($n = 21$).

Table S1 | Antidiabetic medications concomitantly used with metformin.

Table S2 | Medications other than antidiabetic drugs that potentially affect glucose levels.

Table S3 | Frequencies of adverse events with metformin.

Table S4 | Numbers of patients treated concomitantly with different organic cation transporter 1-inhibiting drugs.

Table S5 | Plasma concentration of lactic acid in patients treated with different dosages (A) and dosing frequency (B) of metformin.