Clinical Pharmacology
in Drug Development
2022, 11(3) 364–371
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DOI: 10.1002/cpdd.1010

A Dose-Confirmation Phase 1 Study to Evaluate the Safety and Pharmacology of Glucarpidase in Healthy Volunteers

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Abstract

Glucarpidase rapidly decomposes methotrexate. A phase 1 study of glucarpidase in an open-label, randomized parallel group was conducted to evaluate the safety, pharmacokinetics, and other pharmacologic effects in Japanese healthy volunteers without methotrexate treatment. A dose of 50 U/kg (n = 8) or 20 U/kg (n = 8) of glucarpidase was administered as an intravenous injection, with 1 repeated dose at 48 hours after the first dose. No dose-limiting toxicities, no significant clinical examination findings, and no clinically relevant differences between dose levels were observed. The pharmacokinetic parameters at a first dose of 20 or 50 U/kg were similar to those at a second dose and were as follows: half-life, 7.45 and 7.25 hours; area under the plasma concentration–time curve from time 0 to infinity, 8.25 and 19.05 μg·h/mL; total clearance, 4.85 and 5.47 mL/min; and volume of distribution during the elimination phase, 3.12 and 3.41 L, respectively. The area under the plasma concentration–time curve increased in a generally linear dose-proportional manner. An ethnicity specificity in the pharmacokinetic profile was not observed in Japanese volunteers. The serum folate concentration decreased after glucarpidase administration in all the volunteers. The production of anti-glucarpidase antibody was observed in many cases in both cohorts. Although the long-term effect of anti-glucarpidase antibody will need to be investigated in the future, the effects produced by the anti-glucarpidase antibody were not influenced by the pharmacokinetics of glucarpidase within 96 hours after the first dose. The observed safety and tolerability, pharmacokinetics, and pharmacodynamics support the continued evaluation of glucarpidase in the patients with lethal methotrexate toxicities.

Keywords

anti-glucarpidase antibody, folate, glucarpidase, methotrexate, 5-methyltetrahydrofolate

Methotrexate is a folic acid antimetabolite and an antineoplastic drug that competitively inhibits dihydrofolate reductase. More than 80% of methotrexate is excreted in urine as intact drug by active tubular secretion via the human organic anion transporter-3.[1–3] Inhibitors of organic anion transporter-3 such as nonsteroidal anti-inflammatory drugs decrease the excretion of methotrexate.[4] Less than 10% of methotrexate is oxidized to relatively inactive metabolite 7-hydroxymethotrexate by the enzyme aldehyde oxidase.[1,2,5] The inactive minor metabolite 2,4-diamino-N^{10}-methylpteroic acid is observed in plasma, accounting

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Submitted for publication 8 June 2021; accepted 26 July 2021.

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for <5% of methotrexate.[6] High-dose methotrexate has been established as a standard component of combined chemotherapy for acute lymphoblastic leukemia, malignant lymphoma, osteosarcoma, and other conditions. High-dose methotrexate is inevitably required in 1% to 10% of patients receiving careful supportive care, and the accompanying nephrotoxicity can lead to the exacerbation of hepatotoxicity, serious mucositis, and pancytopenia.[7,8] Several treatments, such as plasmapheresis, dialysis, and high-dose leucovorin, can be used to prevent potentially lethal methotrexate toxicities, but the resulting effectiveness of these treatments has been limited.[8] Accompanying renal disorder seems to arise from disturbances in the elimination of plasma methotrexate, which is mainly excreted in the urine.

Glucarpidase, which was originally isolated from *Pseudomonas* species, has been developed as an enzymatic drug (a 390-amino acid homodimer protein with a molecular weight of 83 kDa) that directly decomposes methotrexate into 2,4-diamino-N^{10}-methylpteroic acid and glutamate to prevent potentially life-threatening toxicity.[9] Currently, glucarpidase is the only and de facto standard drug approved for methotrexate-delayed excretion in Europe and the United States.

Glucarpidase rapidly mediates the degradation of methotrexate and reduces plasma methotrexate concentrations by >95% within 10 minutes to 1 hour.[10–14] A theoretical 50 U/kg dose of glucarpidase, which is sufficient to reduce a high methotrexate concentration, has been used for clinical treatment. In an open-label, single-site study, Phillips et al[15] reported that glucarpidase was safe and effective at a dose of 50 U/kg. Several case reports of glucarpidase treatment at a dose of 50 U/kg, which is recommended for compassionate treatment, have been published. Previous case reports have suggested the efficacy of lower doses of glucarpidase (15-70 U/kg), but these dose-finding studies of glucarpidase were not conducted in humans.

The rebound of methotrexate concentration after the first administration of glucarpidase and the repeated administration of glucarpidase has been reported. Repeated glucarpidase treatment is likely to be less effective, considering the immunogenicity of glucarpidase, and the repeat administration of glucarpidase within 48 hours of the first dose during the same methotrexate course is not recommended.[9,10] On the other hand, continued monitoring of the methotrexate concentration for >48 hours is recommended to monitor potential rebounds in the methotrexate concentration.[9] No pharmacokinetic studies have examined the repeated administration of glucarpidase.

Folate and folate rescue therapy are important for preventing adverse events associated with methotrexate, such as oral ulceration and oral mucositis.[16] However, no prospective studies have evaluated the pharmacology of glucarpidase, and the effect of folate and its derivatives (5-methyltetrahydrofolate [5-MeTHF]) and the production of anti-glucarpidase antibody remain unknown.

Little information is available regarding the safety and pharmacokinetic properties of glucarpidase. There is a need to clarify the pharmacokinetics of plasma and urine glucarpidase in ethnic groups and to confirm that a 50 U/kg dose of glucarpidase is necessary based on clinical trials to evaluate the nondevelopment of dose-limiting toxicity (DLT) at 2 different dose levels. We conducted and evaluated a phase 1 study of the safety, pharmacokinetics, and other pharmacologic effects of glucarpidase at 2 doses, with 1 repeated administration, in a clinical drug development trial in Japanese subjects.

Methods

Study Design and Subjects

This was an open-label, randomized parallel group, phase 1 study in which subjects were randomized into 2 cohorts, with each cohort being allocated a different fixed dose (low dose or standard dose) of glucarpidase. The study took place between November 2011 and January 2012 in healthy Japanese adult volunteers at the Department of Pharmacology, Hamamatsu University School of Medicine, Shizuoka, Japan. Eligible participants were healthy men aged 20 to 45 years weighing 50 to 100 kg with a body mass index of 18.5–25.0 kg/m^2. Subjects were excluded if they had a history of clinically significant neurologic, cardiovascular, pulmonary, hematologic, gastrointestinal, hepatic, renal, endocrine, or adrenal function disease; a drug allergy; alcohol or drug abuse; or abnormal infectious disease blood test results (hepatitis B virus, hepatitis C virus, HIV, or positive serologic test for syphilis). Each cohort contained 8 subjects. Written informed consent was obtained from each subject before participation in this study. This study was conducted in compliance with the Human Institutional Review Board of Hamamatsu University School of Medicine with the ethical principles proposed in the Declaration of Helsinki.

This investigator-initiated clinical trial was supported by the Center for Clinical Trials, Japan Medical Association. The study was registered with the Japan Medical Association Clinical Trial Registry (identifier: JMA-IIA00078).

Dosage and Administration

Glucarpidase (BTG International Ltd., London, UK) was administered as an intravenous injection over 5 minutes. Sixteen healthy young volunteers without methotrexate treatment were randomly assigned to receive 20 U/kg (low dose; cohort 1) or 50 U/kg (standard dose; cohort 2) of glucarpidase. The glucarpidase

dose of 1 unit was equivalent to 2.2 mg in prepared intravenous solution in this study. The contents of the vial reconstituted with 1 mL of saline for injection and the intravenous solution was administered into a peripheral vein over 5 minutes. Blood samples were drawn from a contralateral venous site. Subjects with cancer were not included in this trial. In each cohort of 8 subjects, 2 doses of glucarpidase at the same dose level were administered at a 2-day interval.

Safety Analysis

All observed and self-reported safety parameters were evaluated for 7 days after the start of glucarpidase administration and were assessed by monitoring for adverse events, clinical laboratory data, and vital signs (performance status, body temperature, systolic and diastolic blood pressure, pulse rate), and subjective symptoms.

DLTs were defined by the occurrence of severe toxicities according to the National Cancer Institute's Common Terminology Criteria for Adverse Events classification version 4.0, Japanese translation by the Japan Clinical Oncology Group. The DLT criteria of this study were as follows: (1) grade 2 adverse event with a duration of $\geq$2 days, (2) grade 3 or grade 4 adverse event, and (3) death at 7 to 10 days after the first administration of glucarpidase.

Pharmacologic Effects

Plasma samples for pharmacokinetic assessments of glucarpidase were collected before dosing and at 5 and 15 minutes and 2, 8, 12, 24, and 48 hours after the start of the first dose of glucarpidase; 48 hours after the first dose, the second dose was administered, and plasma samples were collected before dosing and at 5 minutes and 8, 12, 24, and 48 hours after the second dose. Urine samples were collected during the following intervals: 0 to 2 hours, 2 to 12 hours, and 12 to 24 hours after the start of the first administration of glucarpidase only.

The serum folate and plasma 5-MeTHF profiles were evaluated before dosing and at 48 and 96 hours (48 hours after second dose) after the start of the first dose of glucarpidase. Subjects with low folate levels were monitored for 7 to 10 days with no specific treatment administered. Plasma samples for the analysis of the anti-glucarpidase antibody titer were taken before dosing and 4 to 6 weeks after glucarpidase administration. Subjects with positive titer values were monitored for 2 to 7 months thereafter.

Statistical Analyses

The pharmacokinetic parameters of glucarpidase were calculated using WinNonlin software (Pharsight Corp., Mountain View, California). The pharmacokinetic evaluations included maximum plasma concentration (C_{max}), time to C_{max}, area under the plasma concentration–time curve (AUC) from time 0 to 24 hours ($AUC_{0\text{-}24}$), AUC from time 0 to infinity ($AUC_{0\text{-}\infty}$),total clearance, volume of distribution during the elimination phase, steady-state volume of distribution, and half-life. Each AUC was calculated using the linear trapezoidal rule. Less than the lower limit of quantification (LLOQ) of the subjects was recorded as below the limits of quantitation, which was represented as 0 in the calculations of the pharmacokinetic parameters.

Statistical analyses were performed using JMP Pro 15 (SAS Institute Inc., Cary, North Carolina). An unpaired *t*-test with Welch's correction was used for the statistical analyses of continuous variables in 2 independent groups. A P value $<.05$ was considered statistically significant.

Bioanalyses

Blood samples were centrifuged for 15 minutes, separated immediately after centrifugation, and stored at –70°C until analysis. Plasma and urine concentrations of glucarpidase were determined using an enzyme-linked immunosorbent assay (ELISA).

In the analysis of glucarpidase, the ELISA plate was coated with goat purified antibody against glucarpidase overnight and incubated with calibration standards, quality controls, and study samples. After excess samples had been washed away 4 times, affinity purified anti-glucarpidase immunoglobulin G solution as a secondary antibody was added to the plate and incubated. The wells were then washed before addition of horseradish peroxidase conjugated goat anti-rabbit immunoglobulin G (H+L–chain specific). The optical density of each well was measured by the dual-wavelength method, using a detection wavelength of 450 nm and a reference wavelength of 630 nm. The calibration ranges for glucarpidase were defined by the LLOQ and the upper limit of quantification (ULOQ) with 7 calibration standards of different concentration levels, including the LLOQ and the ULOQ, with a correlation coefficient $\geq$0.999. The LLOQ and the ULOQ of the urine and plasma concentrations of glucarpidase were 1 ng/mL and 640 μg/mL, respectively. The interassay variability of the urine and plasma levels were $\leq$12.1% and $\leq$7.8 %, respectively.

Plasma anti-glucarpidase antibody titers were determined using ELISA. In the analysis of anti-glucarpidase antibody, briefly, glucarpidase-coated ELISA plates were loaded with samples. After excess samples had been washed away, biotin-binding glucarpidase was added to the plate, and the wells were washed again. A color reaction was elicited by adding

Table 1. Summary of Participant Demographics and Baseline Characteristics in 2 Cohorts of Glucarpidase

Characteristics	Cohort 1 20 U/kg (n = 8)	Cohort 2 50 U/kg (n = 8)	*P* Value	Total (n = 16)
Mean age, (range)	28.0 (21-43)	21.9 (20-27)	.060	24.9 (20-40)
Mean height, cm (range)	168.0 (162.6-174.2)	171.3 (166.1-184.8)	.224	169.6 (162.6-184.8)
Mean weight, kg (range)	61.1 (54.6-66.9)	60.6 (54.3-66.7)	.823	60.9 (54.3-66.9)
Mean BMI, kg/m^2 (range)	21.6 (20.2-22.9)	20.7 (19.1-23.1)	.142	21.2 (19.1-23.1)

BMI, body mass index.
Sixteen healthy volunteers were randomly assigned to receive cohort 1 or cohort 2.

peroxidase-labeled avidin D using a detection wavelength of 450 nm and a reference wavelength of 540 nm. The interassay variability of the anti-glucarpidase antibody titer was ≤16.3%. A positive anti-glucarpidase antibody titer was judged as any value over the cut point, which was defined by the average value of drug-naive specimens obtained before the administration of glucarpidase.

Serum concentrations of folate were measured by a chemiluminescent enzyme immunoassay using the Access Folate Reagent and UniCel DxH 800 (Beckman Coulter, Inc., Indianapolis, Indiana). The LLOQ and the ULOQ of the serum concentrations of folate were 1 ng/mL and 22 ng/mL, respectively. The interassay variability of the serum level was ≤2.2%.

Plasma concentrations of 5-MeTHF were measured with 5-Me-d3-THF (mixture of diastereomers) as an internal standard using a high-performance liquid chromatography (LC-20A HPLC system, Shimadzu Corp., Kyoto, Japan) coupled with tandem mass spectrometry (API 4000, AB Sciex Pte. Ltd., Framingham, Massachusetts) assay. The liquid chromatography–tandem mass spectrometryMS/MS analysis of 5MeTHF was performed using an Inertsil C8-4 HP (2.1 × 250 mm, 3 μm column; GL Sciences Inc., Torrance, California) at 50°C. The mobile phase A contained 10 mmol/L formic acid/ammonium formate (1000:1, v/v), and phase B contained formic acid/methanol (1000:1, v/v) and were delivered at 1.0 mL/min. Detection was performed using multiple reaction monitoring modes at *m/z* 458→329 (for 5-MeTHF) and *m/z* 461→332 (for 5-Me-d3THF). The LLOQ and the ULOQ of the plasma concentrations of 5-MeTHF were 5 and 1000 ng/mL, respectively. The interassay variability of the plasma level was ≤5.5%.

The glucarpidase and 5-MeTHF levels and the anti-glucarpidase antibody titer in plasma or urine were analyzed by Shin Nippon Biomedical Laboratories, Ltd. (Wakayama, Japan). The serum folate level was analyzed by SRL laboratory, Inc. (Tokyo, Japan). All of the analytical methods were validated according to the Guidelines on Bioanalytical Method Validation in Pharmaceutical Development in Japan.

Table 2. Adverse Effects of Clinical Laboratory Parameters in Cohort 1 and Cohort 2

Adverse Events[a]	Cohort 1 (n = 8)	Cohort 2 (n = 8)
Anemia	3	0
Blood bilirubin increased	0	1
Creatinine increased	1	1
Hematocrit increased	2	1
Hyperkalemia	0	1
Hypertriglyceridemia	1	0
Hyponatremia	1	0
Platelet count decreased	2	0
Proteinuria	1	2
White blood cell count decreased	1	0

[a]All adverse events are grade 1.

Results

Safety

Sixteen randomized subjects (Table 1) who received glucarpidase were included in the safety and pharmacologic analyses. Two cohorts at repeated dose levels of 20 U/kg (cohort 1) and 50 U/kg (cohort 2) were examined; no DLTs or significant clinical examination findings were observed. Among the clinical laboratory parameters, some grade 1 events were reported. The rates of adverse events in cohorts 1 and 2 were 75.0% and 62.5%, respectively. No clinically relevant differences between glucarpidase dose levels (20 U/kg and 50 U/kg) were seen (Table 2).

Pharmacologic Analyses

Glucarpidase. The plasma concentrations after repeated dosing in cohorts 1 and 2 are shown in Figure 1. The pharmacokinetics parameters after the administration of glucarpidase in both cohorts are shown in Table 3. The AUC increased in a generally linear, dose-proportional manner in both cohorts and was similar for the first and second doses. No accumulation of glucarpidase at the time of the second administration was seen, similar to the theoretical accumulation rate calculated using the half-life. Glucarpidase was not

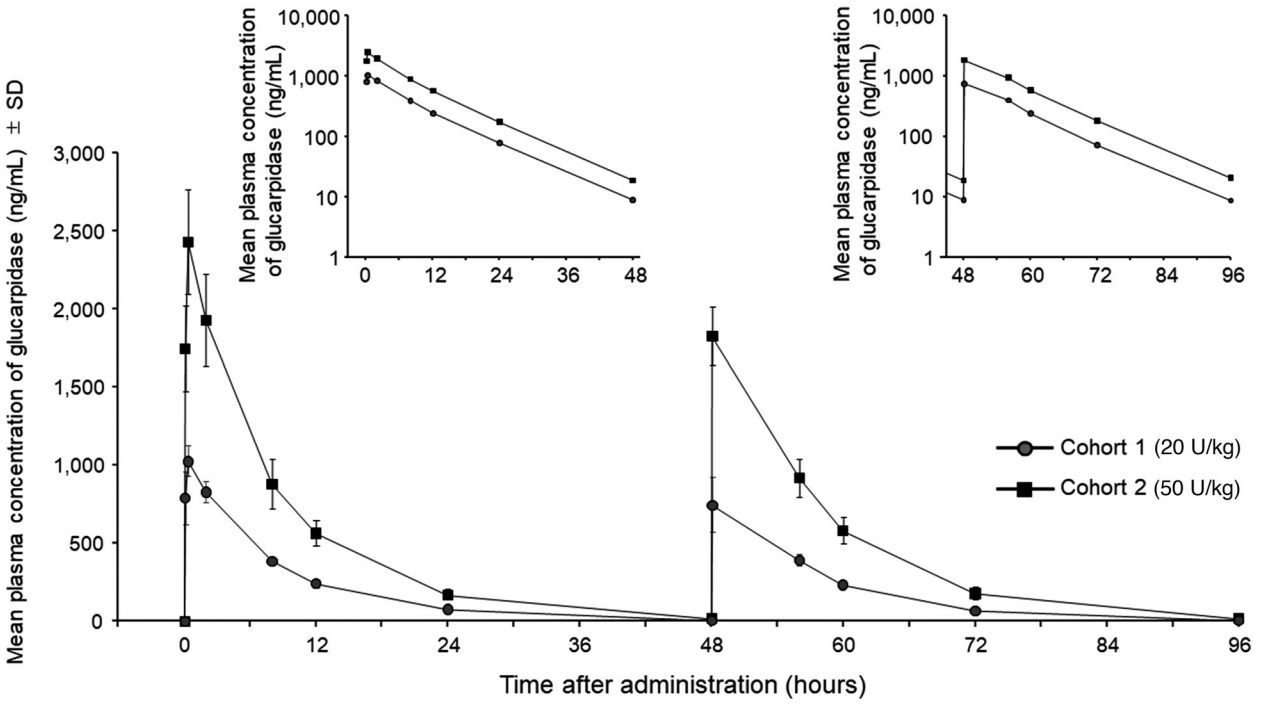

Figure 1. Plasma concentration of glucarpidase on linear and semilogarithmic scales. Total number of 16 healthy young volunteers without methotrexate treatment were randomly assigned to receive 20 U/kg (cohort) or 50 U/kg (cohort 2) of glucarpidase. The glucarpidase dose of 1 unit was equivalent to 2.2 mg in prepared intravenous solution in this study. Below the limits of quantitation has been entered as 0 and included in calculating the mean. SD, standard deviation.

Table 3. Pharmacokinetic Parameters After Intravenous Administrations of Glucarpidase in Healthy Adults

	Group	Test Article	C_{max} (ng/mL)	t_{max} (min)	$t_{1/2}$ (h)	$AUC_{0\text{-}24}$ (μg·h/mL)	$AUC_{0\text{-}\infty}$ (μg·h/mL)	CL (mL/min)	V_z (L)	V_z /BW (mL/kg)	V_{dss} (L)
First Dose	Cohort 1 (n = 8)	20 U/kg	1026 (98)	15 (15-15)	7.45 (0.49)	8.25 (0.47)	9.10 (0.58)	4.85 (0.47)	3.12 (0.28)	51.2 (3.6)	2.83 (0.30)
	Cohort 2 (n = 8)	50 U/kg	2430 (336)	15 (15-15)	7.25 (0.41)	19.05 (2.85)	20.88 (3.25)	5.47 (1.09)	3.41 (0.57)	56.1 (7.1)	3.11 (0.54)
Second dose	Cohort 1 (n = 8)	20 U/kg	748 (179)	5 (5-5)	7.48 (0.59)	7.27 (0.62)	8.07 (0.66)	5.50 (0.72)	3.55 (0.45)	58.1 (6.0)	3.44 (0.64)
	Cohort 2 (n = 8)	50 U/kg	1827 (183)	5 (5-5)	7.39 (0.44)	17.62 (1.99)	19.61 (2.46)	5.79 (1.09)	30.68 (0.57)	60.7 (8.1)	3.59 (0.53)

$AUC_{0\text{-}24}$, area under the plasma concentration–time curve from time 0 to 24 hours; $AUC_{0\text{-}\infty}$, area under the plasma concentration–time curve from time 0 to infinity; BW, body weight; C_{max}, maximum plasma concentration; CL, total clearance; t_{max}, time to C_{max}; $t_{1/2}$, half-life; V_{dss}, steady-state volume of distribution; V_z, volume of distribution during the elimination phase.
The glucarpidase dose of 1 unit was equivalent to 2.2 mg in this study.
Values are mean (SD), except median (range) for t_{max}.

detected in the urine after administration in any of the patients.

Anti-Glucarpidase Antibody. The anti-glucarpidase antibody titer was negative in all the subjects before dosing. In cohorts 1 and 2, positive anti-glucarpidase antibody results were obtained at 4 to 6 weeks after glucarpidase administration in 4 and 7 cases, respectively (Table 4). With the exception of 1 case, positive antibody titers continued to be observed in both groups for 5 to 7 months.

Folate. The effects of glucarpidase on the plasma-concentration profile for folate following the administration of glucarpidase are shown in Figure 2 for both cohorts. The mean (±standard deviation [SD] values) concentrations of folate before dosing and at 48 and 96 hours were as follows: cohort 1: 5.19 ± 1.97, 3.40 ± 0.92, and 3.58 ± 0.88 ng/mL; and cohort 2: 4.19 ± 0.98/mL, 2.86 ± 0.87, 3.04 ± 0.78 ng/mL.

5-MeTHF. 5-MeTHF was detected in 4 of the 8 cases in cohorts 1 and 2 of the 8 cases in cohort 2.

Table 4. Number of Subjects With Positive and Negative of Anti-Glucarpidase 2 Antibody Titer in Human Plasma

Group	Antibody Production[a]	Before Dosing	4 to 6 Weeks After Dosing		2 to 4 Months' Follow-Up	5 to 7 Months' Follow-Up
Cohort 1 (20 U/kg)	Positive	0	4	Positive	3	3
				Negative	1	1
	Negative	8	4		N/A	N/A
Cohort 2 (50 U/kg)	Positive	0	7	Positive	7	6
				Negative	0	1
	Negative	8	1		N/A	N/A

N/A, not applicable.
[a]Antibody production was set as follows: negative (absorbance $<$ cut point), positive (absorbance $\geq$ cut point). Cut point = mean absorbance of negative control samples from treatment naïve subjects $\times$ normalization factor.
Subjects with positive titer values were monitored for 2 to 7 months.

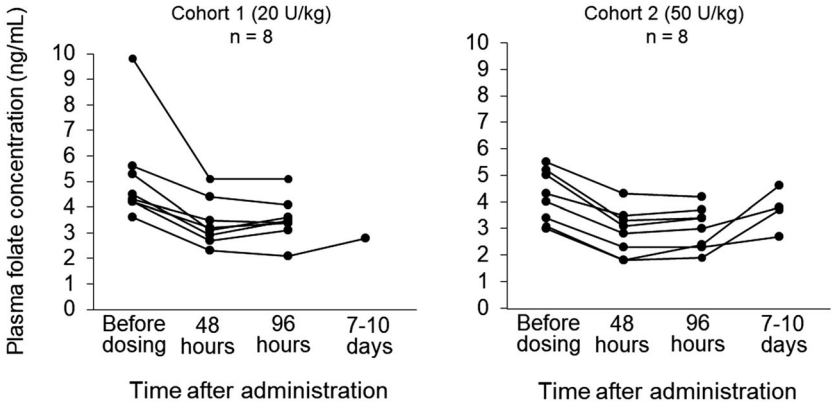

Figure 2. Plasma folate concentration after intravenous administrations of glucarpidase in healthy volunteers without methotrexate treatment. Subjects with low folate levels ($\leq$3 ng/mL) continued to monitor for 7 to 10 days.

Table 5. Serum 5-Methyltetrahydrofolate Concentration and the Number of Subjects With Concentrations Below or Above the LLOQ (5 ng/mL)

Group		Before Dosing	48 Hours After First Dosing[a1]	48 Hours After Second Dosing
Cohort 1 (20 U/kg)	Detected concentration, ng/mL	13.4, 6.9, 6.0, 5.5	6.0, 5.0	5.8
	Detectable (n)	4	2	1
	Not detectable (n)	4	6	7
Cohort 2 (50 U/kg)	Detected concentration, ng/mL	6.0, 5.9	-	-
	Detectable (n)	2	0	0
	Not detectable (n)	6	8	8

LLOQ, lower limit of quantification.
[a]1: Before second dosing.

The concentrations of 5-MeTHF decreased or were not detectable after the administration of glucarpidase (Table 5).

Discussion

This glucarpidase phase 1 study was conducted to confirm tolerability and the absence of DLTs and to evaluate the pharmacodynamics and pharmacokinetics of repeated administration at 2 dose levels. Glucarpidase was tolerated in both cohorts, with an acceptable safety profile, no DLTs, and no clinically relevant differences between dose levels (Table 2).

In the pharmacokinetics study, the total clearance and distribution volume of glucarpidase at steady state were similar between the 2 cohorts and between the first and second doses (Table 3). Proportional dose-dependent increases in in C_{max} and $AUC_{0-\infty}$ were confirmed for both cohorts. An unchanged form of glucarpidase 2 was not detected in any of the urine

samples in the present study, supporting the finding reported by Phillips et al[15] that the pharmacokinetics were unaltered in patients with impaired renal function. Consequently, dose adjustments of glucarpidase are not required for patients with renal impairment. The pharmacokinetic parameters obtained at a dose level of 50 U/kg in the Japanese subjects were a C_{max} of 2430 ng/mL and an $AUC_{0-\infty}$ of 20.88 μg·h/mL, which were similar to previously reported results for healthy subjects of White and African descent (C_{max}, 2970 ng/mL; $AUC_{0-\infty}$, 22.4 μg·h/mL).

The estimated distribution volume of glucarpidase per body weight was 56.1 mL/kg, which was calculated using a volume of distribution during the elimination phase of 50 U/kg at first dose and individual body weight. This apparent distribution volume, similar to previous study (steady state, 58.0 mL/kg),[15] suggests that glucarpidase of high molecular weight is mainly distributed in the plasma. A linear correlation between blood volume and body weight in pediatric subjects has been reported, with reported blood volumes of 52.3 $\pm$ 8.3 in boys and 47.9 $\pm$ 7.7 in girls (mL/kg).[17] The metabolism of glucarpidase does not depend on organ function or pediatric growth. These findings provide important suggestions for the pharmacokinetics in children, which are thought to be similar to those in adults. Actually, a pooled analysis of clinical trials with a median age of 20 years (range, 5 weeks to 84 years) showed a clinical efficacy of glucarpidase corresponding to a $\geq$99% sustained reduction in the methotrexate concentration.[18]

Although the serum folate concentration decreased after glucarpidase administration in all the subjects (Figure 1), significant clinical symptoms were not observed and the serum folate level was easily restored by regular food intake. Quantitative evaluations of the reductions in serum folate concentrations and plasma 5-MeTHF concentrations were difficult because of the low baseline concentrations. Restricted food intake often occurs during high-dose methotrexate therapy; therefore, the administration of intravenous folate is recommended on the day following glucarpidase administration.

The production of anti-glucarpidase antibody was observed in many cases in both cohorts (Table 4). The high molecular weight of glucarpidase may result in a strong immunogenicity, but a National Cancer Institute study reported that the prevalence of anti-glucarpidase antibody decreases after 6 months. Thus, a possible reduction in efficacy caused by the presence of a neutralizing antibody and subsequent allergic reaction is unlikely if readministration occurs after a long interval.

The effect of anti-glucarpidase antibody on efficacy and safety during the second dose of a methotrexate course remains unknown. However, the pharmacokinetic parameters of a second dose administered at 48 hours after the first dose were similar to those of the first dose. Although the long-term effect of anti-glucarpidase antibody must be evaluated in future investigations, anti-glucarpidase antibody was not thought to affect the pharmacokinetics of glucarpidase within 96 hours after the start of the first dose.

Conclusion

No DLTs or significant clinical examination findings were observed in a repeated-dose phase 1 study of glucarpidase conducted at 2 dose levels in healthy Japanese adult subjects. The 50-U/kg dose of glucarpidase may be suitable as a safe intervention that is capable of achieving a maximum effect. From a pharmacokinetics point of view, repeat dosing with glucarpidase within 96 hours after the start of the first dose administration has the potential to reduce high methotrexate concentrations. The administration of intravenous folate on the day following glucarpidase administration is recommended for high-dose methotrexate therapy because of the degradation of serum folate. The observed safety and tolerability, pharmacokinetics, and pharmacodynamics support the continued evaluation of glucarpidase in the patients with lethal methotrexate toxicities in cancer chemotherapy.

Acknowledgments

We thank Ohara Pharmaceutical Co., Ltd. and BTG International Ltd., which provided the investigational drug and information deemed important to conduct the clinical trial.

Conflicts of Interest

The authors declare no conflicts of interest.

Funding

This study was supported by the Center for Clinical Trials, Japan Medical Association.

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