Journal of the Neurological Sciences 396 (2019) 150–158

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Efficacy, safety, and pharmacokinetics of intravenous midazolam in Japanese children with status epilepticus

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ARTICLE INFO

Keywords:
Midazolam
Open-label study
Status epilepticus
Pharmacokinetics
Efficacy
Safety

ABSTRACT

Background: No dosing regimen has been established for the initial treatment of pediatric status epilepticus with intravenous midazolam. We therefore evaluated the efficacy, safety, and pharmacokinetics of bolus and continuous midazolam infusion.

Methods: This open-label, prospective, multicenter study involved 34 Japanese children with status epilepticus unresponsive to diazepam. An initial bolus of 0.15 mg/kg midazolam was given, with additional doses of 0.1–0.3 mg/kg up to a cumulative dose of 0.6 mg/kg. A continuous infusion was initiated at 0.1 mg/kg/h (maximum 0.4 mg/kg/h) for patients at high risk of recurrence or in whom seizure reduction was achieved, and continued for 24 h after seizure cessation. Seizure cessation was assessed based on clinical observation (disappearance of motor symptoms regardless of recovery of consciousness), rather than the disappearance of electroencephalography abnormalities.

Results: The seizure cessation rate with bolus midazolam was 88%. The cumulative dose was ≤0.3 mg/kg in 90% of patients who responded to bolus administration. Adverse events were observed in three patients; one had mild respiratory depression that required supplemental oxygen and bag-valve-mask ventilation. Elimination half-life was 0.999 ± 0.241 h in seven patients. Total body clearance ranged from 423 to 1220 mL/h/kg in older children but was notably higher in a 10-month-old infant (2010 mL/h/kg).

Conclusions: The efficacy and safety of midazolam were demonstrated in children with status epilepticus, suggesting that intravenous midazolam is suitable as first-line treatment.

1. Introduction

Midazolam (MDL) is a chemically synthesized imidazobenzodiazepine derivative and has pharmacological effects such as hypnotic, sedative, anesthetic, and anxiolytic effects. Since its approval in Switzerland in 1982 as a short-duration hypnotic sedative, it has been widely used as a pre-anesthetic and sedative, as well as for induction and maintenance of general anesthesia in > 100 countries. In Japan, MDL was approved in 1988, and its indications are pre-anesthetic use and induction and maintenance of general anesthesia. Because of its water solubility, MDL can be easily diluted and administered as a continuous intravenous infusion; it is widely used in patients including children. Like other benzodiazepines, MDL has a strong anticonvulsive effect in addition to its hypnotic and sedative effects [1]. MDL has been used in many patients with status epilepticus, and favorable efficacy and safety profiles have been reported [2–5]. Consequently, intravenous MDL injection therapy is recommended in various guidelines for status epilepticus [6–10]. A US investigation on the use of drugs in patients with status epilepticus reported the use of MDL, especially in refractory cases [11]. In Japan, most of the data concerning the efficacy and safety of MDL in status epilepticus have been collected in children [12–18]. However, according to reported information on doses, the timing of continuous intravenous infusion initiation and the administration methods for MDL vary greatly, and the optimum dosing regimen of MDL has not been established. There

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https://doi.org/10.1016/j.jns.2018.09.035
Received 26 February 2018; Received in revised form 11 September 2018; Accepted 29 September 2018
Available online 04 October 2018
0022-510X/

are many challenges to conducting research into a clinical emergency such as status epilepticus. Few prospective studies have been conducted in children, and most of the current treatment guidelines for status epilepticus are based on findings of studies in adults. Moreover, clinical management of status epilepticus varies greatly depending on the drugs approved in a particular country, availability of the drugs, and discretion of the attending physician [19]. Under these circumstances, there was a demand for implementation of a prospective clinical study of a large number of pediatric patients with status epilepticus to further define the safety profile of MDL therapy.

To establish appropriate treatment strategies, prospective clinical studies with defined treatment protocols are needed to examine the efficacy and safety of intravenous MDL therapy in children with status epilepticus. Therefore, we conducted an open-label, uncontrolled, prospective study to evaluate the efficacy, safety, and pharmacokinetics of intravenous MDL therapy in Japanese children with status epilepticus.

2. Patients and methods

2.1. Patients and inclusion criteria

This study was conducted in 26 study centers throughout Japan from October 2010 to December 2012 (Table 1). It was conducted with strict adherence to the Declaration of Helsinki (including revised versions), the Ministerial Ordinance on Good Clinical Practice for Drugs [dated March 27, 1997; Ministry of Health and Welfare (currently the Ministry of Health, Labour and Welfare)] and the notification of revision of the Ordinance. The study was approved by the Institutional Review Boards of all the study centers.

The study involved children who developed status epilepticus, including impending status epilepticus, and were unresponsive to diazepam. Status epilepticus was defined according to Bancaud et al. [20] (the definition by the International League Against Epilepsy guidelines), and the seizure duration was specified to be 5 min or longer based on Lowenstein et al. [21]. Patients who met all the following requirements were enrolled in the study:

1) Patients aged between 45 weeks, corrected gestational age, and 16 years.

2) Patients with a seizure episode lasting for 15 min or longer, or with multiple seizures lasting for 5 min or longer, who were confirmed to have a history of status epilepticus from medical records.

3) Patients whose seizures did not cease after administration of intravenous diazepam (a cumulative dose of ≥0.3 mg/kg or ≥ 10 mg/body), or those with a recent history of unsuccessful cessation of seizure with intravenous diazepam (a cumulative dose of ≥0.3 mg/kg or ≥ 10 mg/body).

4) Patients whose parents or guardians provided written informed consent. Written consent was obtained in advance and confirmed verbally every 6 months and immediately before treatment. For emergency cases, written consent was obtained using an abbreviated consent form, and a full explanation was provided as soon as possible after administration of the study drug.

Patients with non-convulsive status epilepticus, acute narrow angle glaucoma or myasthenia gravis, those receiving combination therapy with an HIV protease inhibitor or HIV reverse transcriptase inhibitor, and those with a hypersensitivity to MDL or benzodiazepine were excluded.

2.2. Study design

This study was designed as an open-label, uncontrolled study of MDL. The study consisted of four periods (Fig. 1): bolus intravenous injection (bolus iv), continuous intravenous injection (Civ), post-treatment observation (24 h), and follow-up (1 week). During the bolus iv period, an intravenous MDL formulation (10 mg/10 mL) was administered at a dose of 0.15 mg/kg (injection rate: 1 mg/min), and seizure cessation was checked. In emergency cases where it was impractical to

Table 1
Study centers[a].

Name of medical institution	Department	Investigator	Ethics committee approval number
Hokkaido Medical Center for Child Health and Rehabilitation	Department of Pediatrics	Kimio Minagawa	–
Jichi Medical University Hospital	Department of Pediatrics	Hideo Sugie	101004
Saitama Children's Medical Center	Division of Neurology	Shin-ichiro Hamano	–
Saitama Medical University Hospital	Department of Pediatrics	Hideo Yamanouchi	907
Saitama Medical Center, Saitama Medical University	Department of Pediatrics	Masanori Tamura	563
Tokyo Women's Medical University Yachiyo Medical Center	Division of Neurology and Developmental Pediatrics	Kitami Hayashi	2010023
Tokyo Women's Medical University Hospital	Department of Pediatrics	Makiko Osawa	2010022
Keio University Hospital	Department of Pediatrics	Takao Takahashi	10-035
Juntendo University Hospital	Department of Pediatrics and Adolescent Medicine	Akihisa Okumura	2010-020
Juntendo University Nerima Hospital	Department of Pediatrics	Shinichi Niijima	1042
National Center of Neurology and Psychiatry	Department of Child Neurology	Eiji Nakagawa	141
Nihon University Itabashi Hospital	Department of Pediatrics	Ryutaro Kohira	2310-1330
St. Marianna University School of Medicine Hospital	Department of Pediatrics	Hitoshi Yamamoto	A-2042
Kitasato University Hospital	Department of Pediatrics	Masahiro Ishii	2010010
Kanagawa Children's Medical Center	Department of Neurology	Hitoshi Osaka	–
Gifu Prefectural General Medical Center	Department of Pediatrics	Atsushi Imamura	11-234, 11-451
National Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorders	Department of Pediatrics	Hideyuki Otani	–
Shiga University of Medical Science Hospital	Department of Pediatrics	Yoshihiro Takeuchi	11-04
Osaka Medical Center and Research Institute for Maternal and Child Health	Department of Pediatric Neurology	Yasuhiro Suzuki	–
Osaka City University Hospital	Department of Pediatrics	Haruo Shintaku	1616
Nakano Children's Hospital	Department of Pediatrics	Kiyotaka Murakami	–
Osaka City General Hospital	Department of Pediatric Neurology	Hisashi Kawawaki	1893
Osaka Kosei Nenkin Hospital	Department of Pediatrics	Tetsuzo Tagawa	005250
Okayama University Hospital	Department of Child Neurology	Yoko Otsuka	221806
Kumamoto University Hospital	Division of Child Health and Development	Shigemi Kimura	22-71, 23-7, 24-3
Oita University Hospital	Department of Pediatrics	Tatsuro Izumi	A10-011

[a] Information is accurate as of the time the study was conducted.

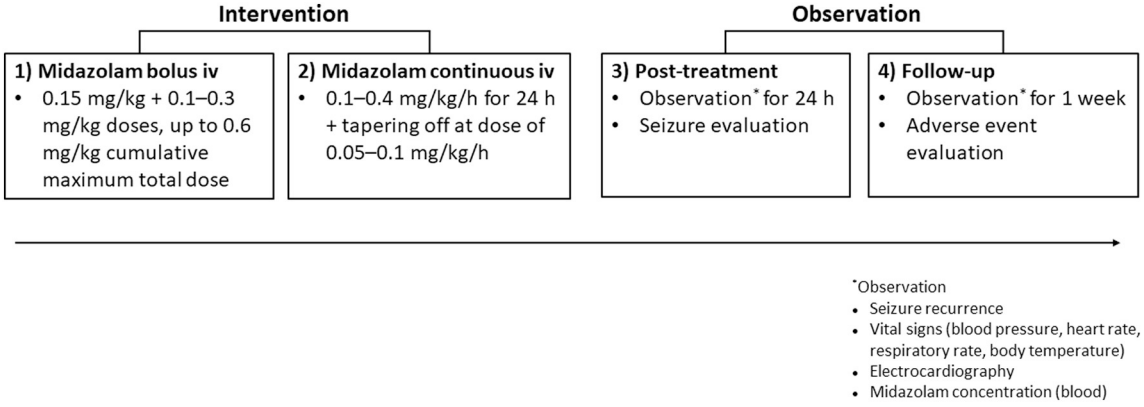

Fig. 1. Study design. Abbreviation: iv, intravenous injection.

measure the weight of the patient prior to administration, weight was informed by the parent or caregiver. For patients whose seizures did not cease after the initial dose, additional doses (0.1–0.3 mg/kg/dose) were administered up to a maximum cumulative dose of 0.6 mg/kg until seizure cessation was achieved. Patients who achieved seizure cessation but were deemed to have a higher risk of recurrence on the basis of past medical history, or those whose seizures were reduced after administration of bolus doses up to the maximum cumulative dose (0.6 mg/kg), were judged as eligible to receive Civ. The continuous intravenous infusion was initiated at 0.1 mg/kg/h. For patients whose seizures did not cease or recurred within 24 h after infusion initiation, the dose was increased in increments of 0.05 to 0.1 mg/kg/h up to 0.4 mg/kg/h. The Civ period was defined as 24 h after cessation of the last seizure, during which administration of MDL at 0.1 to 0.4 mg/kg/h was continued. The post-treatment observation period was defined as 24 h after the end of the last dose for patients receiving intravenous bolus treatment only, and as 24 h after completion of dose reduction (in decrements of 0.05 to 0.1 mg/kg/h) for patients initiating Civ. During the post-treatment observation period, the presence or absence of seizure recurrence, vital signs, electrocardiography, and blood MDL concentrations were monitored. It was specified that patients who were non-responders to MDL during either the bolus iv period or the Civ period should be promptly switched to another appropriate treatment.

2.3. Efficacy endpoints

The primary endpoint was achievement of seizure cessation by intravenous bolus. The assessment criterion for seizure cessation by intravenous bolus treatment was defined as "cessation of the seizure within 10 minutes after the end of MDL treatment and no seizure recurrence within 30 minutes after the end of treatment." Cessation was assessed based on clinical observation (disappearance of motor symptoms regardless of recovery of consciousness), rather than the disappearance of electroencephalography abnormalities. A one-sample proportion test (binomial distribution) based on a null hypothesis that the seizure cessation rate is 50.0% was performed to calculate the proportion of patients achieving seizure cessation (seizure cessation rate) for the bolus iv period, along with the 95% confidence interval (CI). In addition, the seizure cessation rate was calculated by the cumulative dose of intravenous bolus MDL.

2.4. Safety endpoints

Adverse events (AEs) were tabulated by severity, interventions required, time of onset, and causal relationship with MDL for each symptom, and their incidences were calculated. The evaluation of vital signs and electrocardiography was carried out intermittently using a biological information monitor. For continuous data such as vital signs, summary statistics were calculated by testing time point.

2.5. Pharmacokinetics

Blood sampling was performed at four time points (30 min and 1, 2, and 4 h after the end of treatment) for patients who received intravenous bolus and at three time points (before initiation of Civ and 12 and 24 h after initiation of Civ at the last dose level) for patients who initiated Civ. The plasma MDL concentrations (lower limit of quantification: 10 ng/mL) were obtained by liquid chromatography with tandem mass spectrometry (LC/MS/MS).

For each bolus iv period and Civ period, a pharmacokinetic analysis by a model-independent approach was performed using plasma MDL concentrations. In the analysis, the elimination half-life ($t_{1/2}$) was calculated in patients who received bolus iv only, and the total body clearance (CL_{tot}) was calculated in patients in whom Civ was initiated.

The pharmacokinetic analysis was performed in patients stratified by age because the clearance of midazolam varies according to the developmental stage (infants, school-age children, and adolescents) of the patient [22]. Midazolam is metabolized mainly by CYP3A4, which reaches peak activity within the first year of life. Therefore, we analyzed patients aged > 1 month to < 1 year and compared them against patients aged ≥1 year. Furthermore, the age of onset of seizures is usually < 6 months; therefore, after consultation with the PMDA, it was decided that the following age groups would be utilized: a) 1 month to < 1 year; b) 1 to 5 years; c) 6 to 11 years; and d) ≥12 years.

2.6. Statistical analysis

The estimate for the primary endpoint was specified as 70.0% based on five retrospective clinical studies conducted in children with status epilepticus in Japan [16,23–26]. Additionally, based on the specialist's opinion that achievement of seizure cessation in half of the patients enrolled in this study is of great clinical significance, the threshold value was specified as 50.0%.

Based on a threshold level and expected value for the null hypothesis of 50.0% and 70.0%, respectively, with a type I error (two-tailed) of 0.05 and a type II error of 0.20, the target sample size was determined to be 49 subjects, using a one-sample proportion test (binomial distribution).

3. Results

3.1. Patient characteristics

Thirty-four patients participated in this study; their characteristics are shown in Table 2. The mean age (± SD) was 6.0 ± 4.2 years, and the mean body weight was 19.9 ± 17.0 kg. Boys accounted for 55.9% of the patients. The seizure type leading to status epilepticus was partial seizures in 26 patients, of whom 19 had secondary generalized seizures

Table 2
Patient characteristics.

	Number of patients	(%)
Sex		
Male	19	(55.9)
Female	15	(44.1)
Age (years)		
1 month to < 1 year	2	(5.9)
1 to < 6 years	17	(50.0)
6 to < 12 years	10	(29.4)
≥12 years	5	(14.7)
Mean ± SD	6.0 ± 4.2	
Median	5.3	
Range	0.5 to 13.7	
Body weight (kg)		
Mean ± SD	19.9 ± 17.0	
Median	15.5	
Range	6.0 to 83.0	
Seizure types		
Partial seizures	26	(76.5)
Secondary generalized seizures	19	(55.9)
Focal motor seizures	7	(20.6)
Generalized seizures	8	(23.5)
Etiology		
Epilepsy	30	(88.2)
Symptomatic/cryptogenic localization-related epilepsy	23	(67.6)
Undetermined epilepsy	3	(8.8)
Symptomatic generalized epilepsy	2	(5.9)
Idiopathic generalized epilepsy	1	(2.9)
Unknown	1	(2.9)
Acute diseases	4	(11.8)
Febrile seizures	2	(5.9)
Meningitis/encephalitis/encephalopathy	1	(2.9)
Cerebrovascular accident	1	(2.9)
Time from seizure onset to study drug treatment		
≤30 min	8	(23.5)
> 30 min to 1 h	7	(20.6)
> 1 to 2 h	5	(14.7)
> 2 to 3 h	4	(11.8)
> 3 to 6 h	5	(14.7)
> 6 to 12 h	0	
> 12 to 24 h	2	(5.9)
> 24 h	3	(8.8)

and 7 had focal motor seizures. Eight patients had generalized seizures. The etiology was epilepsy in 30 patients (88.2%), including 23 patients with symptomatic or cryptogenic localization-related epilepsy, and acute diseases in 4 patients (11.8%) only, consisting of 2 patients with febrile seizures, 1 patient with acute encephalopathy, and 1 patient with cerebrovascular accident. The time from seizure onset to the initiation of intravenous bolus MDL was ≥60 min in the majority (55.9%) of patients and was ≤30 min only in 8 patients (23.5%). There were 20 patients (58.8%) who did not respond to diazepam injected intravenously after seizure onset who were therefore given intravenous bolus MDL. The median cumulative dose of diazepam in these 20 patients was 0.31 mg/kg (0.12–1.25 mg/kg). In the remaining 14 patients who had not responded to intravenous diazepam in the past, MDL was used as first-line therapy in this study.

3.2. Efficacy

All 34 patients received intravenous MDL bolus treatment, and seizure cessation was achieved in 30 patients (Table 3). The seizure cessation rate by intravenous bolus, which was the primary endpoint, was 88.2% (30 of 34 patients) (95% CI: 72.5–96.7%). This result was found to be significant ($p < .001$) by the one-sample proportion test (binomial distribution). Civ was initiated in 11 of the 30 patients in whom seizure cessation was achieved and in 1 patient who was classified as a case of seizure "reduction" without complete seizure cessation even with the intravenous bolus MDL dose reaching 0.6 mg/kg. In the remaining three patients, bolus MDL failed to suppress seizures and was therefore discontinued during the bolus iv period, and seizure suppression was achieved with other drugs (Fig. 2). Considering the cumulative dose, the seizure cessation rate achieved by intravenous bolus showed that the cumulative dose was ≤0.3 mg/kg in 93.3% of the 30 responders.

Table 3
Efficacy of midazolam.

	Seizure cessation rate	(95% CI)
Bolus iv period	88.2% (30/34)	(72.5–96.7%)
By cumulative dose during bolus iv period		
≤0.15 mg/kg	52.9% (18/34)	
≤0.2 mg/kg	70.6% (24/34)	
≤0.3 mg/kg	82.4% (28/34)	
≤0.4 mg/kg	85.3% (29/34)	
≤0.5 mg/kg	85.3% (29/34)	
> 0.5 mg/kg	88.2% (30/34)	

Nineteen patients were subjected to post-treatment observation after receiving intravenous bolus treatment only. Of 12 patients in whom Civ was initiated, 3 patients had recurrence. These patients were switched to other drugs, and seizure suppression was achieved. In the remaining nine patients, seizure suppression was maintained for > 24 h. However, one of these patients was withdrawn from the study owing to inadvertent use of an MDL formulation (provided at a different concentration, and with different indications) other than the designated product in this study and therefore did not undergo post-treatment observation. A total of 27 patients were subjected to post-treatment observation, consisting of 19 patients from the bolus iv period and 8 patients from the Civ period. Of these, nine patients (seven from the bolus iv period and two from the Civ period) were withdrawn from the study because of recurrence during the post-treatment observation period or for other reasons. As a result, the follow-up period was completed in 18 patients.

3.3. Safety

AEs for which a causal relationship with the drug could not be ruled out were observed in three patients (8.8%). One of these patients was a 9-year-old girl who received an intravenous bolus injection at 0.15 mg/kg. She developed a fever 30 min after the injection, and blood tests performed on the following day revealed an elevated aspartate aminotransferase level. The fever subsided within 2.5 h and required no particular treatment, and the aspartate aminotransferase level returned to normal in 6 weeks. A 6-month-old boy developed a rash 20.5 h after two intravenous bolus doses at 0.15 mg/kg. Because he had been receiving oral treatment with carbamazepine, the drug was discontinued, and resolution of the event was confirmed 6 days later. In the remaining patient, a 2.5-year-old boy, respiratory depression occurred after the initial intravenous bolus dose at 0.15 mg/kg. He recovered within 23 min with oxygen therapy and bag-valve-mask ventilation. At the occurrence of the event, the bolus injection rate of MDL was 4.2 mg/min, which was faster than the specified rate. Thereafter, an additional dose of MDL at 0.15 mg/kg was given at a rate of 2.1 mg/min, and no respiratory depression occurred. This patient had been receiving oral treatment with clonazepam and valproate for the treatment of epilepsy. These three patients did not receive continuous intravenous MDL infusion and the AEs were judged as "possibly related" to the study drug.

3.4. Pharmacokinetics

Data on the pharmacokinetic endpoint were obtained in 25 patients (of 36 patients who initially received the study drug, 2 patients were excluded for Good Clinical Practice or protocol violations, and 9 patients failed to undergo blood collection). Of 16 patients receiving bolus iv only, 14 patients had measurements (except for data below the lower limit of quantification). In addition, additional data during the bolus iv

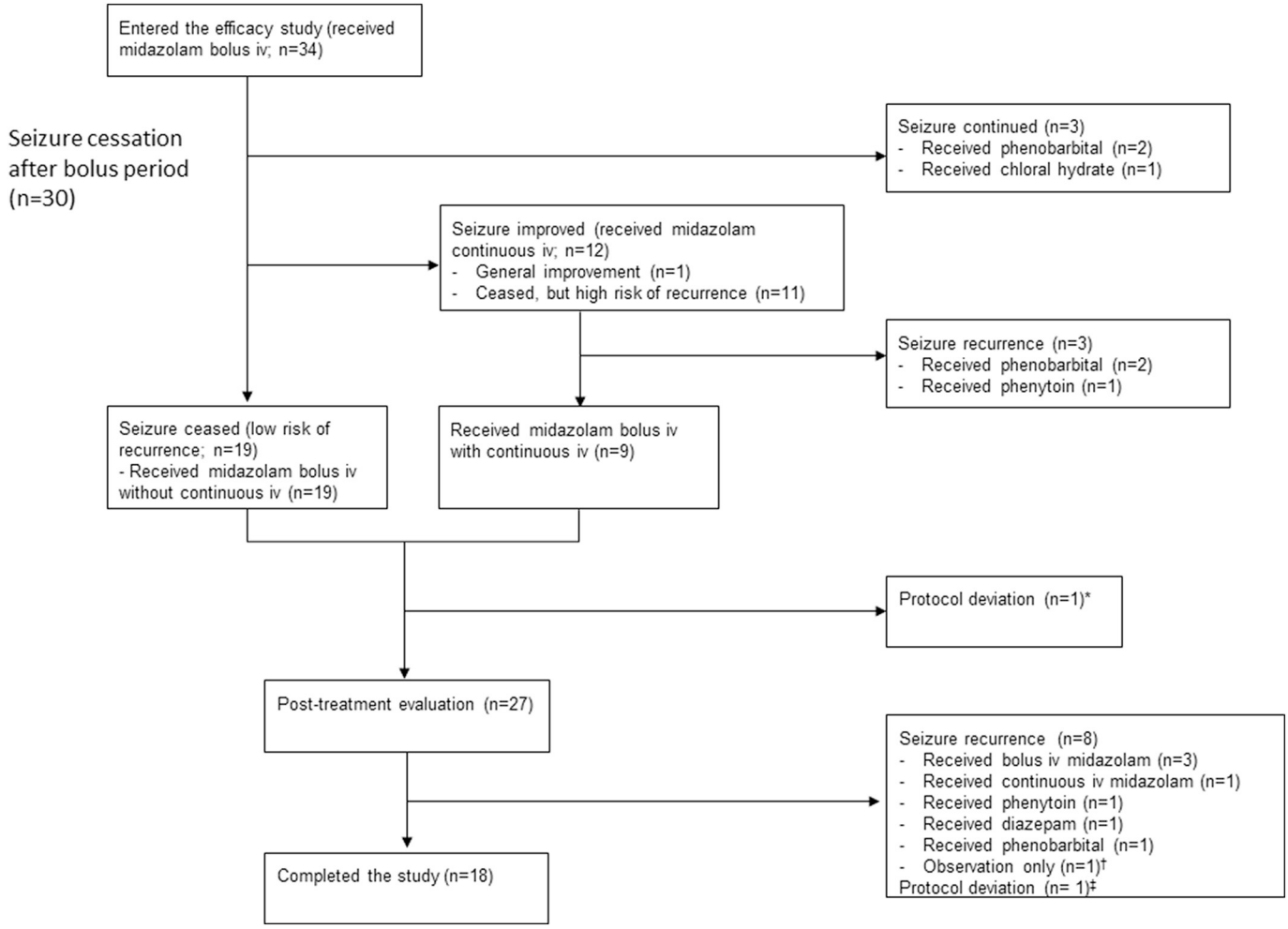

Fig. 2. Patient disposition. Abbreviation: iv, intravenous injection. *A midazolam preparation differing from the designated preparation was used during continuous iv. †Seizure recurred but disappeared within several minutes without any treatment. ‡The patient was administered a diazepam suppository for the prophylaxis of febrile seizure associated with transient pyrexia during the post-treatment observation.

period were obtained from eight patients in whom Civ was initiated and blood sampling was performed before initiation of Civ. Thus, data from the above 22 patients were plotted to show changes in plasma MDL concentrations (Fig. 3). In the 22 patients, samples were obtained from 19 patients after a single intravenous bolus dose of MDL (dose: 0.144–0.155 mg/kg), from 2 patients after two doses and from 1 patient after three doses. All the patients receiving multiple intravenous bolus doses received the initial dose at 0.150 mg/kg, but their cumulative doses were 0.25 mg/kg, 0.30 mg/kg, and 0.60 mg/kg. Therefore, the data in Fig. 3 were normalized for the dose of 0.15 mg/kg. The plasma MDL concentration 30 min after intravenous bolus treatment was 122.6 ± 249.5 ng/mL, and thereafter MDL was eliminated rapidly. The $t_{1/2}$ in 7 patients receiving only intravenous bolus treatment in whom measurements were obtained for at least two time points was 0.999 ± 0.241 h (Table 4).

Among the patients who received a continuous infusion, data on plasma MDL concentrations at 12 h and around 24 h after initiation of the infusion were available from seven patients who underwent blood sampling. These data are shown in Fig. 4, after normalization for the 0.10 mg/kg/h dose. The dose at the time of blood sampling ranged between 0.10 and 0.16 mg/kg/h in six patients and 0.40 mg/kg/h in one patient. No significant change was observed in plasma MDL concentrations from 12 h to 24 h after the initiation of continuous infusion. This suggests that the plasma MDL concentration had reached a steady state within 12 h after initiation of continuous infusion. The CL_{tot} was 864 ± 584 mL/h/kg, but it varied greatly among individuals, showing

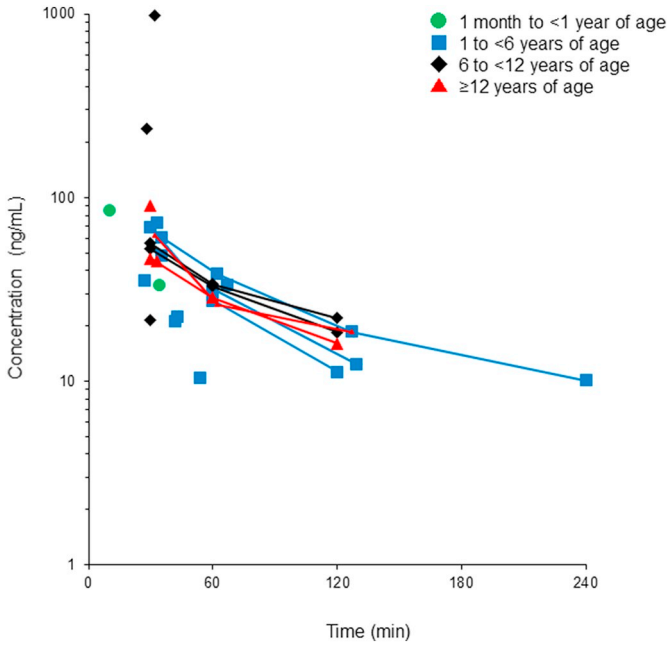

Fig. 3. Changes in plasma midazolam concentrations after intravenous bolus injection by age group (data were normalized for the dose of 0.15 mg/kg).

Table 4
Midazolam half-life ($t_{1/2}$) after bolus iv period.

Age group	$t_{1/2}$ (h)
1 month to < 1 year (n = 0)	–
1 to < 6 years (n = 3)	0.938 ± 0.395
6 to < 12 years (n = 2)	1.09 (1.02, 1.16)
≥12 years (n = 2)	1.00 (1.00, 1.00)
Total (n = 7)	0.999 ± 0.241

For n = 2, mean (min, max) values are shown.
For n ≥ 3, mean ± SD are shown.

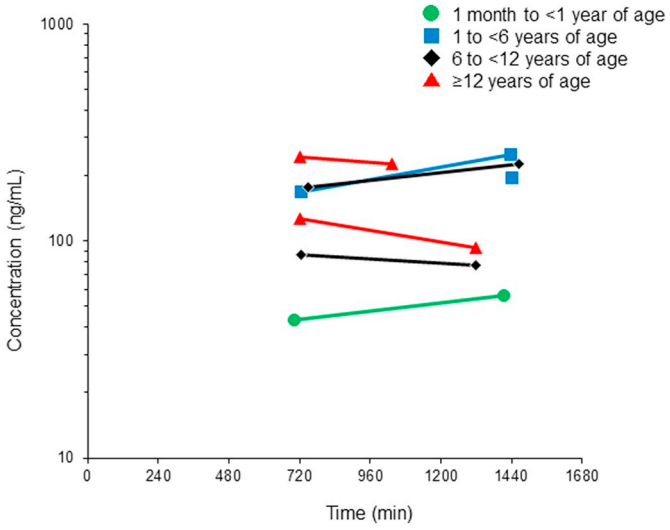

Fig. 4. Changes in plasma midazolam concentrations during continuous intravenous infusion by age group (data were normalized for the dose of 0.10 mg/kg/h).

a high value (2010 mL/h/kg) in an infant at 10 months of age. In other age groups, the CL_{tot} ranged from 423 to 1220 mL/h/kg (Table 5).

4. Discussion

When MDL was administered to 34 children aged 6 months to 13 years who were experiencing convulsive seizures for 5 min or longer, seizure cessation was achieved in 30 patients (88.2%) by intravenous bolus injection, and AEs were observed only in 3 patients. Previous studies that have reported MDL dosing regimens are highly diverse, particularly in terms of the initial bolus dose, the upper dose limit for repeated bolus administration, switching to continuous infusion, and the upper dose limit of continuous infusion [27]. Thus, the optimal dosing regimen and dose escalation method have not been established for MDL. Here, we have identified that there are patients in whom an intravenous bolus dose of MDL alone can suppress seizures, and we believe that this finding has great clinical significance. Thus, the efficacy and safety of MDL were demonstrated, and these results contribute to the establishment of an MDL dosing regimen.

Table 5
Total body clearance during continuous intravenous midazolam infusion.

Age group	mL/h/kg
1 month to < 1 year (n = 1)	2010
1 to < 6 years (n = 2)	494 (478, 510)
6 to < 12 years (n = 2)	858 (496, 1220)
≥12 years (n = 2)	668 (423, 912)
Total (n = 7)	864 ± 584

For n = 1, individual value is shown.
For n = 2, mean (min, max) values are shown.
For n = 7, mean ± SD are shown.

Most studies of MDL conducted thus far in children with status epilepticus have also reported a high response rate (≥80%) (Table 6). Although the majority of these are retrospective studies, prospective studies [28–30] also reported comparable response rates (71–90.8%). A recent meta-analysis has also reported that, among three benzodiazepine derivatives (lorazepam, diazepam, and MDL) to be listed as first-line treatment for status epilepticus, MDL has the highest efficacy in terms of seizure suppression [31]. However, as shown in Table 6, the dose of MDL varies greatly across the studies, either for intravenous bolus injection or for continuous intravenous infusion. In this study, important points on the cumulative dose for intravenous bolus injection have been clarified. Of the 30 patients who responded to intravenous bolus MDL, 28 patients (93%) achieved seizure cessation even at a cumulative MDL dose of ≤0.3 mg/kg (Table 3). Papavasiliou et al. [29] also reported that, of all 69 responders to MDL who had been administered repeatedly up to five times at dose increments of 0.1 mg/kg, the cumulative dose was ≤0.3 mg/kg in 68 patients (99%). These findings suggest that, to enable intravenous bolus MDL to fully exert its effect, a dose of 0.1–0.15 mg/kg up to a total of 0.3 mg/kg can be used. In addition, for patients whose seizures did not cease with a cumulative bolus dose of 0.3 mg/kg, prompt switching to a continuous intravenous infusion of MDL or switching to other drugs should be considered. When administering an intravenous midazolam bolus to treat status epilepticus, it is necessary to restrict the maximum dose to 0.3 mg/kg in an environment where intensive care management is unavailable (i.e., outside of a pediatric intensive care unit). This restriction applies to patients prone to respiratory depression due to complications or contraindications, and in benzodiazepine-resistant patients in whom non-benzodiazepine therapy should not be delayed. However, in an environment that provides highly specialized medical care (even in the event of respiratory depression), no serious AEs have been reported with a higher dose of intravenous bolus and continuous intravenous infusion. Therefore, a high-dose intravenous bolus is supported by the literature [32].

In addition, in all the studies reporting the seizure cessation rate of ≤50% by intravenous bolus MDL, the dose was 0.1 mg/kg or 0.15 mg/kg, without repeated intravenous bolus injections or without initiation of a continuous intravenous infusion [33,34]. In the present study, the initial intravenous bolus dose was set at 0.15 mg/kg, and repeated injections up to the maximum cumulative dose of 0.6 mg/kg, and if necessary, initiation of a continuous intravenous infusion, were allowed. Previous studies have reported high response rates of ≥70% achieved by repeated intravenous bolus injections or by a subsequent continuous intravenous infusion.

In a previous study conducted in patients with epilepsy only, the response rate to intravenous MDL bolus injection, without continuous intravenous infusion, was 90.8% [29]. In the present study, patients with epilepsy accounted for 88.2% of all the patients, and the use of continuous intravenous infusion, which was left to the discretion of attending physicians, was limited to 12 of 34 patients. Hayashi et al. examined 358 patients and reported that in early status epilepticus where seizures last < 30 min, the response rate was 90% in epileptic patients but was 59% in acute symptomatic patients. They suggested that the efficacy of MDL varied depending on the etiology [17]. This may indicate that continuous intravenous MDL infusion might not be necessary for early status epilepticus in epileptic patients. It should be noted that there was a relatively high proportion of patients with epilepsy in our study, which may have influenced the overall response rate.

Buccal midazolam bolus therapy is widely used in the EU and is a safe and effective treatment that allows immediate intervention at home. However, in Japan, buccal midazolam bolus therapy is not currently available because it has not been approved. In patients with status epilepticus, the risk of becoming refractory to treatment increases

Table 6
Clinical reports to date on intravenous MDL therapy in children with status epilepticus.

Author (ref)	Study design	Number of patients	MDL bolus iv dose (mg/kg)	MDL Civ dose (mg/kg/h)	Seizure cessation rate	Adverse events (%, *n*)
Kumar A, et al. [41]	Retrospective	3	0.18 ± 0.18 (0.02–0.38)	0.2 ± 0.17 (0.06–0.39)	100%	Hypotension (33%, 1)
Rivera R, et al. [42]	Prospective observational	24	0.15	0.14 (0.06–1.08)	100%	Pharyngeal secretion increase (13%, 3)
Parent JM, et al. [43]	Retrospective	1 (2 adults)	0.18	0.66	100%	Hypotension (50%, 1 adult)
Koul RL, et al. [44]	Retrospective	20	0.15	0.12 ± 0.07 (0.06–0.30)	95%	SpO_2 decreases (10%, 2)
Minagawa K, et al. [12]	Retrospective	16[a]	0.15	0.22 (0.1 − 0.3)	85.4%	No adverse events
Igartua J, et al.[b] [45]	Retrospective	8	0.15	0.84 ± 0.36 (0.24–1.44)	87.5%	No cardiocirculatory adverse events (All patients under artificial respiration management)
Yoshikawa H, et al. [13]	Retrospective	27[c]	0.16 (0.06 − 0.6)	0.16 (0.06–0.6)	89.5%	N.D.
Singhi S, et al. [27]	Open-label RCT (vs DZP)	21	0.2	0.32 ± 0.16 (0.12–0.6)	85.7%	Hypotension (38%, 8) Respiratory depression (19%, 4)
Hamano S, et al. [15]	Retrospective	45[d]	0.35 ± 0.22 (0.15 − 0.90)	0.30 ± 0.17 (0.06–0.72)	73.6%	SpO_2 decreases (11%, 5) Agitation in withdrawing (2%, 1)
Ozdemir D, et al. [46]	Retrospective	27	0.2	0.19	96.3%	No significant adverse events
Brevoord JCD, et al.[b] [33]	Retrospective	122	0.1	0.24 (0.05–0.8) (following PHT iv)	48% (iv only) 89% (including PHT iv and MDL civ)	N.D.
Morrison G, et al. [5]	Retrospective	17	0.5	0.73 ± 0.66	76% (≤30 min) 88% finally	No significant adverse events
Hayashi K, et al. [17]	Retrospective	358	0.25 ± 0.21 (0.03–1.15)	0.26 ± 0.25 (0.04–1.2)	64.5%	Respiratory depression (8%, 29) Cardiovascular depression (0.5%, 2)
Fallah R, et al. [34]	Open-label RCT (vs LDC)	10	0.15	0.06–0.36	50%	N.D.
Papavasiliou AS, et al. [29]	Prospective observational	76	0.17 ± 0.09 (0.1–0.5)	not applied	90.8%	Respiratory depression (13%, 10)
Tasker RC, et al. [30]	Prospective observational	42	0.11 (0.09–0.22)	0.10 (0.06–0.5) in responders	71%	Requirement of vasoactive drug (29%, 12)
Current study	Open-label prospective	34	0.23 ± 0.15 (0.1–0.6)	0.19 ± 0.13[e] (0.1–0.4)	88.2% (bolus iv only)	Serum AST increase (3%, 1) Rash (3%, 1) Respiratory depression (3%, 1)

Abbreviations: AST, aspartate aminotransferase; civ, continuous intravenous injection; DZP, diazepam; IQR, interquartile range; iv, intravenous injection; LDC, lidocaine; MDL, midazolam; N.D., not described; PHT, phenytoin; RCT, randomized control trial; SE, status epilepticus; SpO_2, oxygen saturation.
Dose and duration shows average ± SD and (ranges).
[a] 48 episodes of status epilepticus in 16 patients were included.
[b] Includes patients who received rectal MDL.
[c] 38 episodes of status epilepticus in 27 patients were included.
[d] 62 episodes of status epilepticus in 45 patients were included.
[e] 12 patients were administered MDL civ, but one patient was excluded from these data because the wrong MDL preparation was used.

over time because of the internalization of GABA receptors. Early suppression of seizures is clinically important to reduce brain damage from status epilepticus; therefore, we eagerly await approval of buccal midazolam bolus in Japan.

In the present study, AEs occurred in three patients (8.8%). Of these patients, one experienced fever and elevated aspartate aminotransferase levels, and another developed a rash. Based on the time of occurrence and clinical course of these AEs, it appears unlikely that these events were caused by MDL, although we were unable to rule out this possibility entirely. The remaining patient developed respiratory depression. In previous studies, the incidence of respiratory depression was 8–10% (Table 6). Therefore, respiratory depression is one of the most noteworthy AEs attributable to intravenous MDL therapy, in addition to hypotension. Of the drugs used for the treatment of status epilepticus, benzodiazepine derivatives have a higher risk of respiratory depression than lidocaine and valproic acid. Of benzodiazepine derivatives, lorazepam and MDL are regarded to have less risk of respiratory depression than diazepam [31]. In this study, the patient who developed respiratory depression was a 2.5-year-old boy who had been receiving oral treatment with clonazepam and valproate. In this case, respiratory depression occurred at the time of the initial intravenous bolus injection. He recovered within 23 min with oxygen therapy and bag-valve-mask ventilation. The bolus injection rate of MDL was 4.2 mg/min, which was faster than the specified rate. Thereafter, an additional dose of MDL at the same dose was given at a slower rate, and no respiratory depression occurred. In this study, the injection rate of intravenous bolus MDL was specified as 1 mg/min. In many studies conducted so far, no injection rate was specified, and many patients developed respiratory depression. As shown in Table 6, the incidence of cardiorespiratory AEs, such as respiratory depression, was lower than in other studies. This may have been attributable to the intravenous bolus MDL being given at a slower injection rate. This assumption is supported by the finding that no respiratory depression occurred when the MDL injection was repeated again at a slower injection rate in the patient who developed respiratory depression in this study. Thus, it is important to set the injection rate at around 1 mg/min to minimize the development of respiratory depression with the use of MDL.

In this study, no circulatory AEs, such as hypotension, were observed. Further, in a larger study conducted by Papavasiliou et al. [29] in patients with epilepsy only, no circulatory AEs were observed. In studies by Singhi et al. [28] and Tasker et al. [30], which reported a high incidence of circulatory AEs as shown in Table 6, more than half of

the study patients had acute symptomatic causes, such as meningoencephalitis. Circulatory AEs, such as hypotension, may be largely associated with the etiology of status epilepticus. For patients with acute symptomatic etiology, it is desirable to manage them in the intensive care unit, in preparation for situations where supportive therapy for circulatory dynamics or respiratory depression are required, as well as for treatment of status epilepticus, in consideration of the risk of a high incidence of circulatory AEs.

The incidence of AEs and serious AEs in the present study was lower than what has been previously reported. This may be attributable to MDL being delivered as an intravenous bolus or that a lower maximum dose (0.4 mg/kg/h or 6.7 μg/kg/min) was used when providing a continuous intravenous infusion in our study. Prior studies have also used MDL in the same manner for the indication of general anesthesia when treating refractory status epilepticus. In this study, patients were not characterized as having refractory status epilepticus but instead were characterized with either status epilepticus or with impending status epilepticus. Taken together, this may be why MDL was efficacious at relatively lower doses and why the incidence of AEs, especially serious AEs, was also lower. The study by Papavasiliou et al., which was similarly conducted in patients with impending status epilepticus rather than patients with refractory status epilepticus, showed a similar response rate as that observed in our study [29]. Additionally, the incidence of serious AEs was also similar to our observations. We have therefore shown that MDL can be administered as a standalone intravenous bolus for early or impending status epilepticus, which allows patients to recover safely and rapidly from seizures.

Although the sample size was small and represents a limitation of our study, the elimination $t_{1/2}$ of MDL in children in this study was 0.999 ± 0.241 h. This result was comparable with the values reported in previous studies [35,36]. The total body clearance was 864 ± 584 mL/h/kg in 7 patients who underwent blood sampling after initiation of the continuous intravenous infusion, and varied markedly among individuals. Also, a study reported by Minagawa et al. showed a marked inter-individual variability (22–657 mL/h/kg) [36]. A review article by Blumer et al. reported similar findings and did not identify any clear trend associated with childhood age groups [35]. In this study, the total body clearance was significantly higher (2010 mL/h/kg) in a 10-month infant than in other age groups. In general, the clearance tends to be lower in adulthood because of various comorbidities [35]. However, the activity of CYP3A4, a metabolic enzyme of MDL, is extremely low during the fetal period, increases after birth, and reaches the level observed in adults at around 1 year of age. From this point of view, it is predicted that infants have a longer elimination $t_{1/2}$ of MDL, and therefore a lower clearance, than adults do. The result obtained from this study showed a surprisingly high level. Because this is a result obtained from only one patient, further investigation is warranted. Importantly, the pharmacokinetics of MDL may vary greatly among individuals, especially during infancy, because the pharmacokinetics of MDL during infancy are greatly affected by CYP3A4 activity, the extent of the development of the renal excretory system, and the general condition of the patient. For continuous intravenous MDL infusion in infants, it may be necessary to continuously assess its efficacy through blood concentration monitoring or continuous electroencephalographic monitoring.

It has been reported that continuation of intravenous MDL infusion for several days or a longer period increases resistance and also causes tachyphylaxis and prolongation of $t_{1/2}$ [37]. In consideration of these points, it is important to set the maximum dose of 0.4 mg/kg/h for the dose increase during the continuous intravenous MDL infusion and to reduce the dose and discontinue the drug during a 24-h period from the last seizure, as specified in our protocol. In addition, as described above, if seizure suppression is achieved by intravenous bolus in status epilepticus in patients with underlying epilepsy, non-administration of continuous intravenous infusion therapy should also be considered. A drawback of continuous intravenous MDL infusion is that the therapy makes it difficult to assess the level of consciousness in patients with acute symptomatic causes, such as acute encephalopathy. Furthermore, occurrence of breakthrough seizures is not rare during continuous intravenous MDL infusion [5,38,39]. This is also reported as a disadvantage in the treatment of status epilepticus in patients with an acute symptomatic etiology. Infantile status epilepticus occurs mostly by acute symptomatic causes, such as acute encephalitis or encephalopathy. As described above, pharmacokinetic profiles vary greatly among individuals. Therefore, it is desirable that continuous intravenous MDL infusion is performed in an intensive care environment or in an environment where its efficacy can be continuously evaluated through electroencephalographic monitoring [40].

Conflicts of interest

Shin-ichiro Hamano has received a grant from the Ministry of Health, Labour and Welfare of Japan and research funding from Alfresa Pharma Corporation. Kenji Sugai and Makiko Osawa have received a grant from the Ministry of Health, Labour and Welfare of Japan and research funding from Alfresa Pharma Corporation. Masuo Miki, Toshiyuki Tabata, and Takako Fukuyama are employees of Alfresa Pharma Corporation.

Funding source

This study was funded by Alfresa Pharma Corporation, Japan.

Acknowledgements

The authors would like to thank William Ng, PhD, and Mary Richardson, MSc, of Edanz Medical Writing for editorial support, which was funded by Alfresa Pharma Corporation, Japan.

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