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Optimising the oral midazolam dose for premedication in people with intellectual disabilities and/or autism spectrum disorder

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Abstract

Background: In people with intellectual disabilities and/or autism spectrum disorder, oral midazolam (OM) is very effective as premedication for facilitating medical treatment. In this retrospective study, we investigated the optimal dosage of OM for premedication.

Methods: Patients with intellectual disability and/or autism spectrum disorder who were given OM as a premedication were selected from anaesthesia records. The primary outcome variable was the dose of OM (mg/kg) required to produce an adequate sedation.

Results: The mean OM dose required was 0.32 ± 0.10 mg/kg. The required OM dose decreased significantly as age and weight increased, and age and weight were also shown to be significantly associated with the dose of OM in the multivariate linear regression analysis.

Conclusion: The dosage of OM to achieve adequate sedation should decrease as the patient ages. Furthermore, adequate sedation can be achieved with even lower doses of OM in obese people.

KEYWORDS
autism spectrum disorder, intellectual disabilities, oral midazolam, premedication, sedation

1 | INTRODUCTION

People with intellectual disabilities and/or autism spectrum disorder have the same need for invasive medical procedures as people without disabilities, but they are often unable to accept the necessity of such procedures because they do not understand the need for a procedure or are extremely fearful of it. In such cases, general anaesthesia or sedation is employed to ensure their safety. However, they sometimes refuse anaesthesia management, and difficulties often arise during the administration of anaesthesia. In such cases, premedication with oral midazolam is very effective at providing adequate sedation to allow the induction of anaesthesia (Hanamoto et al., 2016, 2023; Maeda et al., 2012).

Many studies have already reported on the use of oral midazolam for sedation in children, and the optimal dosage is generally considered to be 0.5 mg/kg in such cases (Manso et al., 2019). However, the pharmacokinetics of the drug differ between children and adults, as does its optimal dosage. In addition, the patient's weight, the type of disorder they have, and any medicine they are taking regularly may affect the optimal dose of oral midazolam. However, no previous

studies have evaluated the optimal dosage of oral midazolam for people, especially adults, with intellectual disabilities and/or autism spectrum disorder, and determining the optimal dosage in clinical practice remains a challenge.

The purpose of this study was to determine the optimal dose of oral midazolam that produces adequate sedation during the premedication of people with intellectual disabilities and/or autism spectrum disorder, and to evaluate the factors that influence it. This is the first study of the optimal dosage of oral midazolam for premedication in people with intellectual disabilities and/or autism spectrum disorder.

2 | METHODS

2.1 | Study sample

We designed and performed this retrospective cohort study, which was approved by the ethics committee of the Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences and Okayama University Hospital (approval number: 1805-008, date of approval: May 25th, 2018). The need to obtain written informed consent for this study was waived in accordance with the Japanese Government's Ethical Guidelines for Life Science and Medical Research involving Humans because this was a retrospective study. We also did not register this study in a publicly accessible database for the same reason.

Dental patients with intellectual disabilities and/or autism spectrum disorder who underwent dental treatment under general anaesthesia or intravenous sedation at the Center of Special Needs Dentistry, Okayama University Hospital, between August 2017 and November 2022 because they had difficulty fully following the treating dentist's instructions, making it difficult to provide adequate dental care, were eligible for inclusion in this study. All of the subjects had previously been diagnosed with intellectual disabilities and/or autism spectrum disorder by medical doctors when they came to our centre, and we recorded these diagnoses during medical interviews. When general anaesthesia or intravenous sedation was used for dental treatment, the details were explained, and written consent was obtained from the dental patient's legal guardians. The inclusion criteria of this study were having an American Society of Anesthesiologists (ASA) physical status of 1 or 2 and requiring premedication with oral midazolam because of difficulty following instructions for anaesthesia induction. All perioperative anaesthesiologic data were collected from the dental patients' anaesthesia or medical records. Cases in which accurate data could not be collected from these sources were excluded. The dental treatment often involved multiple treatments, and multiple episodes of anaesthetic management over a short period of time were required in some cases. Therefore, the following approach was adopted for dental patients who underwent anaesthesia management more than once during the study period: When two anaesthesia management procedures were performed less than 1 year apart, the second procedure was excluded as a similar case, whereas when two anaesthesia management procedures were performed more than 1 year apart the second procedure was included in the study as a new case.

2.2 | Administration of oral midazolam for premedication

All patients fasted (food: 6 h; drink: 2 h) before the anaesthesia management, based on the relevant guidelines (The American Society of Anesthesiologists Task Force, 2017; Working Group on Guidelines Development for Intravenous Sedation in Dentistry, 2018). We instructed them to continue taking their regular medications, with a few exceptions, such as antidiabetic agents.

Midazolam injections (10 mg/2 mL) were used for premedication. The dose was decided by the dental anaesthesiologist in charge, depending on the dental patient's situation and/or background. Midazolam was mixed with the dental patient's favourite drink (10∼20 mL), and the dental patient was encouraged to drink it in the preoperative waiting room. The dental patient was kept in the preoperative waiting room until the oral midazolam had started to take effect and was encouraged to enter the dental treatment room when the dental anaesthesiologist determined from their sedation level that they were able to start anaesthesia induction. Upon the entry of the dental patient into the dental treatment room, we routinely evaluated their sedation level using the sedation scoring system developed by Yuen et al. (Sheta et al., 2014; Yuen et al., 2010) (1: Alert and awake; 2: Drowsy, sleepy, and lethargic; 3: Asleep but responds only to mild prodding or shaking; 4: Asleep and does not respond to mild prodding or shaking).

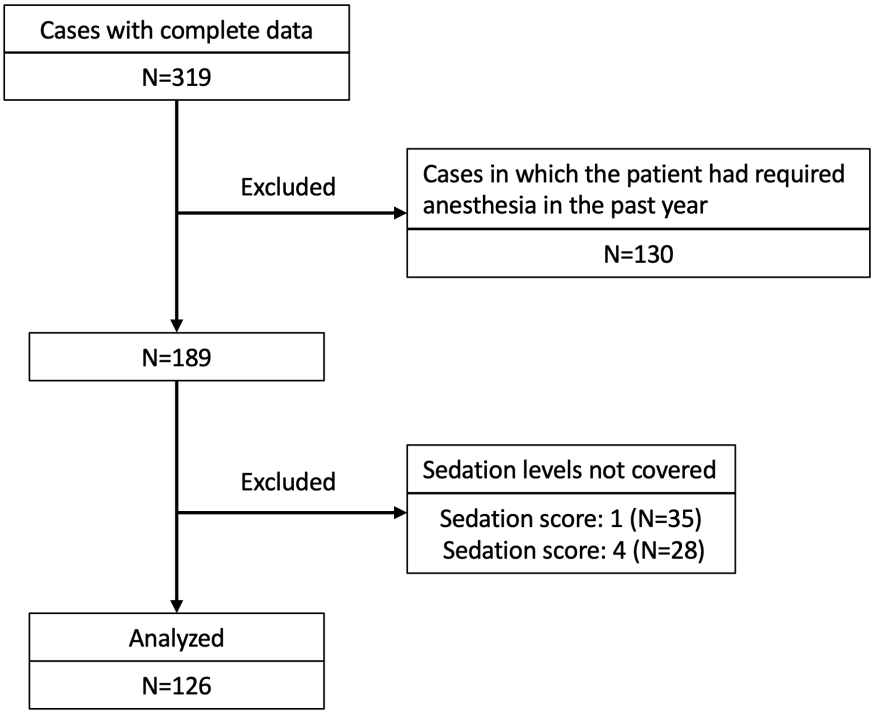
After the dental patient entered the dental treatment room, the scheduled anaesthetic management (general anaesthesia or intravenous sedation) was started via intravenous catheter insertion or sevoflurane inhalation if intravenous catheter insertion was impossible, depending on the dental patient's responses. All dental treatments were performed under anaesthetic management.

2.3 | Data collection methods

Perioperative anaesthesiologic data were collected from anaesthesia records. For this study, we judged that a sedation score of 1 indicated a light sedation level, sedation scores of 2 or 3 indicated an effective sedation level, and a sedation score of 4 indicated a deep sedation level, and dental patients with sedation scores of 2 or 3 were selected for this study as cases in which adequate sedation was achieved.

The primary outcome variable of this study was the dose per kg of body weight of oral midazolam required to achieve a sedation score of 2 or 3. The primary predictor variables were (1) sex; (2) age; (3) weight; (4) body mass index (BMI); (5) the type of disorder the dental patient had; (6) whether the dental patient was regularly taking antiepileptic and/or psychotropic medication; (7) the number of central nervous system (CNS)-acting drugs, such as antiepileptic and/or psychotropic medication, regularly being taken by the dental patient;

FIGURE 1 Participant selection flowchart.



and (8) whether the dental patient was regularly taking carbamazepine (CBZ) and/or phenytoin (PHT). We tested the relationships between the primary outcome variable and each primary predictor variable.

2.4 | Data analysis

To confirm the optimal midazolam dosage for such cases, midazolam dosages were compared for each primary predictor variable using the *t*-test or one-way analysis of variance. In addition, multivariate linear regression was used to control for potential confounding variables and to determine independent predictors of the required dose per kg of body weight of oral midazolam. Five factors (sex (Buchanan et al., 2009; Chen et al., 2006), age (Albrecht et al., 1999), weight (Brill et al., 2014), whether the dental patient was regularly taking CNS-acting drugs (Kodama et al., 2020), and whether the dental patient was regularly taking CBZ and/or PHT (Backman et al., 1996; Hayashi et al., 2016)), which were considered to potentially affect the oral midazolam dosage, were included as potential predictors. All analyses were performed with the statistical software GraphPad PRISM® version 8 (GraphPad Software, Inc., CA, USA) or JMP 9.0.0 (SAS Institute Inc., Cary, NC). *P*-values of <0.05 were regarded as significant.

3 | RESULTS

Figure 1 shows a flow diagram of the participant enrolment process for this study. We were able to collect complete data for 319 cases in which oral midazolam was used for premedication. Of the 319 cases, 130 were excluded because the same dental patient had required anaesthesia within the past year. Of the remaining cases, 35 and 28 were found to have a sedation score of 1 and 4, respectively, and were excluded. Finally, 126 cases were analysed in this study.

The demographic characteristics of the eligible cases are presented in Table 1. The mean oral midazolam dose per kg of body weight required to produce a sedation score of 2 or 3 was 0.32 ± 0.10 mg/kg, and the mean time from premedication to the start of anaesthesia was 30.0 ± 5.7 min. In all cases, anaesthesia management and dental treatment were able to be implemented.

Table 2 shows the differences in the midazolam dose (mg/kg) within each category. For age, body weight, and BMI (adults; 15 years and older only), the required midazolam dose decreased significantly as age, weight, and BMI increased. Significantly, more midazolam was needed in people without intellectual disabilities and in people with autism spectrum disorder. In addition, the required midazolam doses were significantly lower in those that were regularly taking CNS-acting drugs. However, the number of CNS-acting drugs being taken by the dental patient did not affect the midazolam dose, and CBZ and PHT, which are known to affect midazolam metabolism, also had no effect on the dose of midazolam required.

A multivariate linear regression model was constructed with the midazolam dose as the dependent variable and the following predictors as independent variables: sex, age, weight, regularly taking CNS-acting drugs, and regularly taking CBZ and/or PHT. The estimated coefficient, standard error, and *P*-values for these variables are presented in Table 3. In the multivariate regression analysis, age and weight were shown to be significantly associated with the midazolam dose. This indicates that less oral midazolam was required to achieve an effective sedation level in older and heavier patients.

TABLE 1 Demographic, clinical, and anaesthetic characteristics of the eligible cases.

Sex (male/female) (*n*)	81 (64.3) / 45 (35.7)[a]
Age	24.0 (13.2) [5–55][b]
<15 (*n*)	31 (24.6)[a]
≥15 (*n*)	95 (75.4)[a]
Height (cm)	151.6 (19.0) [102–184][b]
Body weight (kg)	55.1 (22.0) [16.7–122][b]
BMI	23.0 (6.3) [13.0–42.7][b]
Intellectual disability (*n*)	113 (89.7)[a]
Autism spectrum disorder (*n*)	84 (66.7)[a]
Cerebral palsy (*n*)	5 (4.0)[a]
Epilepsy (*n*)	42 (33.3)[a]
Down syndrome (*n*)	8 (6.3)[a]
Medication (Yes/No) (*n*)	83 (65.9) / 43 (34.1)[a]
No. of medications (*n*)	
0	43 (34.1)[a]
1–3	56 (44.4)[a]
≥4	27 (21.4)[a]
CBZ or PHT (*n*)	20 (15.9%)[a]
Midazolam dose (mg)	16.1 (5.5) [5–30][b]
Midazolam dose per kg of body weight (mg/kg)	0.32 (0.10) [0.14–0.71][b]
Time to the start of anaesthesia (min)	30.0 (5.7) [17–44][b]
Sedation score (2/3) (*n*)	87 (69.0) / 39 (31.0)[a]

Abbreviations: BMI, body mass index; CBZ, carbamazepine; PHT, phenytoin.
[a]*n* (%).
[b]Mean (SD) [range].

TABLE 2 The differences in the midazolam dose per kg of body weight within various categories.

	Midazolam dose per kg of body weight (mg/kg)	*P*-value
Sex (male / female)	0.32 (0.10) / 0.32 (0.11)	$P = 0.96$[a]
Age		
≤9	0.42 (0.10)	<0.0001[b]
10–19	0.32 (0.07)	
20–29	0.31 (0.11)	
30–39	0.27 (0.07)	
≥40	0.25 (0.07)	
Body weight (kg)		
≤19	0.46 (0.11)	<0.0001[b]
20–29	0.41 (0.10)	
30–49	0.36 (0.11)	
50–69	0.29 (0.08)	
70–89	0.25 (0.05)	
≥90	0.23 (0.05)	
BMI (15 years and older only)		
≤19	0.36 (0.12)	<0.0001[b]
20–24	0.29 (0.08)	
25–29	0.27 (0.06)	
≥30	0.23 (0.05)	
Intellectual disability (yes/no)	0.31 (0.10) / 0.40 (0.09)	$P = 0.0015$[a]
Autism spectrum disorder (yes/no)	0.33 (0.11) / 0.29 (0.08)	$P = 0.0175$[a]
Cerebral palsy (yes/no)	0.30 (0.12) / 0.32 (0.10)	$P = 0.722$[a]
Epilepsy (yes/no)	0.29 (0.10) / 0.33 (0.10)	$P = 0.071$[a]
Down syndrome (yes/no)	0.26 (0.08) / 0.32 (0.10)	$P = 0.131$[a]
Medication (yes/no)	0.30 (0.09) / 0.35 (0.11)	$P = 0.0153$[a]
No. of medications		
0	0.35 (0.11)	$P = 0.0528$[b]
1–3	0.30 (0.10)	
≥4	0.30 (0.08)	
CBZ or PHT (yes/no)	0.30 (0.13) / 0.32 (0.10)	$P = 0.465$[a]

Note: Data are shown as mean (SD) values.
Abbreviations: BMI, body mass index; CBZ, carbamazepine; PHT, phenytoin.
[a]According to *T*-test analysis.
[b]According to one-way analysis.

4 | DISCUSSION

This retrospective study showed that the mean dosage of oral midazolam required for premedication in people with intellectual disabilities and/or autism spectrum disorder who had difficulty following instructions for anaesthesia induction was 0.32 ± 0.10 mg/kg, and the required dose was lower in older and heavier people.

Sedation with oral midazolam for premedication or a medical procedure is widely used in children, and a dose of 0.5 mg/kg is commonly used in many studies (Manso et al., 2019). In adults, a few randomised trials showed that 7.5 mg oral midazolam was effective as premedication for reducing anxiety and/or improving overall tolerance of medical procedures (Abdul-Latif et al., 2001; Mui et al., 2005; Short & Galletlyt, 1989). However, it was unclear whether these midazolam doses were suitable for people with intellectual disabilities and/or autism spectrum disorder, especially adults, who find it difficult to follow the instructions of healthcare providers during medical interventions. Oral midazolam premedication has been reported to be useful in adult people with intellectual disabilities or autism spectrum disorder, but a paediatric dose (0.3∼0.5 mg/kg) was used in those cases (Hanamoto et al., 2016, 2023). We must consider such dosages carefully because too low a dosage will result in inadequate sedation or difficulties during medical procedures, and too high a dosage may cause complications, such as over sedation or delayed anaesthetic effects.

Oral bioavailability represents the fraction of an orally administered drug that reaches the systemic circulation. It is a very important factor when considering the pharmacokinetics of oral administration,

TABLE 3 Results of the multiple regression analysis of predictors of the required midazolam dose per kg of body weight.

Variable	Estimated coefficient	Standard error	*P*-value
Sex (female)	0.0058141	0.007507	0.4402
Age	−0.002824	0.000656	<0.0001
Weight	−0.002034	0.000376	<0.0001
Medication	0.0045376	0.008118	0.5772
CBZ or PHT	−0.018069	0.010514	0.0883

Abbreviations: CBZ, carbamazepine; PHT, phenytoin.
Note: $R^2 = 0.45$.

and the bioavailability of oral midazolam has previously been reported to be affected by age and weight. In children, the bioavailability of oral midazolam was reported to be 15%–27% (Payne et al., 1989), 36% (Reed et al., 2001), or 20.8% (Brussee et al., 2018). On the other hand, in adults it was reported to be 31%–72% (Heizmann et al., 1983), 41% (Palkama et al., 1999), 31% (Saari et al., 2006), or 56% (Shord et al., 2010). In both paediatric and adult studies, large degrees of variability in bioavailability were seen, but it tends to be lower in children, and this means that higher doses per kg of body weight are required in children than in adults. Moreover, the bioavailability of oral midazolam has been reported to be significantly increased in obese people (Brill et al., 2014), indicating the need for dose reduction in such people. Furthermore, it is known that elderly people are more sensitive to midazolam than young people (Albrecht et al., 1999; Platten et al., 1998), and hence, the requirement for midazolam is reduced in the elderly. These findings indicate that the amount of oral midazolam required decreases as age and weight increase. Our results also support these predictions in terms of the use of oral midazolam for premedication in people with intellectual disabilities and/or autism spectrum disorder.

Drug interactions may also affect the required dose of oral midazolam, especially in people with intellectual disabilities and/or autism spectrum disorder, because many people with intellectual disabilities and/or autism spectrum disorder are regular users of antiepileptic and antipsychotic drugs. In particular, it is known that the typical antiepileptic drugs CBZ and PHT induce the expression of CYP3A, which is responsible for midazolam metabolism (Patsalos et al., 2002). This indicates that CBZ and/or PHT decrease the pharmacological effects of midazolam by promoting its metabolism. Backman et al. reported that the blood concentration of oral midazolam was significantly decreased in people taking CBZ or PHT, and differences were also noted in the sedative and amnesic effects of oral midazolam (Backman et al., 1996). However, in our study regularly taking CBZ and/or PHT did not influence the required dose of oral midazolam. Another factor that may affect the required dose of oral midazolam is sex. Previous studies showed that midazolam is less effective in females than in males (Sun et al., 2008). The reason for this is that females exhibit higher CYP3A activity (Chen et al., 2006), which may accelerate the metabolism of midazolam, and female hormones are also considered to influence the pharmacological effects of midazolam (Buchanan et al., 2009). However, sex did not affect the required oral midazolam dosage in our study. In other words, sex and the regular use of medications such as CBZ and/or PHT may not be major clinical factors affecting the dosage of oral midazolam required in people with intellectual disabilities and/or autism spectrum disorder.

Our study had several limitations. First, this study was a single-centre study conducted at an academic outpatient dental clinic, and the premedication was administered in the waiting room of the outpatient clinic. The environment is one of the most important factors determining whether people with intellectual disabilities and/or autism spectrum disorder accept medical care and its effectiveness. Therefore, the generalizability of our results may be limited, and different facilities and treatment environments may yield different results. Second, since this study was a retrospective cohort study, decisions regarding the dosage of oral midazolam were left to each dental anaesthesiologist, and each dental anaesthesiologist's experience and thoughts may have influenced the dosage. To reduce this bias, we only selected cases with a sedation level of 2 or 3, which was evaluated using a standard index, for this study. However, the sedation level was estimated by each dental anaesthesiologist and may have been affected by operator bias. The third limitation is the inclusion of some people more than once in the study population, and it is undeniable that previous doses may have been used as a reference in these cases, which may have influenced the statistical analysis. For this reason, we excluded patients who had undergone anaesthesia management within the past year, but it is not clear whether this affected our results. Another limitation is that this was a retrospective cohort study, and the sample size was not large. In fact, we were concerned that there may have been sample bias due to the large proportion of people with intellectual disabilities and small proportion of people who only had autism spectrum disorder. This means that our sample may not reflect the target population as a whole and that selection bias and unexamined confounding factors, such as the level of intellectual disability or autism spectrum disorder, may have increased the error in the estimates. To clarify this, it will be necessary to conduct a prospective interventional study with a large sample size; however, there are ethical issues with studies of people with intellectual disabilities because it is difficult for them to understand all the details of such studies and to give written consent to participate in them of their own volition. Therefore, a retrospective cohort study is a useful research method for people with intellectual disabilities.

Despite these limitations and the need for caution in interpreting the results, we consider that our study suggests the optimal oral midazolam dosage for premedication for people with intellectual disabilities and/or autism spectrum disorder, and hence, will help to improve the safety and quality of the medical care provided to people with intellectual disabilities and/or autism spectrum disorder.

5 | CONCLUSIONS

This study demonstrated that oral midazolam is very useful for premedication in children and adults with intellectual disabilities and/or

autism spectrum disorder. We examined the dose required in cases in which adequate sedation was achieved and found that the mean required dose was 0.32 ± 0.10 mg/kg, with the required dose decreasing with increasing age and weight. In addition, age and weight were identified as independent factors that affect the required dose of midazolam in such cases. This study suggests the dosage of oral midazolam to achieve adequate sedation should decrease as the patient ages. Furthermore, adequate sedation can be achieved with even lower doses of oral midazolam in obese people. However, because this is a retrospective study and has several limitations, future prospective studies with larger sample sizes and multiple sites are needed to further validate the results of this study.

AUTHOR CONTRIBUTIONS

Hitoshi Higuchi contributed to the conception, design, and data analysis and drafted and critically revised the manuscript. Kota Miyake contributed to data collection and data analysis and drafted the manuscript. Saki Miyake contributed to data collection and drafted the manuscript. Maki Fujimoto contributed to the organisation of data and drafted the manuscript. Yukiko Nishioka contributed to the organisation of data and drafted the manuscript. Shigeru Maeda contributed to critically revised the manuscript. Takuya Miyawaki contributed to the conception, design, data, and interpretation, and critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of the work.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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