Research Article

Abnormal Movements of Japanese Infants following Treatment with Midazolam in a Neonatal Intensive Care Unit: Incidence and Risk Factors

Mitsuru Irikura,¹ Eri Minami,¹ Yoichi Ishitsuka,¹ Akihiko Kawase,²
Yuichi Kondo,² and Tetsumi Irie^{1,3}

¹ Department of Clinical Chemistry and Informatics, Graduate School of Pharmaceutical Sciences, Kumamoto University, 5-1 Oe-honmachi, Kumamoto 862-0973, Japan

² Neonatal Medical Center, Kumamoto City Hospital, 1-1-60 Kotoh, Kumamoto 862-8505, Japan

³ Center for Clinical Pharmaceutical Sciences, Faculty of Pharmaceutical Sciences, Kumamoto University, 5-1 Oe-honmachi, Kumamoto 862-0973, Japan

Correspondence should be addressed to Mitsuru Irikura, ikura@gpo.kumamoto-u.ac.jp

Received 31 January 2012; Accepted 19 February 2012

Academic Editors: H. Y. Lane and T. B. Vree

Copyright © 2012 Mitsuru Irikura et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Background. This study was conducted to investigate the incidence of, and factors associated with, myoclonus-like abnormal movements of Japanese infants following treatment with midazolam in a neonatal intensive care unit (NICU). **Methods.** We retrospectively investigated abnormal movements and associated risk factors in Japanese infants (less than 1 year old) who received continuous intravenous midazolam treatment in the NICU of the Neonatal Medical Center, Kumamoto City Hospital, Japan, between April 2007 and March 2009. **Results.** The study included 94 infants who received 119 sessions of midazolam treatment in total. Nine infants (9.6%) developed abnormal movements attributable to midazolam. These nine patients had a significantly lower gestational age at birth, a significantly lower number of weeks after conception at the start of midazolam treatment, and significantly lower body weight compared with patients free of abnormal movements. Logistic regression analysis revealed neonatal asphyxia as a factor associated with an elevated risk of abnormal movements ($P = 0.03$). **Conclusion.** The incidence of abnormal movements after midazolam treatment was about 9.6% among the Japanese NICU infants. This result suggests that neonatal asphyxia may be involved in the onset of abnormal movements in infants treated with midazolam.

1. Introduction

Infants in a neonatal intensive care unit (NICU) often receive repeated painful and/or stressful manipulations, tests, and treatments [1]. Neonates are sensitive to pain [2, 3], and it has been reported that prolonged exposure to pain or stress can adversely affect the mental and physical development of sick children [4–8]. Therefore, administration of safe and appropriate analgesic and sedative treatments is important for these patients.

Midazolam is a short-acting water-soluble benzodiazepine derivative and is now approved only in adults in Japan as a means of “sedation during mechanical ventilation.”

Meanwhile, this sedative is already used as a nonapproved treatment in neonates and infants [9, 10]. Thus, efforts are being made to expand the indications for midazolam to be administered to children.

An adverse reaction, myoclonus-like abnormal movements, has been reported after midazolam administration in neonates, particularly premature and low-birth-weight infants [11]. Magny et al. [12] reported abnormal movements in six (5.9%) of 102 neonates managed at the Antoine Beclere Hospital NICU (Clamart, France). In a prospective study at the Paediatric Intensive Care Unit of Alder Hey Children's Hospital (Liverpool, UK), Hughes et al. [13] observed abnormal movements in four (7.5%) of 53 critically

ill infants/children at the Paediatric Intensive Care Unit of Alder Hey Children's Hospital (Liverpool, UK). To date, however, very few reports have been published concerning the risk factors associated with development of abnormal movements after administration of midazolam.

The present study was conducted to investigate risk factors involved in the development of abnormal movements in patients managed at the NICU of the Neonatal Medical Center, Kumamoto City Hospital, Japan, focusing on abnormal movements associated with midazolam.

2. Methods

We performed a retrospective analysis of medical records of Japanese infants aged less than 1 year who received continuous midazolam treatment at the NICU of the Neonatal Medical Center, Kumamoto City Hospital, Japan, between April 2007 and March 2009. The study was approved by the Ethics Committee of Kumamoto City Hospital (no. 169).

The cases included those infants in whom the physician noted abnormal movements after the start of midazolam treatment and which disappeared after discontinuation of midazolam. The following data were collected: gender; gestational age at birth; birth weight; Apgar score at 1 and 5 minutes; age at the start of midazolam treatment; number of weeks after conception; body weight; dose level at the start of treatment; presence/absence of neonatal asphyxia, intracranial bleeding, neonatal seizure, hypocalcemia, vitamin K deficiency, hydrocephalus, apnea, and hypoxia.

The infants were classified into two groups; the abnormal movement (+) group and the abnormal movement (−) group. The abnormal movement (+) group included infants who developed abnormal movements on administration of midazolam. The abnormal movement (−) group included infants free of abnormal movements on administration of the drug.

Data of the two groups were compared using the Students *t*-test (parametric continuous variables), the Mann-Whitney *U* test (nonparametric continuous variables), or Fisher's exact test (categorical variables). Logistic regression analysis was used to identify factors associated with the appearance of abnormal movements. Statistical analysis was performed using PRISM (version 3.0, GraphPad Software, Inc., San Diego, CA, USA) and Microsoft Excel. A two-tailed *P*-value < 0.05 was considered to indicate statistical significance.

3. Results

Midazolam was continuously administered to 94 patients (119 sessions). Abnormal movements were identified in nine patients, an incidence of 9.6% in the infants less than 1 year of age admitted to the NICU. Abnormal movements were never observed after discontinuation of midazolam in patients included in abnormal movement (+) group. Comparison of the background variables between the abnormal movement (+) group and the abnormal movement (−) group is shown in Table 1. There was no significant difference in terms of gender, Apgar score at 1 or 5 minutes,

birth weight, age at the start of midazolam treatment, or dose at the start of midazolam treatment between the two groups. The gestational age at birth, number of weeks after conception at the start of midazolam treatment, and body weight at intervention were significantly lower in the abnormal movement (+) group.

The individual background variables of the nine patients with abnormal movements are shown in Table 2. The time from the start of midazolam treatment to appearance of abnormal movements was 0.1–42 h (mean, 7.2 h). Of these nine patients, eight had neonatal asphyxia and three were diagnosed as having intracranial bleeding.

The results of multiple logistic regression analysis are shown in Table 3. A diagnosis of neonatal asphyxia was identified as a factor associated with increased risk of developing abnormal movements after midazolam administration (*P* = 0.03).

4. Discussion

This retrospective study showed that the incidence of abnormal movements following treatment with midazolam was 9.6% among the Japanese infants aged less than 1 year managed at the NICU of the Neonatal Medical Center, Kumamoto City Hospital. Furthermore, multiple logistic regression analysis suggested neonatal asphyxia as a factor associated with increased the risk of developing abnormal movements. In the present study, the gestational age at birth, the number of weeks after conception at the start of midazolam treatment, and the body weight were lower in the abnormal movement (+) group than in the abnormal movement (−) group, suggesting that the infants with abnormal movements were preterm births than the infants who did not develop abnormal movements. Magny et al. [12] reported that the gestational age at birth was 27–34 weeks and the birth weight was 970–2060 g in six children with abnormal movements, and Waisman et al. [14] reported that the gestational age at birth was 24–26 weeks and the birth weight was 617 (170) g (mean (standard deviation)) in three children with abnormal movements. Our results were consistent with these previous findings and suggest that the abnormal movements were associated with prematurity, that is, gestational age at birth and birth weight.

In the present study, logistic regression analysis revealed neonatal asphyxia as a factor significantly associated with midazolam-induced abnormal movements, whereas none of the indicators of prematurity (gestational age at birth, number of weeks after conception at the start of midazolam treatment, age, birth weight, etc.) was found to be significantly associated with the appearance of abnormal movements. It, therefore, seems probable that these indicators of prematurity are confounding factors related to neonatal asphyxia, while neonatal asphyxia, a condition associated with prematurity, is a risk factor for midazolam-induced abnormal movements in infants.

In this study, the midazolam dosing period was much shorter in the abnormal movements (+) group than in the abnormal movements (−) group, indicating that abnormal

TABLE 1: Characteristics of the infants.

	Abnormal movement (+)	Abnormal movement (–)	P-value
Case (male/female)	9 (4/5)	110 (67/43)	0.34
Gestational age (weeks) ^a	30.1 (5.8)	34.3 (5.8)	0.04
Apgar score 1 ^b	3.5 (1–8)	7 (0–10)	0.07
Apgar score 5 ^b	7 (5–9)	8 (1–10)	0.68
Birth weight (g) ^a	1492 (1045)	2109 (1074)	0.10
Postnatal age when midazolam administration was started (days) ^a	17.2 (26.8)	41.9 (59.3)	0.25
Postconceptional age when midazolam administration was started (weeks) ^a	32.5 (5.0)	40.1 (9.1)	0.01
Body weight when midazolam administration was started (g) ^a	1531 (961)	2592 (1331)	0.02
Dose of midazolam (mg·kg ^{−1} ·h ^{−1}) ^a	0.14 (0.06)	0.21 (0.10)	0.05
Duration of midazolam administration (h) ^a	7.2 (13.3)	162.3 (234.2)	<0.0001

^aData are expressed as mean (standard deviation).^bData are expressed as median (range).

TABLE 2: Characteristics of infants in the abnormal movement (+) group.

No	Sex	At birth		At the start of midazolam treatment				Duration of midazolam administration (h)	Birth asphyxia	Intracranial hemorrhage
		GA (weeks)	Apgar score 1/5 min	Weight (g)	PNA (days)	PCA (weeks)	Weight (g)	Dose (mg/kg/h)		
(1)	F	27.0	5/7	862	0	27.0	862	0.17	6.0	+
(2)	M	25.1	4/5	757	16	27.4	826	0.09	42.0	++
(3)	M	25.3	1/5	814	20	28.2	814	0.09	6.0	++ ++
(4)	M	30.4	3/7	1232	1	30.6	1232	0.08	5.8	++ +++
(5)	F	30.7	–/–	1405	1	30.9	1331	0.23	1.7	+ ++
(6)	M	29.0	2/7	1451	32	33.6	1524	0.10	0.1	++
(7)	F	24.4	3/7	559	82	36.1	1108	0.20	1.5	++
(8)	F	38.0	7/8	2580	3	38.4	2306	0.21	0.7	+
(9)	F	40.7	8/9	3773	0	40.7	3773	0.13	1.0	

GA, gestational age; PNA, postnatal age; PCA, postconceptional age.

movements occurred within a few hours after the start of midazolam treatment, resulting in withdrawal of midazolam. This indicates that close monitoring of adverse reactions to midazolam is essential in the few hours after administration. However, one patient developed abnormal movements 42 h after the start of midazolam treatment. This case suggests that it is necessary to be aware of the possibility that abnormal movements can appear even several days after the start of midazolam treatment. Further studies are required regarding the time of appearance of abnormal movements after the start of midazolam treatment.

The present study has the following limitations. First, the cases included those infants in whom the physician noted abnormal movements after the start of midazolam treatment and which disappeared after discontinuation of midazolam in this retrospective study. Although the infants in our neonatal intensive care unit have been observed by physician

and trained medical staffs, no definitive methods of determination of the abnormal movements (such as, frequency and duration of observation, and onset time the abnormal movements) have been defined. Second, the development of abnormal movements was investigated retrospectively, and patients were rated as having abnormal movements if the following criteria were met: (1) medication was suspended at the discretion of the attending physician because of detection of abnormal movements and (2) abnormal movements disappeared after discontinuation of the drug. In addition, discrimination between abnormal movements associated with midazolam and unrelated convulsive seizures is extremely difficult, because there is no distinction in the clinical signs nor a definitive differential diagnosis for the two entities. Therefore, the incidence of abnormal movements induced by midazolam may not have been accurately determined. Besides, the incidence of “midazolam-unrelated

TABLE 3: Logistic regression analysis of factors associated with the appearance of abnormal movements.

	Number	Odds ratio (95% CI)	P-value
Sex			
Female	38	1 (Reference)	0.12
Male	56	0.10 (0.01–1.82)	
Gestational age (weeks)	94	0.50 (0.21–1.20)	0.12
Apgar score 1	94	1.23 (0.37–4.11)	0.73
Apgar score 5	94	3.20 (0.88–12.33)	0.08
Birth weight (g)	94	1.00 (0.99–1.00)	0.46
Postnatal age (days)	94	0.94 (0.86–1.04)	0.24
Postconceptional age (weeks)	94	1.00 (0.97–1.03)	0.98
Body weight (g)	94	1.00 (0.99–1.00)	0.65
Dose of midazolam (mg/kg/h)	94	<0.001 (<0.001–>999.999)	0.26
Birth asphyxia			0.03
No	64	1 (Reference)	
Yes	30	108.04 (1.50–>999.999)	
Intracranial hemorrhage			0.27
No	86	1 (Reference)	
Yes	8	5.41 (0.27–109.63)	
Neonatal seizure			0.32
No	87	1 (Reference)	
Yes	7	10.99 (0.09–>999.999)	
Hypocalcemia			0.88
No	68	1 (Reference)	
Yes	26	0.83 (0.077–8.98)	
Vitamin K deficiency			0.78
No	81	1 (Reference)	
Yes	13	0.62 (0.02–17.04)	
Hydrocephalus			0.99
No	91	1 (Reference)	
Yes	3	<0.001 (<0.001–>999.999)	
Apnea			0.65
No	85	1 (Reference)	
Yes	9	0.37 (0.005–28.49)	
Hypoxia			0.99
No	91	1 (Reference)	
Yes	3	<0.001 (<0.001–>999.999)	

CI, confidence interval.

abnormal movements” in Japanese infants in our neonatal intensive care unit cannot be exactly determined. It may be desirable to objectively assess the appearance of abnormal movements by using electroencephalography, and so forth. Further studies could analyze the relationship between the appearance of abnormal movements and the pharmacokinetics of midazolam. Some investigators reported that the half-life of midazolam was extended in preterm newborns and low-birth-weight newborns, accompanied by reduced drug clearance [15–17]. In view of these reports, we cannot rule out the possibility that metabolism and excretion of midazolam are delayed in preterm and low-birth-weight newborns, resulting in high plasma levels. In this study, we did not survey the concurrent medications

which can modulate the pharmacokinetics of midazolam and can solely be a risk factor of abnormal movements. It would be desirable to conduct a prospective study, taking these factors into account, to further investigate midazolam-associated abnormal movements in Japanese infants managed at NICUs, and also to investigate whether there is an association of intracranial bleeding (a proposed risk factor) with abnormal movements.

5. Conclusion

The present study provided data on the incidence of midazolam-induced abnormal movements among the Japanese

infants managed at the NICU and suggested that neonatal asphyxia was a risk factor for such abnormal movements. The results indicate that, when treating highly preterm neonates, particularly those diagnosed as having neonatal asphyxia, careful use and monitoring of midazolam is essential.

Conflict of Interests

The authors declare that they have no conflict of interests to disclose.

References

- [1] R. Carbajal, A. Rousset, C. Danan et al., "Epidemiology and treatment of painful procedures in neonates in intensive care units," *Journal of the American Medical Association*, vol. 300, no. 1, pp. 60–70, 2008.
- [2] K. J. S. Anand, "Pharmacological approaches to the management of pain in the neonatal intensive care unit," *Journal of Perinatology*, vol. 27, no. 1, pp. S4–S11, 2007.
- [3] M. Fitzgerald, A. Shaw, and N. MacIntosh, "Postnatal development of the cutaneous flexor reflex: comparative study of preterm infants and newborn rat pups," *Developmental Medicine and Child Neurology*, vol. 30, no. 4, pp. 520–526, 1988.
- [4] K. J. S. Anand, "Pain, plasticity, and premature birth: a prescription for permanent suffering?" *Nature Medicine*, vol. 6, no. 9, pp. 971–973, 2000.
- [5] K. S. Anand, R. E. Grunau, and T. F. Oberlander, "Developmental character and long-term consequences of pain in infants and children," *Child and Adolescent Psychiatric Clinics of North America*, vol. 6, no. 4, pp. 703–724, 1997.
- [6] J. W. B. Peters, R. Schouw, K. J. S. Anand, M. Van Dijk, H. J. Duivenvoorden, and D. Tibboel, "Does neonatal surgery lead to increased pain sensitivity in later childhood?" *Pain*, vol. 114, no. 3, pp. 444–454, 2005.
- [7] M. A. Ruda, Q. D. Ling, A. G. Hohmann, Y. B. Peng, and T. Tachibana, "Altered nociceptive neuronal circuits after neonatal peripheral inflammation," *Science*, vol. 289, no. 5479, pp. 628–630, 2000.
- [8] M. Bartocci, L. L. Bergqvist, H. Lagercrantz, and K. J. S. Anand, "Pain activates cortical areas in the preterm newborn brain," *Pain*, vol. 122, no. 1–2, pp. 109–117, 2006.
- [9] P. Lago, A. Guadagni, D. Merazzi, G. Ancora, C. V. Bellieni, and A. Cavazza, "Pain management in the neonatal intensive care unit: a national survey in Italy," *Paediatric Anaesthesia*, vol. 15, no. 11, pp. 925–931, 2005.
- [10] B. Gharavi, C. Schott, M. Nelle, G. Reiter, and O. Linderkamp, "Pain management and the effect of guidelines in neonatal units in Austria, Germany and Switzerland," *Pediatrics International*, vol. 49, no. 5, pp. 652–658, 2007.
- [11] J. N. Van den Anker and P. J. J. Sauer, "The use of midazolam in the preterm neonate," *European Journal of Pediatrics*, vol. 151, no. 2, p. 152, 1992.
- [12] J. F. Magny, A. M. d'Alest, H. Nedelcoux, V. Zupan, and M. Dehan, "Midazolam and myoclonus in neonate," *European Journal of Pediatrics*, vol. 153, no. 5, pp. 389–390, 1994.
- [13] J. Hughes, A. Gill, H. J. Leach et al., "A prospective study of the adverse effects of midazolam on withdrawal in critically ill children," *Acta Paediatrica*, vol. 83, no. 11, pp. 1194–1199, 1994.
- [14] D. Waisman, Z. Weintraub, A. Rotschild, and Y. Bental, "Myoclonic movements in very low birth weight premature infants associated with midazolam intravenous bolus administration," *Pediatrics*, vol. 104, no. 3, p. 579, 1999.
- [15] P. Burtin, E. Jacqz-Aigrain, P. Girard et al., "Population pharmacokinetics of midazolam in neonates," *Clinical Pharmacology and Therapeutics*, vol. 56, no. 6, pp. 615–625, 1994.
- [16] T. C. Lee, B. G. Charles, G. J. Harte, P. H. Gray, P. A. Steer, and V. J. Flenady, "Population pharmacokinetic modeling in very premature infants receiving midazolam during mechanical ventilation: midazolam neonatal pharmacokinetics," *Anesthesiology*, vol. 90, no. 2, pp. 451–457, 1999.
- [17] E. Jacqz-Aigrain, C. Wood, and I. Robieux, "Pharmacokinetics of midazolam in critically ill neonates," *European Journal of Clinical Pharmacology*, vol. 39, no. 2, pp. 191–192, 1990.