Adverse Drug Events due to Central Nervous System Depressant Drugs in Pediatric Patients With or Without Surgery

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OBJECTIVES To identify differences in the incidence and severity of adverse drug events (ADEs) due to CNS depressant drugs among pediatric patients with and without surgery.

METHODS The Japan Adverse Drug Events Study was a cohort study enrolling pediatric inpatients. Potential ADEs were identified by onsite review of medical charts, incident reports, and prescription queries. Two independent physicians classified ADEs and severity. We compared the incidence and characteristics of ADEs between pediatric patients with surgery (surgery group) and without surgery (non-surgery group). We evaluated severity of ADEs due to CNS depressant drugs among both groups.

RESULTS We enrolled 944 patients, 234 in surgery group and 710 in non-surgery group. A total of 480 ADEs due to any drugs occurred in 225 patients. Among 81 ADEs due to CNS depressant drugs, 42 ADEs were in surgery group, whereas 39 were in non-surgery group. The risk of fatal or life-threatening ADEs due to CNS depressant drugs was significantly higher than other drugs (12% vs. 2%, $p < 0.001$). In the surgery group, anesthetics led to 2 fatal or life-threatening, 8 serious, and 30 significant ADEs, whereas in the non-surgery group anesthetics led to 2 fatal or life-threatening, 5 serious, and 4 significant ADEs. Anesthetics were higher risk in the non-surgery group ($p = 0.049$).

CONCLUSIONS The risks of fatal and life-threatening ADEs were significantly higher with CNS depressant drugs than other drugs. Pediatric patients without surgery have higher risks of fatal or life-threatening ADEs due to anesthetics than those with surgery.

ABBREVIATIONS ADE, adverse drug event; CNS, central nervous system; CT, computed tomography; ICU, intensive care unit; IQR, interquartile range; MRI, magnetic resonance imaging; NICU, neonatal intensive care unit

KEYWORDS adverse drug events; central nervous system depressant drug; epidemiology; patient safety; pediatric inpatient

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Introduction

Pediatric patients are vulnerable to the side effect of sedation drugs, and they may have a higher risk of adverse drug events (ADEs) due to such drugs than adult patients.^{1,2} The risks of ADEs due to sedation drugs have been reported although the incidences varied between studies. For example, an observational cohort study reported that 22% of pediatric patients receiving sedation drug including chloral hydrate, benzodiazepine, or barbiturate for MRI and CT experienced adverse events, which were respiratory failure required management or inadequate sedation.¹ Another study using prospectively collected data showed that 184 ADEs occurred among 1341 sedation procedures in children (13.7%) in emergency departments.² In contrast, another study reported a much lower rate of ADEs of 0.4% in sedation procedures for pediatric patients.³

These studies reported ADEs due to the use of sedation drugs for procedures, imaging, or interventional radiology, and their results cannot be generalized for the use of sedation drugs in other settings, such as for surgery or minor procedures.

Because keeping children calm in such cases is more challenging than with adults, the frequency of using anesthesia is expected to be higher with children.⁴ For example, 3.4% of pediatric patients who underwent deep sedation for cardiac MRI experienced ADEs.⁵ Contrary to specific procedural sedation, ADEs due to sedation drugs during surgery and examinations during hospitalization are not well investigated. Epidemiological data, such as the incidence or severity of ADEs due to such drug use, would be useful to their parents and healthcare professionals. Therefore, we scrutinized ADEs due to CNS depressant drugs, including anes-

Table 1. CNS Depressant Drug Classifications and Indications

Classifications	Indications	Drugs
Anesthetics	For surgery	Fentanyl
		Isozole
		Pentazocine
		Propofol
		Remifentanyl
		Sevoflurane
Anticonvulsants	For convulsion	Carbamazepine
		Clonazepam
		Diazepam
Antipsychotics	For short-term sedation situations	Olanzapine
		Quetiapine fumarate
Sedatives	For invasive procedure or examination	Midazolam
		Monosodium
		Trichloroethyl phosphate

thetics, anticonvulsants, antipsychotics and sedatives, among pediatric patients with surgery compared with those without surgery using a historical cohort study.

Materials and Methods

Study Design and Patient Population. The JADE study for pediatrics is a historical cohort study that was carried out in pediatric inpatient settings in 2 tertiary care teaching hospitals in Japan. The details of the study have been described elsewhere.⁶ Briefly, patients aged ≤15 years old who were admitted to any ward, which included NICUs and pediatric ICUs, and those aged >15 years old who were admitted to pediatric wards during the 3-month study period were included in 2009. Neonates at well-baby nurseries were excluded because they were healthy and were not treated by pediatricians. However, we included neonates who had problems at birth and were admitted to NICUs where they were treated by neonatologists.⁶

When a patient was transferred from one ward to another, these consecutive admissions were merged into 1 hospitalization for the patient. Patients who underwent any surgery during their hospital stays were considered patients with surgery (surgery group), and those who did not were considered patients without surgery (non-surgery group). Any invasive procedure or examination, such as catheter insertion, were not considered as surgery and those with such invasive procedure or examination were included in both surgery and non-surgery groups. If patients received several surgeries, invasive procedures, or examinations, we classified such patients in hierarchical order according to the most invasive treatment (i.e., surgery > invasive procedure or examination). No matter the frequency

of surgery or invasive examination or procedure, when patients experience any of them, all of their ADEs were included in the group where they were classified.

Definitions. The primary outcome of the study was the occurrence of ADE due to CNS depressant drug, which we compared between the surgery group and non-surgery group. An ADE was defined as any event that caused patient harm due to drug use. For example, nausea or vomiting in a patient receiving an opiate was considered an ADE.

We classified all drugs into CNS depressant drugs or others. We defined CNS depressant drugs included anesthetics, anticonvulsants, sedatives, and antipsychotics depending on usage. These drugs can cause impairment in activities and cognitive functions.^{7–10} Among CNS depressant drugs, anesthetics included sevoflurane, propofol and isozole, fentanyl, remifentanyl, and pentazocine, which were used for surgery. Anticonvulsants included clonazepam, diazepam, and carbamazepine, which were used for convulsion. Sedatives included midazolam and monosodium trichloroethyl phosphate for invasive procedure. Antipsychotics included olanzapine, quetiapine fumarate, and aripiprazole, which were used for short-term sedation situations (Table 1). The categories of ADE symptoms were nausea/vomiting/loss of appetite, altered mental status/somnolence, hypotension, respiratory failure, anaphylaxis/allergy, arrhythmia, constipation, convulsion, dizziness, renal dysfunction, numbness in limbs, tachycardia, stomatitis, psychosis, tremor, gastrointestinal bleeding, and others. Categories of severity of ADEs included fatal, life-threatening, serious, and significant.¹¹ Fatal ADEs resulted in death; life-threatening ADEs caused issues such as anaphylactic shock or requiring manual ventilation; serious ADEs included

Figure 1. Study flowchart.

ADE, adverse drug event

* Consecutive admissions of one patient to different wards were merged to one observation

conditions such as altered mental status, excessive sedation, increased creatinine levels, and decreased blood pressure; and significant ADEs included cases such as rash, diarrhea, and nausea.¹¹

Data Collection and Review Process. To identify ADEs from disease-related symptoms, we conducted data collection and review process in the following way. The board-certified pediatrician trained the on-site reviewers in a standardized manner reported elsewhere.¹¹ The on-site reviewers consisted of a pediatrician, pediatric nurses, and a dietitian. All medical charts, laboratory results, incident reports, and prescription queries by pharmacists were screened by trained reviewers based at each participating hospital. Potential ADEs and their details, such as symptoms and drug names, were identified by reviewers after collecting the characteristics and related data for all patients. Two independent physicians assessed potential ADEs and determined whether they should be categorized as ADEs or disease-related symptoms. The classification method was generally based on the Naranjo algorithm and described elsewhere.¹¹ If 2 or more drugs could be considered the causal drugs of ADEs, each physician determined the most likely drugs as the causal drugs. When discrepancy happened for classification between independent physicians, the consensus was reached based on discussion adding another independent physician. Those categorized as ADEs were further classified in terms of their severity, symptoms, and class of drug.

Statistical Analyses. Descriptive statistics are shown as median (IQR) for continuous variables and as number and percentage for categorical variables. We used Wilcoxon rank sum test or χ^2 test to compare patient characteristics between patients with and without surgery. We assessed the prevalence of causal drugs and symptoms of ADEs in the stratified 2 groups. We also compared the severity of ADEs due to each CNS depressant drug: anesthetics, anticonvulsants, sedatives, and antipsychotics. We used the χ^2 test to compare the severity of ADEs between fatal or life-threatening ADEs and CNS depressant drugs. We also used the χ^2 test to compare the severity of ADEs between the surgery group and non-surgery group for these 4 CNS depressant drug groups and for each drug. All analyses were performed using JMP 13.1 (SAS Institute, Inc, Cary, NC) software. Two-tailed p values <0.05 were considered statistically significant.

Results

Patient Characteristics. From 1189 admissions in the JADE study for pediatrics, after consolidating consecutive admissions, we found that 944 patients were admitted to any ward (Figure 1). Among the 944 patients, the surgery group included 234 patients, whereas the non-surgery group had 710 patients. The age distribution was significantly different between patients with and without surgery ($p < 0.001$), and school-age children and teenagers were more frequent among those with

Table 2. Patient Characteristics

Variables	All Patients (N = 944)	With Surgery (n = 234)	Without Surgery (n = 710)	p value
Age category				
Neonates (<1 mo), n (%)	201 (21)	17 (7)	184 (26)	<0.001
Infants (≥1 mo, <1 yr), n (%)	122 (13)	22 (9)	100 (14)	
Preschoolers (≥1 yr, <7 yr), n (%)	386 (41)	102 (44)	284 (40)	
School-age children (≥7 yr, <13 yr), n (%)	146 (15)	57 (24)	89 (13)	
Teenagers (≥13 yr, <19 yr), n (%)	79 (8)	36 (15)	43 (6)	
Adults (≥19 yr), n (%)	10 (1)	0 (0)	10 (1)	
Sex, males, n (%)	544 (58)	137 (59)	407 (57)	0.74
History of allergy, n (%)	87 (9)	29 (12)	58 (8)	0.053
Congenital abnormality, n (%)	120 (13)	41 (18)	79 (11)	0.01
Difficulty breathing, n (%)	186 (20)	16 (7)	170 (24)	<0.001
Oxygen therapy	125 (14)	10 (5)	115 (17)	<0.001
Ventilator, n (%)	47 (5)	5 (2)	42 (6)	0.02
Length of stay (days), median (IQR)	6 (3–10)	6.5 (3–13)	6 (4–9)	0.04
Emergency admission, n (%)	581 (62)	40 (17)	541 (76)	<0.001
Resident physician (trained < 3 yr), n (%)	116 (12)	44 (19)	72 (10)	<0.001
Number of drugs before admission, median (IQR)	1 (0–3)	0 (0–1)	1 (0–3)	<0.001
Number of drugs at admission, median (IQR)	4 (2–6)	3 (2–5)	4 (2–6)	0.02

surgery than among those without (24% and 15%, respectively). There were more patients with congenital abnormalities in the surgery group (18% with surgery versus 11% without surgery, $p = 0.01$). More patients without surgery were admitted emergently (76% without surgery versus 17% with surgery, $p < 0.001$). Resident physicians were more likely to be in charge of patients with surgery than patients without surgery (19% versus 10%, respectively, $p < 0.001$) (Table 2).

ADE in Pediatric Patients With or Without Surgery.

Among the 944 patients, 480 ADEs due to any drug occurred in 225 patients (24%). Among the 234 patients in the surgery group, 80 ADEs (17%) occurred in 59 patients (26%). Among the 710 patients in the non-surgery group, 400 ADEs (83%) occurred in 166 patients (74%). Among those with congenital abnormality 18 patients (44%) had ADEs in surgery group, whereas 10 patients (13%) had ADEs in non-surgery group ($p < 0.001$). Among those with difficulty breathing, 9 patients (56%) had ADEs in surgery group, whereas 52 patients (31%) had ADEs in non-surgery group ($p = 0.04$).

The number of ADEs caused by CNS depressant drugs was 81, whereas the number of ADEs caused by other than CNS depressant drug was 399 (Table 3). In the surgery group, there were 80 ADEs due to any drug; 42 ADEs (52%) were ADEs due to CNS depressant drugs and 38 ADEs (48%) were ADEs due to others. In the non-surgery group, there were 400

ADEs due to any drug; 39 ADEs (10%) were ADEs due to CNS depressant drugs and 361 ADEs (90%) were ADEs due to others. The number of ADEs caused by CNS depressant drugs were higher in the surgery group than in the non-surgery group ($p < 0.001$). In the surgery group, more than half (53%) of the ADEs were caused by CNS depressant drugs. In the surgery group, the most frequent causative drug among ADEs was anesthetics (50%). In contrast, a small proportion of ADEs among patients in the non-surgery group were due to anesthetics (3%). Sedatives caused the similar percentage of ADEs in the surgery and non-surgery group (3% and 4%, respectively).

ADE due to CNS Depressant Drugs. Among 81 ADEs caused by CNS depressant drugs, 10 cases (12%) were fatal or life-threatening ADEs, whereas among 399 ADEs caused by other drugs, 7 cases (2%) were fatal or life-threatening ADEs; CNS depressant drugs had a higher risk ($p < 0.001$). All conditions of fatal or life-threatening ADEs due to CNS depressant drugs were respiratory failure. Among 81 ADEs caused by CNS depressant drugs, the most common symptoms of ADEs were nausea, vomiting, or loss of appetite, and accounted for 33 ADEs (41%). Nineteen ADEs (23%) resulted in altered mental status or somnolence, followed by 12 respiratory failure (15%).

Severity and Symptoms in Patients With or Without Surgery. There were 4 cases of fatal or life-threatening

Table 3. Drug Classifications by ADEs

Classifications	All ADEs (N = 480), n (%)	ADEs in Surgery Group (n = 80), n (%)	ADEs in Non-surgery Group (n = 400), n (%)
Anesthetics	51 (11)	40 (50)	11 (3)
Anticonvulsants	10 (2)	0 (0)	10 (3)
Antipsychotics	4 (0.8)	0 (0)	4 (1)
Sedatives	16 (3)	2 (3)	14 (4)
Others	399 (83)	38 (48)	361 (90)

ADE, Adverse drug event

ADEs due to CNS depressant drugs in the surgery group and 6 cases in the non-surgery group ($p = 0.42$). In the surgery group, anesthetics led to 2 fatal or life-threatening ADEs, 8 serious ADEs, and 30 significant ADEs, whereas in the non-surgery group, anesthetics led to 2 fatal or life-threatening ADEs, 5 serious ADEs, and 4 significant ADEs. Anesthetics were higher risk in the non-surgery group ($p = 0.049$). Sedatives led to 6 fatal or life-threatening ADEs, 8 serious ADEs, and 2 significant ADEs in both groups. There were 8 serious and 2 significant ADEs caused by anticonvulsants, and 4 significant ADEs caused by antipsychotics only in the non-surgery group (Figure 2).

In the surgery group, nausea, vomiting, or loss of appetite was the most common symptom of ADE due to anesthetics at 64%, followed by altered mental status or somnolence (10%), respiratory failure (5%), and hypotension (5%) among 42 ADEs. In the non-surgery group, the most common symptom of ADEs due to CNS depressant drugs was altered mental status or somnolence (38%), followed by respiratory failure (20%). Altered mental status or somnolence was caused by anesthetics (8%), anticonvulsants (15%), and sedatives (15%). Respiratory failure was caused by anesthetics (10%) and sedatives (10%) (Table 4).

Discussion

We found ADEs due to CNS depressant drugs were more severe than other drugs. The incidence of ADEs due to any drug in pediatric patients who received surgery was similar to that in pediatric patients without surgery during hospitalization. However, the types of causative drugs were different; anesthetics were the most prevalent causative drug in pediatric patients with surgery, whereas other CNS depressant drugs including sedatives, anticonvulsants, and antipsychotics, were frequently used and caused ADEs in patients without surgery in addition to anesthetics. Especially, in the CNS depressant drugs ADEs due to anesthetics and sedatives resulted in fatal or life-threatening ADE when they occurred in pediatric patients.

Sedation for pediatric patients was frequently used for imaging and became a significant risk of ADE. Although comparisons with other studies using other

methodologies are sometimes challenging, there were several reports of ADEs due to sedation drugs used for imaging. Sanborn et al³ reported that 70 (0.4%) respiratory ADEs occurred among the 16,467 sedations for imaging examinations in pediatric patients, and 58 patients among those 70 suffered hypoxia. That study also showed 29% (20/70) of patients with respiratory ADEs had a history of serious respiratory diseases such as asthma.³ Another study reported that 17 ADEs (3.4%) occurred among 506 children who were deeply sedated for cardiac MRI, and these ADEs included 7 airway obstructions, 6 hypotension cases, 2 desaturations, and 2 excessive secretions with coughing.⁵ These reported ADEs were cardiopulmonary symptoms; however, our study showed other organ symptoms, such as nausea and vomiting, or altered mental status. Because our study originally tried to identify any symptom due to drug use in all settings of pediatric care, we could catch other ADEs due to CNS depressant drugs in the broader perspective. Another study also showed that sedatives used for children aged less than 3 years to receive echocardiography resulted in bradycardia (24%) and hypotension (59%).¹² Although the definitions and measurement methods were different from our study, such cardiovascular ADEs were also observed in our study and should be carefully considered during sedation.

Outside the settings of imaging, sedation drugs for painful procedure were associated with ADEs. A multicenter prospective cohort study in emergency departments setting showed that 11.7% of patients who received sedation drugs for painful procedures experienced ADEs.¹³ The most common symptoms in the emergency departments setting were oxygen desaturation (5.6%) and vomiting (5.2%). The severity of ADEs in the emergency departments setting was not high, and only 1.1% of ADEs were considered fatal or life-threatening, whereas the fatal or life-threatening ADEs due to anesthetics accounted for 8% (4/51) in our study. Such higher rates of more severe forms of ADEs in our study indicate that the level of care in the general pediatric wards was not comparable with that in the emergency departments. Such differences might be due to that ketamine was frequently used in the emergency departments for sedation and ketamine

Figure 2. Severity of ADEs among CNS depressant drugs.

ADE, adverse drug event

■ Significant ADE; □ Serious ADE; ▒ Fatal or Life-threatening ADE

was low risk of apnea, whereas CNS depressant drugs other than ketamine were frequently used in our study and such drugs were higher risk for apnea.

The American Academy of Pediatrics Committee on Drugs recommended the monitoring of patients when sedation drugs were used in any setting.¹⁴ Our results are consistent with the recommendation because the most frequent symptom of fatal or life-threatening ADEs due to CNS depressant drug was respiratory failure. Monitoring systems are generally equipped in operating and imaging rooms; such systems should also be considered in general pediatric care wards. Having capable staff should also be important. CNS depressant drugs were sometimes used for pediatric patients without surgery in Japan. The higher risk of fatal and life-threatening ADEs in patients without invasive procedures or examinations should emphasize the need for well-trained staff. To protect pediatric patients, we should be prepared for the occurrence of ADEs with appropriate monitoring and capable staffing. The use of distraction techniques, such as toys, videos, or music, should also be considered.¹⁵

Our study has several limitations. First, the number of pediatric patients with surgery was much smaller than the number without surgery. As a result, we could not draw definitive conclusions. However, the findings should reflect real world data because we conducted a cohort study at 2 tertiary care teaching hospitals and included unselective all inpatients. Sec-

ond, ADEs due to CNS depressant drugs for invasive procedure or examination might affect the results. However, such situation where sedation was needed for invasive procedure or examination should occur in both patients with and without surgery. Third, we did not differentiate the ADEs due to error from others. Such ADEs due to error should be monitored for patient safety. However, the purpose of this manuscript was to explore the incidences of ADEs due to CNS depressant drugs. Fourth, we conducted this pediatric study at 2 tertiary care teaching hospitals. Therefore, the results are not generalizable to non-tertiary care teaching hospitals, where most children receive their medical care in Japan. Fifth, some ADEs may not have been noted in the charts and, thus, may not have been detected, potentially resulting in an underestimation of ADEs. In addition, because some ADEs specific to anesthetics are well-known and noticeable in operation rooms, other ADEs in other settings may have been overlooked. The types and doses should be different between settings even in the same CNS depressant drugs. Also, the comorbidity of patients affected on the usage of CNS depressant drugs, but we did not assess the effects of comorbidity on the incidence. However, this study focused on the epidemiology of ADEs due to CNS depressant drugs and other drugs based on the settings. Finally, the classification of ADEs could be criticized as being arbitrary. Many symptoms were hard to classify as a particular ADE or other condition.

Table 4. Symptoms of ADEs due to CNS Depressant Drugs in Those With (n = 42) and Without (n = 39) Surgery

Classifications	Symptoms of ADEs	With Surgery n (%)	Without Surgery n (%)
Anesthetics	Nausea/vomiting/loss of appetite	27 (64)	4 (10)
	Altered mental status/somnolence	4 (10)	3 (8)
	Hypotension	2 (5)	0 (0)
	Respiratory failure	2 (5)	4 (10)
	Anaphylaxis/allergy	1 (2)	0 (0)
	Arrhythmia	1 (2)	0 (0)
	Constipation	1 (2)	0 (0)
	Convulsion	1 (2)	0 (0)
	Dizziness	1 (2)	0 (0)
Anticonvulsants	Nausea/vomiting/loss of appetite	0 (0)	1 (3)
	Altered mental status/somnolence	0 (0)	6 (15)
	Stomatitis	0 (0)	1 (3)
	Dizziness	0 (0)	2 (5)
Antipsychotics	Constipation	0 (0)	1 (3)
	Psychosis	0 (0)	2 (5)
	Tremor	0 (0)	1 (3)
Sedatives	Nausea/vomiting/loss of appetite	0 (0)	1 (3)
	Altered mental status/somnolence	0 (0)	6 (15)
	Hypotension	0 (0)	1 (3)
	Tachycardia	0 (0)	1 (3)
	Respiratory failure	2 (5)	4 (10)
	Psychosis	0 (0)	1 (3)

ADE, Adverse drug event

We have to recognize these limitations; however, we used an acceptable current standard approach that is used by many studies of ADEs in daily practice.

Conclusion

Generally pediatric patients with surgery have a similar risk of ADEs due to any drug as do those without surgery. However pediatric patients without surgery have higher risks of fatal or life-threatening ADEs due to anesthetics than those with surgery. The risks of fatal and life-threatening ADEs were significantly higher with CNS depressant drugs than other drugs, and all those symptoms were respiratory failure. Thus, monitoring such drugs and symptoms, especially outside surgery, should be emphasized to improve pediatric patient safety.

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