Adverse drug events and medication errors in Japanese paediatric inpatients: a retrospective cohort study

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ABSTRACT

Objectives Knowledge about the epidemiology of adverse drug events (ADEs) and medication errors in paediatric inpatients is limited outside Western countries. To improve paediatric patient safety worldwide, assessing local epidemiology is essential.

Design The Japan Adverse Drug Events (JADE) Study was a cohort study.

Setting Paediatric inpatients at two tertiary care teaching hospitals in Japan.

Main outcome measures ADEs and medication errors identified by onsite review of all medical charts, incident reports and prescription queries by pharmacists. Two independent physicians reviewed all incidents and classified ADEs and medication errors, as well as their severity and preventability.

Results We enrolled 1189 admissions which included 12 691 patient-days during the study period, and identified 480 ADEs and 826 medication errors. The incidence of ADEs was 37.8 (95% CI 34.4 to 41.2) per 1000 patient-days and that of medication errors was 65.1 (95% CI 60.6 to 69.5) per 1000 patient-days. Among ADEs, 4%, 23% and 73% were fatal or life-threatening, serious and significant, respectively. Among the 480 ADEs, 36 (8%) were considered to be preventable which accounted for 4% of all medication errors, while 668 (81%) of all medication errors were judged to have the potential to cause harm to patients. The most common error stage for preventable ADEs was monitoring (78%) whereas 95% of potential ADEs occurred at the ordering stage.

Conclusions ADEs and medication errors were common in paediatric inpatients in Japan, though the proportion of ADEs that were preventable was low. The ordering and monitoring stages appeared most important for improving safety.

INTRODUCTION

Adverse drug events (ADEs) are injuries due to medication use[1]. ADEs represent a serious problem in healthcare because they are the most frequent cause of injuries due to medical care in hospitals in developed countries[2 3] and are associated with substantial increases in morbidity and mortality.[2 4–6]

Paediatric inpatients are also vulnerable to ADEs and medication errors.[7] Physiologically, they often have limited reserves with respect to metabolism and/or fluid volume. Preschoolers and younger children are even more vulnerable, because they cannot describe their symptoms and they also vary substantially in terms of weight. Several studies of ADEs and medication errors in paediatric inpatients have been done,[7–12] and in addition a few studies of medication error prevention strategies have been performed in paediatric inpatients.[13–16] However, most of these studies were from Western countries and their results cannot be extrapolated to other settings globally without basic data from other parts of the world.[17]

Thus, we conducted the Japan Adverse Drug Events (JADE) Study, a multicentre cohort study in several settings in Japan.[6] The JADE Study for paediatrics was conducted in a historical cohort study fashion to estimate the epidemiology and nature of ADEs and medication errors in paediatric inpatients in Japan.

METHODS

Study design and patient population

We conducted this JADE Study in the paediatric inpatient setting in two tertiary

care teaching hospitals in Japan. The total number of beds in these two hospitals is 1754 and 152 beds among them were for paediatric inpatients. One hospital had an electronic medical record with an alert system for a drug-drug interaction and duplicate prescriptions. Another hospital did not have either an electronic medical record or any alert system but had only computerised order entry for simple drug prescriptions, blood tests and radiographs. The study used a cohort study design.

Both hospitals care for adult and paediatric patients. Some paediatric patients were admitted to units including adults such as the regular intensive care units (ICUs), emergent care units or subspecialty wards, such as otolaryngology, a practice which is common in Japan. Others were admitted to the neonatal ICUs (NICUs), the paediatric ICUs (PICUs) or general paediatric wards. A few adult patients were also cared for by paediatricians and admitted to the paediatric ward, though this group comprised less than 1% of the admissions to these units. They generally had complex long-term medical conditions, such as congenital diseases (eg, metabolic disease or cerebral palsy) or multiple disabilities.

There are only a few independent children's hospitals in Japan and they generally have more complex patients in terms of severity than general hospitals, but we did not include any of these hospitals in this study. However, one of the hospitals in this study was a university affiliated hospital which does have very complex patients.

We studied all paediatric wards including the NICU and the PICU. We also studied the ICU, the emergent care unit, and the general adult ward when paediatric patients (≤15 years old) were admitted. Thus, we included all patients aged ≤15 years admitted to any ward and patients aged >15 years old who were admitted to any of the paediatric wards over a 3 month study period in 2009.

We had 'well baby nurseries' in both hospitals. However, neonates at the well baby nursery were excluded from this study because they were healthy and were not cared for by paediatricians. Instead, if neonates at birth had a problem such as temporary dyspnoea or mild cyanosis of the limbs, they were admitted to the NICU and cared for by neonatologists. Therefore, the NICU included relatively healthy neonates as well as critically ill neonates. Because of this dichotomy, we elected to classify neonates in the NICU into two categories according to birth weight; low birthweight (LBW) neonates weighing <2500 g and non-LBW neonates weighing ≥2500 g. The main units of evaluation were patient-day and number of admission. The institutional review boards of the two participating hospitals approved the study. Because all data were obtained as part of routine daily practice, informed consent was waived by the institutional review board.

Definitions

The primary outcome of the study was the ADE, defined as an injury due to a medication use.[1] For example, a rash in a patient receiving ampicillin without another obvious cause was considered an ADE. We also identified medication errors, which were defined as any deviation from appropriate use of medication in any step of the medication use process including ordering, transcribing, dispensing, administering or monitoring.[1] Some ADEs were associated with a medication error and were considered preventable (preventable ADEs), while some were not associated with a medication error and were considered non-preventable. Preventable ADEs included ameliorable ADEs: ameliorable ADEs occurred when care was otherwise appropriate but the patient developed issues that could have been addressed sooner; such injury could be ameliorable when appropriate action was taken during the monitoring stage. An event that had potential for harm but did not result in injury was considered a potential ADE. If potential ADEs were intercepted before reaching the patient, they were considered an intercepted potential ADE. An example would be if a physician ordered ampicillin in a patient with known penicillin allergy, but that order was intercepted and corrected by a pharmacist. A non-intercepted potential ADE would be when a physician administered ampicillin to a patient known to be allergic to penicillin without interception, but nothing occurred by chance.

Data collection and review process

Trained reviewers were based at each participating hospital and reviewed all medical charts along with laboratories, incident reports and prescription queries by pharmacists. The trained reviewers consisted of a board-certified paediatrician, paediatric nurses and a dietitian, and the paediatrician trained all reviewers in a standard manner, as reported elsewhere.[1] They collected the characteristics and administrative data for all enrolled patients in the cohort. Then, they identified incidents such as ADEs, potential ADEs and medication errors, as well as the details of those incidents. Data collected for incidents included the name, dose, route and class of the drug, the details of symptoms if the incidents were ADEs, and the details of errors such as stage, persons who were in charge, or causes if the incidents were errors.

Two independent physician reviewers evaluated all incidents collected by the research assistants and classified them as ADEs, potential ADEs, medication errors and exclusions. The physician reviewers rated ADEs and potential ADEs according to the severity of injuries or potential injuries to the patient using a 4-point scale as well as their preventability using a 5-point scale. Categories of severity were fatal, life-threatening, serious and significant. Fatal ADEs resulted in death; life-threatening ADEs caused such

issues as transfers to ICU or anaphylactic shock, serious ADEs included gastrointestinal bleeding, altered mental status, excessive sedation, increased creatine or a decrease in blood pressure, and significant ADEs included cases with rash, diarrhoea or nausea, for example. Reviewers considered ADEs as preventable or ameliorable if they were due to an error.

If a medication error was found, the type of error and the error stage in the process where it occurred were classified. The stages of the medication use process were classified into ordering by physicians, transcription by nurses, dispensing by pharmacists or nurses, administration by nurses, patients themselves or caregivers, and monitoring by physicians or other health professionals. When disagreement affected the classification of an incident, the physician reviewers reached consensus through discussion.

Statistical analyses

The incidence per 1000 patient-days, the rates per 100 admissions and the 95% CIs were calculated as a whole, by age group (neonates, infants, preschoolers, school-age children, teenagers or adults) and by ward category (the paediatric general ward, the NICU, the PICU, the ICU, the emergent care unit or the adult ward), respectively. Continuous variables are presented as means with SDs or medians with IQRs, and categorical variables are shown as numbers and percentages. We calculated inter-rater reliabilities using the κ statistics. We carried out all analyses using JMP V.8.0 (SAS Institute, Cary, North Carolina, USA) software.

RESULTS

We enrolled 1189 admissions with 12 691 patient-days on the study wards. The median age was 2 (IQR 0–7) years and 55% (649/1189) were male. The median hospital stay was 5 (IQR 3–9) days, and the median number of medications administered to a patient on admission was 4 (IQR 2–6) (table 1). The patients included 252 (21%) neonates, 174 (14%) infants, 465 (39%) preschoolers, 189 (16%) school-age children, 98 (8%) teenagers and 11 (0.9%) adults (table 2). We had more patients with cancer in the teenagers' group than in other age groups (N=6, 6%). Overall, 169 patients were admitted to the NICU, where 69 (41%) were LBW neonates and 100 (59%) were non-LBW neonates (table 2). The hospital stay was longer in the LBW neonates and more medications were prescribed to the LBW neonates on admission than non-LBW neonates (median hospital stay; 26 days vs 4 days, the median number of medications on admission; 4 vs 2). Among the 37 patients admitted to the ICU, 35 patients (95%) had had an operation and came to the ICU directly after a procedure, and 15 of these 35 patients were transferred to the PICU from the ICU as a step to be back to the general paediatric ward. Thus, 83% (15/18) of the PICU-admitted patients were transferred from the ICU. Physician reviewers had moderate to excellent agreement with κ statistics of 0.31–0.86.

Adverse drug events

The onsite research assistants identified 1767 incidents during the study period. Among these incidents, physician reviewers judged that there were 480 ADEs in 234 patients (20%), for the incidence of 37.8 (95% CI 34.4 to 41.2) per 1000 patient-days and the rate per 100 admissions of 40.4 (95% CI 36.8 to 44.0) (figure 1). Among those 234 patients who had ADEs, 26 patients (11%) had three or more ADEs.

The incidence of ADEs was the highest in teenagers (table 2). Among neonates, incidence was lower in non-LBW neonates in the NICU than LBW neonates in the NICU and neonates in the general paediatric ward (table 2). The incidence in infants, preschoolers and school-age children were almost similar, and those age groups accounted for 70% of all patients. The incidence by ward category was the highest in the ICU and the lowest in non-LBW neonates in the NICU (table 2).

Seventeen fatal or life-threatening ADEs occurred in 15 patients during their hospital stay, which accounted for 3.5% of the 480 ADEs. Fatal or life-threatening ADEs included respiratory depressions, allergic reactions with dyspnoea, sepsis, airway bleeding and hypoglycaemia. Among the 17 fatal or life-threatening ADEs, 6 ADEs involved sedatives, 4 narcotics and 3 antibiotics. Serious ADEs and significant ADEs accounted for 23% and 73% of all ADEs, respectively.

Regarding organ systems affected by ADEs, gastrointestinal were most frequent, accounting for 45% of all ADEs followed by allergic or skin symptoms (12%) and metabolic or liver dysfunction (11%) (table 3).

Among drug classes, antitumour agents and antibiotics accounted for 31% and 30% of all ADEs, respectively. Narcotics and steroids were the next leading

Table 1 The number of medications on admission according to the ward category

	Total	Paediatric ward	NICU		PICU	ICU	Emergent care unit	Adult ward
			LBW neonates	Non-LBW neonates				
The number of medications on admission, median (25, 75%)	4 (2, 6)	4 (2, 6)	3 (2, 4) 4 (3, 6)	2 (2, 3)	6 (5, 7)	7 (4, 10)	5 (4, 7)	3 (1, 6)

ICU, intensive care unit; LBW, low birth weight; NICU, neonatal intensive care unit; PICU, paediatric intensive care unit.

Table 2 Incidence of adverse drug events and medication errors

Adverse drug events	N	Patient-days	ADEs	Incidence*	95% CI	Rate†	95% CI
Total	1189	12 691	480	37.8	34.4 to 41.2	40.4	36.8 to 44.0
Age category							
Neonates (<1 month)	252	4757	53	11.1	8.1 to 14.1	21.0	15.4 to 26.7
LBW neonates, NICU	69	3270	44	13.5	9.5 to 17.4	63.8	44.9 to 82.6
Non-LBW neonates, NICU	100	944	2	2.1	0.26 to 7.7	2.0	0.24 to 7.2
General paediatric ward	83	543	7	12.9	5.2 to 26.6	8.4	3.4 to 17.4
Infants (1 month=< <1 year)	174	1923	84	43.7	34.3 to 53.0	48.3	38.0 to 58.6
Preschoolers (1 year =< <7 year s)	465	3425	157	45.8	38.7 to 53.0	33.8	28.5 to 39.0
School-age children (7 years=< <13 years)	189	1459	73	50.0	38.6 to 61.5	38.6	29.8 to 47.5
Teenagers (13 years=< <19 years)	98	1081	112	103.6	84.4 to 122.8	114.3	93.1 to 135.5
Adults (19 years=<)	11	46	1	21.7	0.55 to 121.1	9.1	0.23 to 50.7
Ward category							
Paediatric ward	704	7007	364	51.9	46.6 to 57.3	51.7	46.4 to 57.0
NICU	169	4214	46	10.9	7.8 to 14.1	27.2	19.4 to 35.1
LBW neonates	69	3270	44	13.5	9.5 to 17.4	63.8	44.9 to 82.6
Non-LBW neonates	100	944	2	2.1	0.26 to 7.7	2.0	0.24 to 7.2
PICU	18	157	2	12.7	1.5 to 46.0	11.1	1.3 to 40.1
ICU	37	107	9	84.1	38.5 to 159.7	24.3	11.1 to 46.2
Emergent care unit	98	197	11	55.8	22.8 to 88.8	11.2	4.6 to 17.9
Adult ward	163	1009	48	47.6	34.1 to 61.0	29.4	21.1 to 37.8
Medication errors	**N**	**Patient-days**	**Medication errors**	**Incidence***	**95% CI**	**Rate†**	**95% CI**
Total	1189	12 691	826	65.1	60.6 to 69.5	69.5	64.7 to 74.2
Age category							
Neonates (<1 month)	252	4757	161	33.8	28.6 to 39.1	63.9	54.0 to 73.8
LBW neonates, NICU	69	3270	112	34.3	27.9 to 40.6	162.3	132.3 to 192.4
Non-LBW neonates, NICU	100	944	36	38.1	25.7 to 50.6	36.0	24.2 to 47.8
General paediatric ward	83	543	13	23.9	10.9 to 37.0	15.7	7.1 to 24.2
Infants (1 month=< <1 year)	174	1923	70	36.4	27.9 to 44.9	40.2	30.8 to 49.7
Preschoolers (1 year =< <7 year)	465	3425	283	82.6	73.0 to 92.3	60.9	53.8 to 68.0
School-age children (7 year=< <13 year)	189	1459	175	119.9	102.2 to 137.7	92.6	78.9 to 106.3
Teenagers (13 year=< < 19 year)	98	1081	125	115.6	95.4 to 135.9	127.6	105.2 to 149.9
Adults (19 year=<)	11	46	12	260.9	113.3 to 408.5	109.1	47.4 to 170.8
Ward category							
Paediatric ward	704	7007	440	62.8	56.9 to 68.7	62.5	56.7 to 68.3
NICU	169	4214	148	35.1	29.5 to 40.8	87.6	73.5 to 101.7
LBW neonates	69	3270	112	34.3	27.9 to 40.6	162.3	132.3 to 192.4
Non-LBW neonates	100	944	36	38.1	25.7 to 50.6	36.0	24.2 to 47.8
PICU	18	157	1	6.4	0.16 to 35.5	5.6	0.14 to 31.0
ICU	37	107	15	140.2	69.2 to 211.1	40.5	20.0 to 61.1
Emergent care unit	98	197	82	416.2	326.1 to 506.3	83.7	65.6 to 101.8
Adult ward	163	1009	140	138.8	115.8 to 161.7	85.9	71.7 to 100.1

ADEs, adverse drug events; ICU, intensive care unit; LBW, low birth weight; NICU, neonatal intensive care unit; PICU, paediatric intensive care unit.
*Per 1000 patient-days.
†Per 100 admissions.

categories at 9% and 7%. Other drug classes accounted for less than 5% of all ADEs.

Medication errors and potential adverse drug events

We identified 826 medication errors among 349 patients (29%): the incidence was 65.1 (95% CI 60.6 to 69.5) per 1000 patient-days, and the rate was 69.5 (95% CI 64.7 to 74.2) per 100 admissions. Among those 349 patients who had medication errors, 102 patients (29%) had three or more medication errors.

The incidence was higher in older age groups: adults had the highest incidence followed by school-age children and teenagers, and the lowest in neonates. Among different wards, the incidence was the

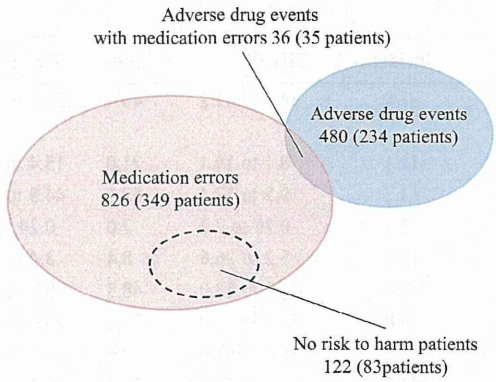

Figure 1 Relationship between adverse drug events and medication errors.

highest in the emergent care unit followed by the ICU and the adult ward. On the other hand, the incidence was lower in the PICU and the NICU (table 2).

Among the 826 medication errors, 36 (4%) resulted in ADEs, so that 8% of all 480 ADEs were considered preventable. Twenty-eight ADEs of these 36 preventable ADEs (78%) occurred at the monitoring stage—ordering and administration were appropriate, but patients had prolonged symptoms related to the medications that were not addressed promptly. Thus, they were classified as preventable ADEs in terms of duration or severity (table 4). Of the remaining 790 medication errors, 668 (81%) had the potential to cause harm for patients, and were thus potential ADEs (figure 1). The incidence of preventable ADEs was 2.8 (95% CI 1.9 to 3.8) and that of potential ADEs was 52.6 (95% CI 48.6 to 56.6) per 1000 patient-days. Nineteen per cent of potential ADEs were intercepted before a drug was administered to a patient, and thus, they were considered intercepted potential ADEs. The remaining 538 potential ADEs were non-intercepted potential ADEs: the patient did not actually take the drug in 113 cases (21%) and took the drug but no injuries occurred in 425 cases (79%). The incidence of intercepted and non-intercepted potential ADEs were 10.2 (95% CI 8.5 to 12.0) and 42.4 (95% CI 38.8 to 46.0) per 1000 patient-days,

Table 3 Symptoms of adverse drug events

Symptoms	ADEs (%)
Bleeding	10 (2)
Central nervous	46 (9)
Allergic/skin	57 (12)
Metabolic/liver	51 (11)
Cardiovascular	16 (3)
Gastrointestinal	214 (45)
Renal	16 (3)
Respiratory	19 (4)
Bone marrow	38 (8)
Others	13 (3)

ADEs, adverse drug events.

Table 4 The details of preventable adverse drug events

Error stage	The number of ADEs (%)	Examples of event
Ordering	7 (19)	Excessive sedation, tachycardia by overdosing or rash by administration of medication with the past history of allergy
Administering	1 (3)	Worsen a symptom by forgetting to administer the medication
Monitoring	28 (78)	Prolonged sever eczema due to diarrhoea by antibiotics, prolonged rash by medication or intravenous administration related extravasations with tissue damages

ADEs, adverse drug events.

respectively. The remaining 122 (15%) medication errors had very low potential to harm patients. The most common stage for preventable ADEs was the monitoring stage (78%) whereas 95% of potential ADEs arose at the ordering stage (table 5).

The most common drug class involved in preventable ADEs was antibiotics (58%) while laxatives was the most common in potential ADEs (18%). Although antitumour agents were the most frequent drug class associated with ADEs, only one case was judged preventable.

DISCUSSION

We found that ADEs were frequent in the paediatric inpatient setting in Japan, with an ADE incidence of 38 per 1000 patient-days, though most were not preventable. There were also 65 medication errors per 1000 patient-days.

The present study used the same methodology as a study in the paediatric inpatient setting by Kaushal *et al*[7] as well as the studies in adult settings in Japan and the USA.[5 6] Kaushal *et al* reported an incidence of ADEs of 7 per 1000 patient-days, about a fifth the rate in this study, and an incidence of medication errors of 157 per 1000 patient-days, which was twice the rate in this study. Other studies have also reported the incidence of ADEs: Holdsworth *et al*[8] reported 8 ADEs per 1000 patient-days; Takata *et al.* reported 22 ADEs per 1000 patient-days,[9] Kunac *et al*[10] reported 22 ADEs per 1000 patient-days, and Agarwal *et al*[18] reported 49 ADEs per 1000 patient-days in PICUs. These incidences were generally similar, but more recent studies reported higher incidences (table 6). The reasons for the higher recent incidences are unclear, but potential hypotheses could be that techniques for finding ADEs have improved, or more drugs might be being used. The differences of patients' demographics and physicians' practice in each study setting also could be related to the incidence because they influenced the class of and the number of medications administered to patients. For example, patients with cancer need chemotherapy, which cause more

Table 5 Stages of primary errors associated with preventable and potential adverse drug events

Event	Ordering n (%)	Transcription n (%)	Dispensing n (%)	Administration n (%)	Monitoring n (%)
Preventable ADEs	7 (19)	0 (0)	0 (0)	1 (3)	28 (78)
Intercepted potential ADEs	130 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Non-intercepted potential ADEs	503 (93)	0 (0)	1 (0.2)	27 (5)	7 (1)
All above events	640 (91)	0 (0)	1 (0.1)	28 (4)	35 (5)

ADEs, adverse drug events.

ADEs. Similarly, physicians in a certain hospital or country may be more likely to order more medications than others. We found that the epidemiological characteristics of ADEs and medication errors between these previous reports and the present study were fairly similar, such as the severity of ADEs,[7 8 10] the drug classes related to ADEs,[8] the proportion of preventable ADEs[7 9] and stages for which medication errors were most frequent.[7–9]

We also compared the results of the present study with our study in the adult inpatient setting.[6] The incidence of ADEs was higher in paediatric than adult patients (37.8 vs 17.0 per 1000 patient-days) while the incidence of medication errors was about eight times higher in this paediatric study than in our adult study (65.1 vs 8.7 per 1000 patient-days). The higher incidence of medication errors in paediatrics could be because of specific complexities in the drug ordering and delivery process in children; individual drug dosage calculation is needed according to age and weight, which can increase opportunities for error with a high risk of 10-fold errors at the ordering stage,[19 20] and young children cannot report to caregivers or healthcare professionals about their symptoms due to ADEs, causing more frequent monitoring errors in the paediatric setting. On the other hand, medication errors were most prevalent in adults in this study, perhaps because they are relatively infrequent in general paediatric wards. School-age children and teenagers also had a higher incidence than younger children. When physicians prescribed medicine for older children and adults, they often made errors in directions around dose and frequency.

We had more patients with cancer in the teenager group than in other age groups, and these patients had received chemotherapy, which resulted in the higher incidence of ADEs in teenagers. Among neonates, non-LBW neonates in the NICU had a lower ADE incidence than LBW neonates in the NICU and neonates in the general paediatric ward because they are relatively healthy. In the PICU, 83% of patients were transferred from the ICU as an interim location before returning to the general paediatric ward for postoperative care. This practice likely differs from that in most Western PICUs which may be the reason that the ADE incidence in the PICU was relatively low in our study.[18] Not surprisingly, ADE incidence was higher in ICUs than in general care units.

In this study, only 8% of ADEs were considered preventable, in that few were associated with an obvious error. This lower proportion of preventable ADEs compared with the previous studies is probably in part due to the high proportion of patients who received chemotherapy in this study; a third of the ADEs were associated with antitumour agents and they occurred due to its high toxicity without errors except one judged as preventable. This situation decreased the proportion of preventable ADEs overall. Except chemotherapy related ADEs, preventable ADEs accounted for 11%, which was consistent with the previous studies.[6 7] From the safety perspective, preventable and non-preventable ADEs are important because those ADEs which are not judged preventable today may be preventable in the future, and both result in harm.

Several studies have reported that interventions with information technologies including computerised physician order entry[21 22], as well as pharmacist participation in physician rounds, have been effective to reduce medication errors in adult inpatient settings.[23] A few studies have reported that the interventions above would be effective to reduce medication errors in paediatric inpatient setting as well.[13–16 24–26] Our finding showing the common epidemiological characteristics of ADEs and medication errors between Japan and Western countries may suggest that such interventions for reducing the medication errors could be beneficial in most developed countries.

Our study has several limitations. We conducted this paediatric study at two tertiary care teaching hospitals. Therefore, our results may not be generalisable to non-tertiary care teaching hospitals where most children received their medical care in Japan. Some ADEs may not have been noted in the charts and may thus have not been detected, which would make our estimates a lower bound. However, more robust alternatives to measure ADEs and medication errors have not yet been developed, so the approach we used is the current standard one.

CONCLUSION

We found that ADEs and medication errors were common in paediatric inpatients in Japan, and that there was a similar nature of ADEs and medication errors to those arising in the paediatric settings in Western countries. The proportion of preventable

Table 6 The comparison of epidemiology of adverse drug events among paediatric settings

Study	JADE study	Agarwal S[18]	Takata GS[9]	Kunac DL[10]	Holdsworth MT[8]	Kaushal R[7]
Country and studied year	Japan, 2012	U.S., 2005	U.S., 2003	New Zealand, 2002	U.S., 2000	U.S., 2000
Patients and setting	All patients admitted at two teaching hospitals	Randomly selected patients from 15 hospitals	5 hospitals participating in the California Paediatric Patient Safety Initiative	All patients admitted at a university-affiliated urban general hospital	All patient admitted at a large metropolitan tertiary care centre	All patient admitted at 2 academic institutions
Wards	Paediatric medical/surgical wards, two NICUs and a PICU*	15 PICUs	Paediatric wards, PICUs, and NICUs	A paediatric ward, a NICU and a postnatal ward	A paediatric ward and a PICU	9 ward including paediatric medical/surgical wards, NICUs, PICUs, and short-stay medical ward
Number of admissions	1189	734	Not available	520	1197	1120
Data acquisition method	Reviewers, historical cohort study	Cross sectional retrospective review with trigger methods	Trigger methods	Review by the principal investigator, prospective cohort study	A reviewer, Prospective cohort study	Reviewers, Prospective cohort study
Incidence of ADEs (ADEs/1000 patient days)	37.8	49	22.3	22.1	7.5	6.6
Rate of ADEs (ADEs/100 admissions)	40.4	34.9	11.2	12.9	6	2.3
Rate of patients who had at least one ADE	20%	Not available	9%	Not available	Not available	Not available

*Studied the patients admitted at the ICU, the emergent care unit and the general adult ward when paediatric patients (≤15 years old) were admitted.
ADEs, adverse drug events; JADE, Japan Adverse Drug Events; NICU, neonatal intensive care unit; PICU, paediatric intensive care unit;.

ADEs and potential ADEs among all medication errors was substantial, and most of the errors occurred at the ordering and the monitoring stages. Interventions to support healthcare providers focusing on ordering to and monitoring patients may improve medication safety among paediatric inpatients, although more testing of the potential benefits of these strategies would be valuable in a variety of settings.

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Contributors Study concept and design: MS, DWB, TM. Acquisition of data: MS, HI, TN, KY, KH, KK, KN, TM. Statistical analysis: MS, SS, TM. Interpretation of data: MS, HI, TN, YO, KY, SS, KH, KK, KN, DWB, TM. Drafting the manuscript: MS, DWB, TM. Critical revision of the manuscript for the important intellectual content: HI, TN, YO, KY, SS, KH, KK, KN. Administrative, technical and material support: HI, KN, YO, KY, SS, KH, KK, KN, DWB, TM.

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Competing interests DWB is on the clinical advisory board for Patient Safety Systems, which provides a set of approaches to help hospitals improve safety. He also consults for Hearst, which develops knowledge resources, and serves on the clinical advisory board for SEA Medical Systems, which makes intravenous pump technology. For other authors, there is nothing to declare.

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Adverse drug events and medication errors in Japanese paediatric inpatients: a retrospective cohort study

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Influence of adverse drug events on morbidity and mortality in intensive care units: the JADE study

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Abstract

Objective. To identify the influence of adverse drug events (ADEs) on morbidity and mortality in intensive care units (ICUs).

Design. A prospective cohort study.

Setting. ICU setting at three acute care hospitals in Japan.

Participants. All patients aged ≥15 years were admitted to all ICUs during a 6-month study period.

Intervention. No intervention.

Main Outcome Measures. Mortality in the ICUs and the length of the ICU stay. .

Results. We included 459 patients with a total of 3231 patient-days. Ninety-nine ADEs occurred in 70 patients (15%), so that the incidence of ADEs was 30.6 per 1000 patient-days and 21.6 ADEs per 100 admissions. Seventy-three patients (16%) died during their ICU stay. Excluding 38 deaths within 3 days after admission, 12 patients (17%) died among the 70 patients who had at least one ADE during their ICU stay and 23 (7%) died among 351 without an ADE ($P = 0.003$). The median ICU length of stay was 3 days. Excluding 73 patients who died during their ICU stay, the median ICU stay of patients with at least one ADE was 13 days, while it was only 2 days in the remainder ($P < 0.0001$). ADEs were associated with longer length of ICU stay but not with mortality even after adjusting for patients' severity of illness.

Conclusions. ADEs were common in ICUs and significantly associated with longer length of ICU stay but did not influence on mortality.

Keywords: adverse drug events, epidemiology, intensive care unit, mortality, length of ICU stay, and patient safety

Introduction

Adverse drug events (ADEs) are injuries due to medication use [1]. ADEs are especially important in intensive care units (ICUs) because ADEs are associated with substantial increases in morbidity and mortality and many drugs are used in ICUs [2–4]. The European Society of Intensive Care Medicine in 2009 declared that there is a clear need to build and evaluate strategies to prevent or ameliorate ADEs and medication errors and thereby improve the outcome of critically ill patients [5].

Several studies have reported that the incidence of ADEs in ICUs is higher than that in general wards [4, 6, 7]. Critical care is complex and commonly requires urgent high-risk decision-making, often with incomplete data and by physicians with varying levels of critical care training [8]. Furthermore, the nature of critical illness reduces both the patients' natural resilience and their ability to defend themselves. The number of high-risk drugs administered to such patients is likely also partly responsible for the high ADE rates. Cullen *et al.* [9] reported that ICU patients received significantly more drugs in the 24 h before an ADE than non-ICU patients (15 vs. 9, $P < 0.0001$). However, the reports that assess the impact of the higher incidence of ADEs in ICU on mortality and morbidity of ICU patients were limited [10, 11]. Furthermore, most reports have been from Western countries, and their results cannot be extrapolated to other parts of the world without