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Epidemiology of Adverse Events and Medical Errors in the Care of Cardiology Patients

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Objectives: There have been epidemiological studies of adverse events (AEs) among general patients but those of patients cared by cardiologist are not well scrutinized. We investigated the occurrence of AEs and medical errors (MEs) among adult patients with cardiology in Japan.

Methods: We conducted a cross-sectional study of adult outpatients at a Japanese teaching hospital from February through November 2006. We measured AE and ME incidents from patient report, which were verified by medical records, laboratory data, incident reports, and prescription queries. Two independent physicians reviewed the incidents to determine whether they were AEs or MEs and to assess severity and symptoms.

Results: We identified 144 AEs and 30 MEs (16.3 and 3.9 per 100 patients, respectively). Of the 144 AEs, 99 were solely adverse drug events (ADEs), 20 were solely non-ADEs, and the remaining 25 were both causes. The most frequent symptoms of ADEs were skin and allergic reactions due to medication. The most frequent symptoms of non-ADEs were bleeding due to therapeutic interventions. Among AEs, 12% was life threatening. Life-threatening AEs were 25% of non-ADEs and 5% of ADEs ($P = 0.0003$). Among the 30 MEs, 21MEs (70%) were associated with drugs.

Conclusions: Adverse events were common among cardiology patients. Adverse drug events were the most frequent AEs, and non-ADEs were more critical than ADEs. Such data should be recognized among practicing physicians to improve the patients' outcomes.

Key Words: adverse drug event, adverse event, epidemiology, medical error, patient safety, cardiology

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Injuries due to medical care, referred to as adverse events (AEs), are an important medical issue because they place an additional burden on the health care system and are associated with symptoms ranging from slight illness to death. Vincent et al[1] have observed that AEs occur frequently, at the rate of 11% of hospitalized patients. In the U.S., adverse drug events (ADEs) have been reported to occur in 3.9 events of hospitalized cardiac patients per 100 patients.[2] Gandhi et al[3] found a higher incidence in a prospective cohort study of adult outpatients where 25 of 100 outpatients experienced ADEs in the U.S., which represent the most frequent cause of injury due to medical care in developed countries,[4,5] and implied that ADEs occur more frequently among outpatients than hospitalized patients.

Adverse events can be either preventable or unpreventable, and preventable AEs are associated with medical errors (MEs). In 2000, the Institute of Medicine (IOM) estimates that MEs kill between 44,000 and 98,000 people every year in U.S. hospitals.[6] James[7] reported updated estimate that a lower limit of 210,000 deaths per year was associated with preventable AEs in U.S. hospital. Phillips et al[8] reported that from 1983 to 1993, the number of outpatient visits in the U.S. increased by 75% and ME deaths rose 8.48-fold (from 172 to 1459).

However, studies of AEs among outpatients and studies using patient reporting of AEs are limited. Therefore, we conducted a cross-sectional survey using patient reporting of AEs among adult Japanese cardiovascular outpatients and investigated AEs and MEs during their hospitalization and ambulatory care.

METHODS

Study Design and Patients

We conducted a cross-sectional study at a Japanese teaching hospital equipped with electronic medical records and computerized physician ordering entry. The computerized physician ordering entry did not offer default doses and did not perform automatic checks for allergies or drug interactions.

We included all consecutive patients aged 18 years or older who visited the cardiovascular outpatient clinic of Kyoto University Hospital from February through November 2006. The cardiovascular outpatients include all outpatient visits, including initial consultation, examinations, and postoperative follow-up. Research assistants who were trained by the investigators in an identical manner conducted the survey using the questionnaire (Supplemental Digital Content 1, http://links.lww.com/JPS/A45) for each patient at the outpatient clinic. The patients reported AE and ADE for their entire medical history including the past hospital admission, which were both cardiac and noncardiac care. The research assistants reviewed the patients' medical records to confirm the potential incidents if reported. They also made telephone calls to the patients if any query needed to be clarified.

The institutional review board of Kyoto University Graduate School of Medicine approved the study, and informed consent was obtained from each patient.

Definitions

The primary outcome was AEs, defined as injuries due to medical care. The causes of all AEs were determined, and multiple

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causes were permitted. For example, hepatitis C virus infection after emergent blood transfusion against hemorrhage during an operation was considered to be associated with both a drug and an operation. Adverse events were classified by type, ADEs, and non-ADEs. Adverse drug events included AEs caused by medication use, and non-ADEs included decision-making AEs such as misdiagnosis, operation-related AEs, procedure-related AEs such as cardiac catheterization, and other AEs. For example, cough after receiving angiotensin-converting enzyme (ACE) inhibitors with no other apparent cause was considered an ADE due to medication use, whereas peripheral neuropathy after an operation with no other apparent cause was considered an operation-related AE. Although MEs can occur at any step of the medical process and may or may not cause AEs, for the purposes of this study, we considered AEs without MEs as unpreventable and those resulting from MEs as preventable because we assumed that AEs associated with MEs could have been prevented if the errors had been avoided or intercepted. For example, allergy due to an ACE inhibitor in a patient without a history of ACE inhibitor-induced allergic symptoms was not considered to be the result of a medication error but was considered a medication error if the patient had a history of such allergic symptoms. Minor errors in medication use that had little or no potential for harm, for example, when a dose of noncritical medication such as docusate was administered several hours late, were not considered potential ADEs, but rather medication errors. An error that had the potential for harm, for example, a dose of critical medication such as an intravenous antibiotic not being administered, was considered both a medication error and a potential ADE. A potential ADE was defined as a medication error with the potential to cause injury but did not actually do so either because of specific circumstances, chance, or because the error was intercepted and corrected, such as a prescription with an overdose of medication being written by the physician but then intercepted by the pharmacist.

Data Classification

The methods of data collection and classification were modified from a previous report.[9] We developed a questionnaire asking patients about their characteristics and any suspicions of AEs or MEs. They also inquired about the details of cardiovascular comorbidities as well as comorbidities listed in the Charlson comorbidity index.[10]

Two independent physician reviewers who were internists without the affiliation with study clinic had enough experience to review AEs and evaluated all incidents and classified them

TABLE 1. Patients' Characteristics

Variables	All (n = 759) n (%)	AEs (n = 124) n (%)	Non-AEs (n = 635) n (%)	*P*-value
Age, mean ± SD, years	65 ± 12	64 ± 13	65 ± 12	0.2
Sex				
Male	423 (56)	70 (56)	353 (56)	0.9
Medical history				
Hypertension	369 (49)	68 (55)	301 (47)	0.1
Myocardial infarction	93 (12)	18 (15)	75 (12)	0.4
Angina	176 (23)	32 (26)	144 (23)	0.5
Congestive heart failure	109 (14)	16 (13)	93 (15)	0.6
Arteriosclerosis	57 (8)	12 (10)	45 (7)	0.3
Cerebral infarction	41 (5)	5 (4)	36 (6)	0.5
Dyslipidemia	157 (21)	36 (29)	121 (19)	0.01
Diabetes	142 (19)	15 (12)	127 (20)	0.04
Osteoporosis	43 (6)	8 (6)	35 (6)	0.7
Lung disease	14 (2)	3 (2)	11 (1)	0.6
Gastric ulcer	82 (11)	19 (15)	63 (10)	0.08
Duodenal ulcer	41 (5)	6 (5)	35 (6)	0.8
Chronic hepatitis	23 (3)	7 (6)	16 (3)	0.06
Malignant tumor	122 (16)	30 (24)	92 (14)	0.01
Others	337 (44)	60 (48)	277 (44)	0.3
Outpatient visits to a doctor				0.5
>2 times/month	86 (11)	17 (14)	69 (11)	
2 times/month	80 (11)	18 (15)	62 (10)	
1 time/month	208 (27)	31 (25)	177 (28)	
1 time/2 months	115 (15)	16 (13)	99 (16)	
1 time/3-6 months	82 (11)	11 (9)	71 (11)	
<1 time/6 months	188 (25)	31 (25)	157 (25)	
Pre hospital admission	665 (88)	116 (94)	549 (86)	0.03
1–3 times	415 (62)	61 (53)	354 (64)	0.07
4–10 times	216 (32)	46 (40)	170 (31)	
≥10 times	8 (1)	3 (3)	5 (1)	
Unknown	26 (4)	6 (5)	20 (4)	

SD, standard deviation

according to whether they were AEs or MEs and judged whether they occurred in the outpatient or hospital setting. They considered the timing of symptoms and whether the patients attributed their symptoms to the medical care they received. The reviewers also classified AEs according to type, severity, and symptoms. Categories of severity were fatal, life threatening, serious, and significant.[9] Briefly, fatal AEs resulted in death; life-threatening AEs required successful cardiopulmonary resuscitation or transfer to intensive care and were anaphylactic shock or critical surgical events such as requiring cardiac reoperation. Serious AEs included gastrointestinal bleeding, altered mental status, excessive sedation, renal dysfunction, a decrease in blood pressure, and peripheral arterial embolism. Significant AEs included, for example, cases with peripheral neuropathy, rash, diarrhea, or nausea. Categories of symptoms were bleeding, central nervous system symptoms,allergic or skin reactions, metabolic or liver disorders, cardiovascular symptoms, gastrointestinal symptoms, kidney injury, respiratory system symptoms, bone marrow depression, and other. When the reviewers disagreed over the classification of an event, consensus was reached through discussion. Inter-rater reliability for reviewer judgments is calculated using percentage of agreement and the kappa statistic.[11] The percentage of agreement is calculated by dividing the number of agreed cases by the total cases. Kappa is calculated from ($Po - Pc$) / ($1 - Pc$), where Po = proportion of observed agreement and Pc = proportion of agreement expected by chance and ranges from −1 (complete disagreement) to +1 (perfect agreement). The significance of kappa are values less than 0 as indicating no agreement and 0 to 0.2 as slight, 0.21–0.4 as fair, 0.41–0.6 as moderate, 0.61–0.8 as substantial, and 0.81-1 as almost perfect agreement.

Statistical Analysis

For AE and ME, crude rates per 100 patients and their 95% confidence intervals (CIs) were calculated. Continuous variables are presented as mean with standard deviation (SD) values or median with interquartile ranges, and categorical variables are shown as numbers and percentages. Relationships between patients' demographics and AEs were assessed using the Student t test or the Wilcoxon rank sum test when the data were continuous or the χ^2 test when the data were categorical. To assess associations between ADEs and severity or durability, and setting and severity for AEs, ADEs, or non-ADEs, we used χ^2 test. We carried out all statistical analysis using JMP version 8 (SAS Institute Inc., Cary, NC). P values of less than 0.05 were considered statistically significant.

RESULTS

Among 1144 eligible patients, 846 (74%) agreed to participate, and valid questionnaire responses were collected from 759 (90%). Among these 759 patients, 423 (56%) were men and the mean age was 65 ± 12 years. Half of the patients had hypertension, and ischemic heart disease and dyslipidemia affected 35% and 21%, respectively. Twenty-seven percent of the patients visited outpatient clinics once a month. Six hundred sixty-five patients (88%) had a history of hospitalization, and 415 patients had been hospitalized less than 4 times (Table 1).

Adverse Events

The patients reported 225 potential incidents in the questionnaires. The kappa score regarding the presence of an AE between reviewers was 0.69. The reviewers identified 144 AEs in 124 patients, and the crude rate per 100 outpatients was 16.3% (95% confidence interval [CI], 13.9%–19.1%). Of the 144 AEs, 99 were solely ADEs, 20 were solely non-ADEs, and the remaining 25 were multiple causes (Table 2). Adverse events by type, including those classified as more than one type, were as follows: 120 ADEs (83%), 22 decision-making AEs (15%), 17 operation-related AEs (12%), 5 procedure-related AEs (3%), and 7 others (5%). Patients experienced 66 AEs (46%) during outpatient visits and 78 AEs (54%) during hospitalization. Among the 66 AEs that occurred during outpatient visits, 60 (91%) were ADEs. Among the 78 AEs that occurred during hospitalization, 60 (78%) were ADEs.

None of the AEs were fatal. Fifteen life-threatening AEs occurred in 13 inpatients and 2 in 1 outpatient (Table 3). There were solely 6 ADEs and solely 8 non-ADEs, and 3 multiple causes. Serious and significant AEs accounted for 41 and 86 AEs, respectively. Among the 41 serious AEs, 35 involved ADEs. Among the 86 significant AEs, 78 involved ADEs. Two life-threatening AEs (3%), 18 serious AEs (27%), and 46 significant AEs (70%) occurred during outpatient visits. Fifteen life-threatening AEs (19%), 23 serious AEs (29%), and 40 significant AEs (51%) occurred during hospitalization (Fig. 1). Non-ADEs were more severe than ADEs and longer failure than ADEs (Table 4). Among 144 AEs, 113 AEs (78%) resulted in transient injury and 31 AEs (22%) resulted in permanent injury or injury that compromised the patient's life.

Allergic or skin reactions were the most frequent symptoms followed by cardiovascular symptoms of all AEs and ADEs. Bleeding was the most frequent symptom followed by allergic

TABLE 2. Causes of AEs

	AEs (n = 144) n (%)	First Cause	Second Cause	Third Cause
Single cause	99 (69)	Drug		
	14 (10)	Operation		
	2 (1)	Procedure		
	4 (3)	Decision-making		
Two causes	1 (1)	Drug	Procedure	
	12 (8)	Drug	Decision making	
	6 (4)	Drug	Other	
	2 (1)	Operation	Decision making	
	2 (1)	Procedure	Decision making	
Three causes	1 (1)	Drug	Operation	Decision making
	1 (1)	Drug	Decision making	Other

TABLE 3. Details of Life-Threatening AEs (n = 17)

	Outpatient		Inpatient	
	Details	**No. of AEs**	**Details**	**No. of AEs**
ADEs	Anaphylactic shock	2	Anaphylactic shock	1
			Steven Johnson syndrome	2
			Loss of consciousness or syncope	2
Non-ADEs	Poor communication about drug with known allergy (multiple causes)	1	Syncope due to delayed diagnosis	1
			Bleeding requiring unexpected transfusion during operation (multiple causes)	6
			Surgical events such as suture failure and infection requiring reoperation	3
			Bleeding postcatheterization requiring operation (multiple causes)	2

or skin reactions and cardiovascular symptoms of non-ADEs (Table 5).

Medical Errors

We identified 30 MEs among 30 patients; the incidence rate was 3.9 (95% CI, 2.8%–5.6%) per 100 patients. Among the 30 MEs, 29 resulted in AEs, meaning that 20% of the 144 AEs were considered preventable. Among the 29 MEs with AEs, 4 MEs (14%) resulted in life-threatening AEs, 12 (41%) in serious AEs, and 13 (45%) in significant AEs. The other ME did not result in AE. This event was a medication error, which had the potential to harm the patient; however, this medication error was intercepted before the drug was administered. Among 30 MEs, 18 MEs (60%) were associated with drugs (Table 6). Fifteen MEs occurred during outpatient visits (50%) and 15 occurred during hospitalization (50%). Among the 15 MEs during outpatient visits, 8 were associated with drugs. Among the 15 MEs during hospitalization, 10 were associated with drugs.

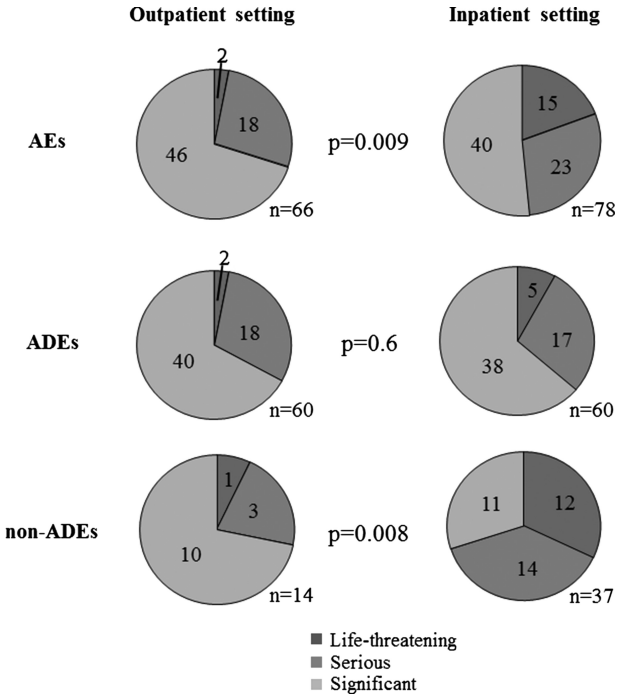

FIGURE 1. Severity of AEs, ADEs, and non-ADEs by setting. Some AEs were attributable to both ADEs and non-ADEs.

DISCUSSION

Studies concerning patient reporting of AEs were limited. Recently, efforts to use patient-reported information would be more important. Yelp[12] jointed with ProPublica are utilized and give consumers satisfaction with medical care. In the United States, a new system for patients to report medical mistakes was constructed. The Obama administration wants consumers to report medical mistakes and unsafe practices by doctors, hospitals, pharmacists, and others who provide treatment.[13] Thus, we considered this survey using the questionnaire for each patient at the outpatient clinic was patient-oriented outcome, and this survey was important.

We assessed the frequency of AEs and MEs in daily practice in Japan and found that they occur often and cause substantial harm. The crude rate of AEs was 16 per 100 outpatients, and 20% of AEs were associated with MEs. Among the 144 AEs, 120 (83%) were ADEs and 51 (35%) were non-ADEs including 17 surgical AEs (12%). Seven ADEs (6%) and 8 surgical AEs (47%) were life-threatening. Adverse drug events were more frequent in outpatients, and surgical AEs were the most dangerous. Although the symptoms among non-ADEs were different, the symptoms among ADEs were similar; allergic or skin reactions were the most frequent symptoms among all ADEs, followed by cardiovascular and gastrointestinal symptoms.

TABLE 4. Relationship Between AEs and Severity or Outcome

	ADEs (%)	**Non-ADEs (%)**	***P***
Severity			
Life threatening	7 (6)	13 (25)	0.0003
Serious	35 (29)	17 (33)	0.6
Significant	78 (65)	21 (41)	0.004
Outcome			
Transient injury	107 (88)	28 (55)	0.6
Permanent injury or injury that compromised the patient's life	13 (11)	23 (45)	0.004

TABLE 5. Symptoms of AEs

Symptoms	AEs (%)	Non-ADEs (%)	ADEs (%)	ADEs in Outpatient (%)	ADEs in Inpatient (%)
Bleeding	12 (8)	13 (25)	4 (3)	3 (5)	1 (2)
Central nervous system	11 (7)	4 (8)	11 (9)	2 (3)	9 (15)
Allergic or skin symptom	45 (31)	9 (18)	43 (36)	21 (35)	22 (36)
Liver disorder or metabolic disorder	10 (7)	2 (4)	9 (7)	2 (3)	7 (11)
Cardiovascular	26 (18)	9 (18)	22 (18)	13 (22)	9 (15)
Gastrointestinal	13 (9)	2 (4)	13 (11)	9 (15)	4 (7)
Kidney injury	1 (1)	0 (0)	1 (1)	1 (2)	0 (0)
Respiratory	5 (3)	0 (0)	5 (4)	4 (7)	1 (2)
Bone marrow depression	3 (2)	1 (2)	3 (2)	0 (0)	3 (5)
Others	18 (12)	11 (22)	9 (7)	5 (8)	4 (7)

Regarding the occurrence of AEs, a systematic review on hospitalized patients found a median rate of 9.2% for AEs and 43.5% for preventable AEs.[14] The occurrence of AEs approximately 20 years ago was fewer than it is now. The Harvard Medical Practice Study I showed 3.7% had AEs.[15] A 1992 study surveying 15,000 patients in Colorado and Utah reported that 3% of patients had AEs.[16] Updated estimate showed 13.5% of hospitalized patients had at least one AE. Overall, at least 44% of these events were judged as being preventable and 51% unpreventable.[17] Landrigan et al[18] reported that among 2341 admissions, internal reviewers identified 588 harms (25.1 harms per 100 admissions) and harms remain common. Merino et al[19] reported that 29% of hospitalized patients had AEs, with 62% not causing any harm. Among the no-harm events, 90% were classified as preventable AEs.

Although methodological differences between these studies and the current study made comparisons difficult, we believe the AE rate in the current study was generally similar to these other reports; however, our ME rate was lower. Because the first step of our methodology was a patient questionnaire, underestimating the incidence of MEs was inevitable. If patients were not aware of MEs that were intercepted or did not cause harm or symptoms, they could not report these in the questionnaire. Another reason why our rate of MEs was lower than that of other recent studies could be due to the increase in awareness of AEs among health care providers. Merino et al reported that the overall rate of AEs was 98% and although surgery-related incidents were few (3%), they were considered to be severe. Our results were consistent with those of Merino et al. Recently, several studies assessing strategies to avoid surgery-related AEs have been performed in the surgical setting and have reported that following interventions are effective in reducing surgical AEs.[20–24] Howell et al[25] reviewed interventions to reduce AEs such as increasing nursing staff, subspecialized services, checklists, team training, safety devices, and care pathways; our finding showing the common epidemiological characteristics of AEs may suggest that such interventions to reduce surgical AEs could be effective.

We showed the occurrence of AEs in the outpatient and hospital settings. The most frequent type of AEs was ADEs in both settings. The incidence of ADEs was the same in both settings, but life-threatening ADEs occurred more frequently in hospitals (8%) than in outpatient settings (3%). The Centers for Medicare and Medicaid services, Partnership for Patients program found that ADEs as the most common AE accounted for 43.8%.[26] The most frequent type of incident in the intensive care unit was also ADEs.[14] A systematic review of the incidence and nature of AEs in hospitalized patients reported that approximately 50% of AEs were surgery-related AEs (39.6%) or ADEs (15.1%).[14]

A systematic review studying ADEs in ambulatory care reported a prevalence of 12.8 per 100 outpatients.[27] Gandhi et al[14] reported that the incidence of ADEs was 27 per 100 outpatients. Cardiovascular agents such as beta-blockers, ACE inhibitors, and calcium-channel blockers were most frequently implicated in these ADEs. Studies from a U.S. ambulatory department reported that cardiovascular medications were the most commonly implicated ADEs.[28] Our results showed that the incidence of cardiovascular symptoms in the outpatient setting was higher than that in the hospital setting, and those cardiovascular symptoms were the second most frequent symptoms of ADEs. Elsewhere, Gandhi et al[29] reported that the most frequent symptoms of ADEs were gastrointestinal followed by sleep disturbances, fatigue, and mood change. Weingart et al[30] reported that the most frequent symptoms of ADEs were gastrointestinal followed by fatigue, dizziness, and rash or itching. We found that the most frequent symptoms of ADE were allergic or skin reactions followed by cardiovascular symptoms including dizziness, and gastrointestinal symptoms. If the patients were prescribed new antihypertensive agents and the physician detected hypotension or the patients recovered after self-cessation of them, we diagnosed the conditions of dizziness or fatigue as hypotension due to antihypertensive agents. Although our results were consistent with past reports, these symptoms were peculiar to cardiovascular outpatients.

Our study had several limitations. First, because the potential incidents were obtained from patient questionnaires and then verified by physicians, our results may not reflect incidents that occurred of which patients were unaware. In addition, we could

TABLE 6. Details of MEs

Causes	Type of Error	Medical Errors (n = 30) n (%)
Drug	Wrong action against the symptoms	11 (37)
	Different drug	2 (7)
	Ignoring interaction	1 (3)
	Wrong dose	1 (3)
	Omission	2 (7)
	Wrong route	1 (3)
	Drug with known allergy	1 (3)
Operation	Inappropriate operation	3 (10)
Procedure	Inappropriate procedure	5 (17)
Decision making	Misdiagnosis	4 (13)

not obtain potential incidents associated with fatalities; thus, we might have missed critical and severe AEs and MEs. Indeed, there were no fatal AEs in our study. Second, the patients were from a single cardiovascular clinic of a teaching hospital. Although the sample was sufficiently large to allow reasonably accurate estimates of AE and ME incidence, the results might not be generalizable to other settings. However, our results may be applicable to Japanese outpatients.

CONCLUSION

We showed that AEs were common among cardiology patients. Adverse drug events were the most frequent AEs, and non-ADEs were more critical than ADEs. Adverse events and non-ADEs were more severe in hospitalized patients than in outpatients. The proportion of MEs was significant, and most were related to medication use. Such data should be recognized among practicing physicians to improve the patients' outcomes.

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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

local data [12]. The lack of such basic data represents one of the barriers to implementing strategies to improve patient safety in ICUs, especially outside the West.

To address this knowledge gap, we evaluated the epidemiology of ADEs in the ICUs as well as their impact on morbidity and mortality. We analyzed the data of the Japan Adverse Drug Events (JADE) study, a multicenter cohort study [6], and we used the length of ICU stay as morbidity.

Methods

Study design and patient population

The JADE study was a prospective cohort study involving all adult patients aged ≥15 years who were admitted to three urban tertiary care hospitals in Japan from January through June 2004[6]. The present study was limited to the patients admitted to all ICUs in these hospitals. The total number of beds among the three ICUs was 32 including the medical and the surgical beds. Patients were followed until transfer, discharge or death. The institutional review boards of three participating hospitals approved the study. Informed consent was waived because all data were collected in the daily practice.

Data collection and classification

The data collection method was based on that described in previous reports [1, 6]. ADE was defined as any unintended injury due to a medication use regardless of existing errors [1, 13]. Investigators trained nurses and nursing students in a standard manner and placed them in the participating hospitals where they reviewed practice data such as charts, laboratories or prescription data. They collected demographic data for all patients on admission to the ICUs and identified ADEs.

Next, two independent physician reviewers evaluated all events and classified collected ADEs as ADEs or exclusion. Then, physician reviewers classified ADEs into 10 categories according to the symptoms as well as rated the severity of ADEs using a four-point scale. The categories of symptoms were bleeding, central nervous, allergic reaction, liver disorder, cardiovascular, gastrointestinal, renal, respiratory, bone marrow suppression, and sepsis. For example, symptoms of bleeding included anemia and gastrointestinal bleeding due to warfarin, antiplatelet agents or NSAIDs; central nervous symptoms included delirium and muscle weakness due to sedative agents; gastrointestinal symptoms included diarrhea, constipation, nausea and vomiting due to antibiotics or opiates; respiratory symptoms included nosocomial infections which could be related to the use of antibiotics. We defined nosocomial infections as a patient who had negative culture on admission became to have positive culture after use of antibiotics. Categories of severity were fatal, life-threatening, serious, and significant. Fatal ADEs resulted in death; life-threatening ADEs caused such issues as anaphylactic shock or cardiopulmonary arrest; serious ADEs included gastrointestinal bleeding, altered mental status, excessive sedation, increased creatinine or a decrease in blood pressure; and significant ADEs included cases with rash, diarrhea or nausea, for example. When disagreements affected the classification of an ADE and its severity, the physician reviewers reached consensus through discussion.

To assess the severity of patients on admission to ICUs, we used the sepsis-related organ failure assessment (SOFA) score, later called the sequential organ failure score because it is not restricted to sepsis, to evaluate the presence of organ dysfunctions objectively [14]. The SOFA score consists of six components of organ systems such as respiratory, coagulation, liver, cardiovascular, central nervous system and renal. Each organ system is evaluated using a score from 0 (normal) to 4 (most abnormal) depending on its severity. To evaluate the presence of each organ dysfunction in this study, we used the SOFA score. The presence of each organ dysfunction was defined as follows: respiratory dysfunction; PaO_2/FiO_2 ≤400 mmHg, coagulopathy; platelets ≤$150 \times 10^3/\mu l$, liver dysfunction; bilirubin ≥1.2 mg/dl, hypotension; mean arterial pressure <70 mmHg, unconsciousness; Glasgow Coma Scale ≤14, and renal dysfunction; creatinine ≥1.2 mg/dl.

Statistical analyses

The ADE incidence per 1000 patient-days and rates per 100 admissions were calculated. Continuous variables are presented as means with standard deviations (SDs) or medians with interquartile ranges, and categorical variables are shown as numbers and percentages. Relationships between patients' demographic data and ADEs were assessed using the Wilcoxon rank sum test when the data were continuous and the chi-square test when the demographic data were categorical. To assess associations between ADEs and mortality, we used the chi-square test. Because patients who died soon after admission had no chance to have an ADE, we did the same comparison eliminating patients who died within 3 days after admission to the ICUs. We used the *t*-test to compare the length of ICU stay between patients with ADEs and without ADEs during the ICU stay among those who were discharged from the ICU alive. We used a Cox proportional hazard model to estimate the hazard ratios (HRs) of ADEs for the risk of mortality along with 95% confidence intervals (CIs). We also used a linear regression model to assess the effects of the ADEs on the length of ICU stay. Both models were adjusted for age and the presence of organ dysfunctions such as respiratory, coagulopathy, liver, hypotension, unconsciousness and renal variables defined using the SOFA score. Patients with missing values for any selected variables were excluded from both analyses. We carried out all statistical analyses using the JMP 8.0 (SAS Institute Inc., Cary, NC). *P* values of <0.05 were considered to be statistically significant.

Results

We enrolled 459 admissions, accounting for a total of 3231 patient-days in the ICUs. Among the 459 patients, 290 (63%) were males and the mean age was 66 (SD 16) years; 60% were 65 years and older. The medical and the surgical ICUs admitted 263 (57%) and 196 (43%) patients, respectively. Of all admissions to the ICUs, 84% were emergent. The median

number of organ dysfunctions which patients suffered from on admission to the ICUs was 2 (inter-quartile range 1–3) and respiratory dysfunction was the most frequent (67%) followed by unconsciousness (46%) (Table 1).

Adverse drug events

We identified 99 ADEs in 70 patients (15%) for an incidence of 30.6 [95% CI 24.6–36.7] per 1000 patient-days and a rate per 100 admissions of 21.6 [95% CI 17.9–25.6]. The median day of the ADE onset after admission was 3 days.

Table 1 Demographic data in study population

	Total (n = 459)
Age, ≥65 (years) (n, %)	276 (60)
Male (n, %)	290 (63)
Departments (n, %)	
Medicine	263 (57)
Surgery	196 (43)
Admission pathway (n, %)	
Scheduled admission	75 (16)
Emergency admission	384 (84)
Principal reason for admission to unit (n, %)	
Cardiac disorders	136 (30)
Vascular disorders	49 (11)
Respiratory disorders	59 (13)
Neurological disorders	50 (11)
Kidney disorders	29 (6)
Gastrointestinal disorders	19 (4)
Trauma	32 (7)
Intoxication	5 (1)
Metabolic disorders	5 (1)
Others	75 (16)
Organ dysfunction on admission (n, %)	
Respiratory disorders (PaO_2/FiO_2 ≤400 mmHg)	306 (67)
Coagulopathy (platelets ≤150 × 10^3/μl)	88 (19)
Liver dysfunction (bilirubin ≥1.2 mg/dl)	73 (17)
Hypotension (mean arterial pressure <70 mmHg)	79 (17)
Unconsciousness (Glasgow Coma Scale ≤14)	211 (46)
Renal dysfunction (creatinine ≥1.2 mg/dl)	152 (33)
Temperature (centigrade degrees) (mean, SD)	36.6 (0.9)
History of allergy (n, %)	21 (5)
Past history and statement (n, %)	
Heart failure, NYHA = 4	253 (55)
Home oxygen therapy	17 (4)
Hemodialysis	64 (14)
The number of medications on admission (median, quartile)	5 (4–7)
Length of experienced years of a doctor in charge (median, quartile)	8 (4–16)

NYHA, New York Heart Association.

Among the 70 patients who had at least one ADE, 49 patients (70%) were 65 years and older and 21 patients (30%) were under 65, and 51 patients (73%) admitted urgently to the ICU and 19 patients (27%) did not. There was a trend for those 65 years and older to have a higher rate of ADEs compared with younger patients though this difference was not statistically significant (P = 0.07). Those admitted urgently to the ICU had a higher risk of ADEs (P = 0.008). The median age of the physician's experience among the doctors in charge who cared for patients with ADE was 6 years (inter-quartile range 3–13) while that without ADEs was 9 years (inter-quartile range 4–16). Thus, having a less experienced physician as the doctor in charge increased the ADE risk compared with having a senior physician (P = 0.01). Having organ dysfunction of any type at ICU admission was not associated with a higher risk of having an ADE (Figs 1 and 2). The number of medications on admission was also not significantly correlated with having an ADE [median 5 (inter-quartile range 3–7) vs. 5 (4–8); P = 0.7] though the median of the number of medications administered within the 24 h before an ADE was 11 (inter-quartile range 6–14).

Seven fatal or life-threatening ADEs occurred in 7 patients, which accounted for 7% of the 99 ADEs. Fatal or life-threatening ADEs included nosocomial infections caused by antibiotic use and shock associated with omitted vasopressor use. Serious ADEs and significant ADEs accounted for 34 and 59% of all ADEs, respectively.

Liver disorders and gastrointestinal disorders were the most frequent types of ADEs, accounting for 29% of all ADEs, respectively (Table 2).

Influence of ADEs on mortality and morbidity

Among the 459 patients admitted to the ICU, 73 patients (16%) died during their ICU stay. The mortalities of patients with ADE and without ADE were 17% (12/70) and 16% (61/389), respectively (P = 0.8). Among the 73 deaths, 38 died within 3 days of admission to the ICU. After excluding those 38 deaths, 12 deaths occurred among 70 patients (17%) who had at least one ADE during their ICU stay and 23 deaths (7%) occurred among 351 patients who had no ADEs during their ICU stay (P = 0.003). A Cox proportional hazard model showed that ADEs did not increase the mortality in the ICUs after adjusting for age and organ dysfunction status (HR: 0.7; 95% CI: 0.3–1.5) (Table 3).

Among the remaining 386 patients after excluding 73 patients who died during their ICU stay, the median ICU stay of those who had at least one ADE was 13 days (inter-quartile range: 6–20), while 2 days (inter-quartile range: 1–6) in those who had no ADEs (P < 0.0001). A linear regression model for the length of ICU stay showed that ADEs significantly increased the length of ICU stay, even after adjusting for age and organ dysfunction status (Table 3).

Discussion

We found that the presence of an ADE was associated with longer ICU stay consistent with previous studies [11, 15].

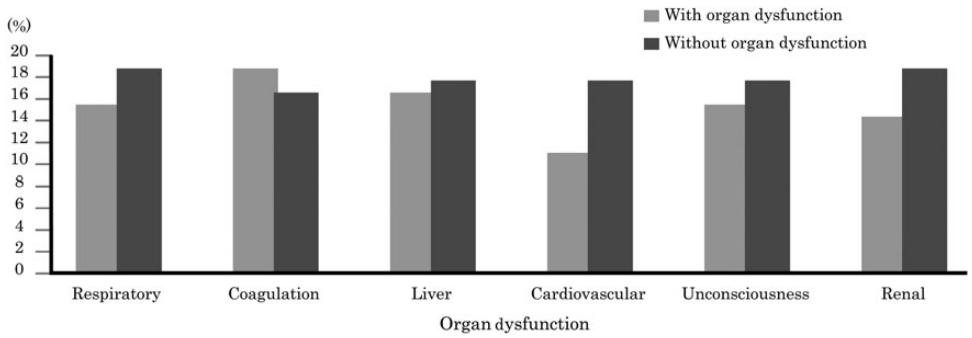

Figure 1 Comparison of the ratio of patients who had at least one ADE during their ICU stay between those who had any organ dysfunction and those without organ dysfunction.

After adjusting for the severity of illness and age, ADEs were still associated with a 10-day longer ICU stay. One interpretation of this result could be that patients with a longer ICU stay were more likely to experience an ADE. However, the median day of onset of ADEs after admission was 3 and the median length of ICU stay among those who had no ADEs was 2. This result suggests that ADEs increased the length of ICU stay rather than that longer ICU stays cause more ADEs, although both could play a role.

ADEs were not associated with increased mortality, although we had limited power to identify such an association. There were three deaths judged to be due to an ADE in this study, all of which were nosocomial infections associated with antibiotic use. Determination of cause is complex in such cases, but many such deaths have been reported previously; for example one study found that nosocomial infections in ICUs contributed to two fatal adverse events [8] and another study reported that nosocomial infections accounted for 24% of the adverse events identified in ICUs [16]. These results suggest that nosocomial infections are especially hazardous in critically ill patients.

We found that ADEs were common in ICUs in Japan, and the incidence of ADEs in ICUs was twice the rate of 16.2 per 1000 patient-days in the general wards [6]. These results were generally similar to previous studies from other countries. For example, Rothschild *et al.* [8] reported in a US study that the incidence of ADEs was 37.6 per 1000 patient-days, and Cullen *et al.* reported in another study from the USA that patients in ICUs experienced a higher rate of ADEs than non-ICU patients [9]. These results suggested that critically ill patients in ICUs are vulnerable to ADEs.

Among the factors contributing to this risk in ICU patients are likely organ dysfunction of a variety of types, the complexity of underlying disease in these patients, and the high number of medications and high-risk interventions they receive [8, 11]. Seynaeve *et al.* [17] reported that the severity of patients in ICUs was strongly associated with ADEs: the mean SOFA score was significantly higher on days when ADEs occurred than on days without ADEs (10 vs. 8). In our study, organ dysfunctions defined using the SOFA score were not related to

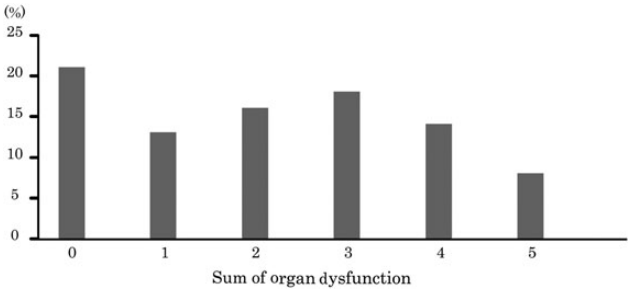

Figure 2 The percentage of patients who had at least one ADE according to the total number of organs dysfunctioning.

Table 2 Types of ADEs

Symptoms	ADEs (%)
Bleeding	5 (5)
Central nervous system	2 (2)
Allergic reaction	20 (20)
Liver disorder	29 (29)
Cardiovascular	7 (7)
Gastrointestinal	29 (29)
Kidney injury	2 (2)
Respiratory	2 (2)
Marrow depression	2 (2)
Sepsis	1 (1)

ADEs, adverse drug events.

ADEs. This could be because our assessment of the patients' severity was not sensitive enough to detect the relationship with ADEs. Because this study was based on the JADE study, which was done in both ICUs and non-ICUs, we did not perform a detailed severity assessment beyond the SOFA. Other studies have reported that a higher number of medications administered is associated with a higher ADE rate; one

Table 3 The influence of ADEs on mortality and morbidity

Variables	Mortality		Morbidity	
	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted coefficient (95% CI)	Adjusted coefficient (95% CI)
ADE	0.7 (0.3 to 1.4)	0.7 (0.3 to 1.5)	10.6 (8.0 to 13.1)	10.2 (7.6 to 12.8)
Age (≥65)	0.9 (0.4 to 2.1)	1.0 (0.5 to 2.4)	2.5 (0.5 to 4.4)	1.9 (−0.02 to 3.9)
Respiratory disorders (PaO_2/FiO_2 ≤400 mmHg)	2.6 (1.2 to 6.6)	2.4 (1.0 to 6.1)	−1.3 (−3.3 to 0.7)	−1.4 (−3.4 to 0.7)
Coagulopathy (platelets $\leq 150 \times 10^3/\mu l$)	1.3 (0.6 to 2.7)	1.0 (0.4 to 2.3)	0.8 (−1.7 to 3.4)	0.8 (−1.8 to 3.4)
Liver dysfunction (bilirubin ≥1.2 mg/dl)	1.7 (0.7 to 3.5)	1.6 (0.7 to 3.6)	−0.7 (−3.5 to 2.2)	−0.4 (−3.2 to 2.4)
Hypotension (mean arterial pressure <70 mmHg)	1.7 (0.6 to 4.1)	1.2 (0.4 to 3.0)	0.2 (−3.3 to 3.8)	0.3 (−3.2 to 3.8)
Unconsciousness (Glasgow Coma Scale ≤14)	2.6 (1.3 to 5.6)	1.9 (0.9 to 4.3)	−0.2 (−1.8 to 2.1)	0.2 (−1.8 to 2.3)
Renal dysfunction (creatinine ≥1.2 mg/dl)	1.6 (0.8 to 3.0)	1.4 (0.7 to 2.9)	0.6 (−1.6 to 2.8)	1.0 (−1.2 to 3.1)

HR, hazard ratio; CI, confidence interval; ADE, adverse drug event.

showed the correlation using a database during a certain period where ADEs increased when more medications were used and another study showed that the number of medications used the month before admission was associated with ADEs [10, 18]. In our study, the number of medications administered on admission was not significantly correlated with having an ADE; however, the number of medications administered within the 24 h before an ADE was 11 and it was higher than 5, which was the number of medications administered on ICU admission. Even though the number of medications among those without ADEs was not assessed, this finding might address the issue that the more medications administered would be related to higher risk of an ADE. Though we assessed the relationship between patients' demographic data evaluated on admission to ICUs and ADEs, only several factors such as urgent admission and the length of experienced year of physicians in charge were associated with a higher ADE rate. Our results suggested that early prediction and prevention of ADEs simply by assessing the patients' demographic status evaluated on admission would likely not produce groups of sufficiently varying risk to be an effective approach.

This study has several limitations. First, 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 have not yet been developed, so that the approach we used is the current standard one. Secondly, our data may not be sensitive enough to evaluate the characteristics or severity of critically ill patients because the JADE study did not focus on ICUs; thus, we evaluated the presence of organ dysfunction using the original SOFA score.

In conclusion, we found that ADEs were common and occurred to patients regardless of the presence of organ dysfunction in ICUs in Japan. ADEs were significantly associated with the length of stay though not related to mortality. Earlier detection of ADEs with close monitoring might improve the morbidity in ICUs.

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Conflict of interest

D.W.B. 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.

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