Frequency and Severity of Adverse Drug Events by Medication Classes: The JADE Study

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Objective: Adverse drug events (ADEs) are a significant concern in daily practice; however, the profile of high-risk drugs remains unclear. Our objective was to categorize high-risk medication classes according to frequency and severity of ADEs.

Methods: The JADE study is a prospective cohort study of 3459 hospitalized adult patients. We investigated the ADEs and medications prescribed to the patients. The rate of ADEs for each medication class was calculated by dividing the number of ADEs by the number of patients who received each medication class on admission.

Results: Overall, 14,435 medications were ordered on admission for patients (median 4; interquartile range, 2–6). Electrolytes and fluids were most frequently prescribed (1876 patients, 54%). Sedatives, antibiotics, peptic ulcer drugs, and analgesics were also commonly prescribed. The frequency was similar in both elderly and younger patients. Among 1010 identified ADEs, antibiotics were most frequently associated with ADEs (31 ADEs per 100 prescribed patients on admission). In patients 65 years and older, corticosteroids, anticonvulsants, laxatives, nonsteroidal anti-inflammatory drugs, and antipsychotics were the 5 most frequent medication classes causing ADEs following antibiotics. In patients younger than 65 years, antibiotics were also the most frequent cause of ADEs, followed by laxatives, lipid-lowering agents, anticonvulsants, and corticosteroids. Among cardiovascular agent-associated ADEs, 46% were fatal or life threatening in elderly patients, whereas antihypertensives were most often associated with fatal or life-threatening ADEs (25%) in younger patients.

Conclusions: The medication classes frequently associated with ADEs did not necessarily induce severe ADEs.

Key Words: adverse drug events, epidemiology, patient safety, risk

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The appropriate use of medication is an essential element in health care; however, medications may induce adverse drug events (ADEs), which are associated with a substantial increase in morbidity and mortality.[1–3]

Bates et al[3] reported that the ADE rate was 6.5 per 100 admissions. We also identified that the ADE rate was 29.2 per 100 admissions and 17.0 per 1000 patient-days.[4] Furthermore, a statistical brief from the Healthcare Cost and Utilization Project, sponsored by the Agency for Healthcare Research and Quality, reported that there was a 52% increase in ADEs in inpatient settings from 2004 and 2008.[5] In addition, they found that the mortality rate among inpatients with an ADE in the hospital was 3%, which was significantly higher than the rate for all stays (2%).[5] Moore et al[6] also reported that reported serious ADEs increased 2.6-fold, and fatal ADEs increased 2.7-fold from 1998 to 2005 using the adverse event reporting system from the US Food and Drug Administration. Thus, ADEs are becoming common and are more frequent and severe than previously reported. However, the risk of ADEs is not equal among all medications in clinical use. Budnitz et al[7] showed that most acute and serious ADEs are caused by a relatively small number of medications among ambulatory elderly adults. Furthermore, the Institute for Safe Medication Practice has identified a number of medications as "high-alert" medications.[8]

The risk and impact of ADEs on patients differ across medications. To improve the safety of medication use, the frequency and severity of ADEs should be assessed according to medication classes, and providing these data to health care professionals should be important. By increasing the awareness of ADEs, physicians can select the appropriate medications by considering the risk profile, and nurses can better monitor for new ADE symptoms in patients. Thus, we investigated the frequency and severity of ADEs according to medication classes.

METHODS

Study Design and Patient Population

The JADE study is a prospective cohort study that was conducted at 3 tertiary care teaching hospitals in Japan to estimate the incidence of ADEs and medication errors in Japanese adult inpatients.[4] In the JADE study, we randomly selected 7 medical wards and 8 surgical wards from a total of 26 adult medical wards and 30 surgical wards at the 3 participating hospitals. We also included all 3 intensive care units (ICUs). This study included 3459 patients aged 15 years and older who were admitted to the 15 medical and surgical wards and 3 ICUs during the 6-month research period. We considered 1 admission during the study period as 1 patient, regardless of whether it was a readmission or new admission. The institutional review boards of the 3 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.

Definition of ADEs and Data Collection Process

In accordance with previous studies, an ADE was defined as any injury caused by medication use, regardless of medication errors.[4,9]

The data collection and review process were previously reported.[9] Trained research assistants based at each participating hospital reviewed all medical charts, along with laboratories, incident reports, and prescription queries. They collected administrative data, including details of the medications prescribed by a physician in charge on admission, by considering each patient's medical condition. Medications were classified into 24 classes. Research assistants identified ADEs and collected medication details that were related to ADEs, including the name, dose, route, and class of medication. Independent physicians reviewed all collected data and determined whether the ADEs collected by the research assistants were ADEs or exclusions. All determinations were based on the Naranjo algorithm, the established scale for determining the likelihood of whether an ADE was caused by a particular medication, as well as on published reports that showed an association between a particular medication and an ADE.[9]

They also rated ADEs according to the severity of injuries using a 4-point scale: fatal, life-threatening, serious, and significant. To clarify, fatal ADEs resulted in death; life-threatening ADEs caused ICU transfers or anaphylactic shock; 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.

Interrater reliability was assessed using κ statistics. The κ scores for ADE presence between reviewers were 0.75 (ADE versus potential ADE or exclude) and 0.77 (exclude versus ADE or potential ADE). The κ scores for severity were 0.31 (life threatening versus serious or significant) and 0.64 (significant versus serious or life threatening).[4]

Statistical Analyses

The primary units of analyses were the number of medications and ADEs. Medications included both those that were prescribed to patients on admission and those that were associated with an ADE. We estimated the rate of ADEs per 100 patients for each medication class using the number of ADEs in each medication class as a numerator and the number of patients to whom each medication class was prescribed on admission as a denominator.

The trend test was performed to assess the difference in ADE severity between elderly patients and younger patients. We divided patients into 2 groups: those 65 years and older (elderly

TABLE 1. Adverse Drug Events and Medication Classes

	All Patients			Elderly Patients (≥65 y)			Younger Patients (<65 y)		
Medication Classes	**No. Patients***	**No. ADEs**	**Rates of ADEs†**	**No. Patients***	**No. ADEs**	**Rates of ADEs†**	**No. Patients***	**No. ADEs**	**Rates of ADEs†**
Electrolytes and fluids	1876	27	1	1130	23	2	746	4	1
Sedatives	1406	87	6	867	71	8	539	16	3
Antibiotics	1167	365	31	754	275	36	413	90	22
Peptic ulcer drugs	1130	40	4	722	33	5	408	7	2
Analgesics	1083	49	5	651	30	5	432	19	4
Antihypertensives	856	52	6	637	44	7	219	8	4
NSAIDs	826	78	9	478	54	11	348	24	7
Cardiovascular agents	631	14	2	448	11	2	183	3	2
Laxatives	598	73	12	433	54	12	165	19	12
Diuretics	495	20	4	344	14	4	151	6	4
Anticoagulants	395	30	8	293	23	8	102	7	7
Antidiabetics	375	12	3	255	8	3	120	4	3
Corticosteroids	244	32	13	136	21	15	108	11	10
Antipsychotics	217	22	10	141	16	11	76	6	8
Lipid-lowering agents	192	14	7	135	8	6	57	6	11
Antiasthmatics	176	7	4	119	5	4	57	2	4
Muscle relaxants	111	0	0	68	0	0	43	0	0
Antihistamines	110	1	1	74	1	1	36	0	0
Anticonvulsants	105	13	12	59	8	14	46	5	11
Antiarrhythmics	97	2	2	77	1	1	20	1	5
Antitumor agents	84	26	31	44	11	25	40	15	38
Antiparkinson drugs	52	0	0	44	0	0	8	0	0
Antidepressants	39	3	8	21	2	10	18	1	6
Experimental drugs	3	1	33	2	0	0	1	1	100
Others	2167	42	2	1424	33	2	743	9	1
Total	14,435	1010	—	9356	746	—	5079	264	—

*The number of patients to whom each medication class was prescribed on admission.

†The number of ADEs per 100 patients to whom each medication class was prescribed on admission.

NSAIDs, nonsteroidal anti-inflammatory drugs.

TABLE 2. Severity of ADEs in Each Medication Class

	All Patients				Elderly Patients (≥65 y)				Younger Patients (<65 y)			
Medication Classes	**No. ADEs**	**Fatal and Life-Threatening (%)**	**Serious (%)**	**Significant (%)**	**No. ADEs**	**Fatal and Life-Threatening (%)**	**Serious (%)**	**Significant (%)**	**No. ADEs**	**Fatal and Life-threatening (%)**	**Serious (%)**	**Significant (%)**
Electrolytes and fluids	27	0 (0)	1 (4)	26 (96)	23	0 (0)	1 (4)	22 (96)	4	0 (0)	0 (0)	4 (100)
Sedatives	87	15 (17)	67 (77)	5 (6)	71	11 (16)	57 (80)	3 (4)	16	4 (25)	10 (63)	2 (13)
Antibiotics	365	17 (5)	85 (23)	263 (72)	275	16 (6)	67 (24)	192 (70)	90	1 (1)	18 (20)	71 (79)
Peptic ulcer drugs	40	0 (0)	12 (30)	28 (70)	33	0 (0)	10 (30)	23 (70)	7	0 (0)	2 (29)	5 (71)
Analgesics	49	8 (16)	13 (27)	28 (57)	30	5 (17)	10 (33)	15 (50)	19	3 (16)	3 (16)	13 (68)
Antihypertensives	52	7 (13)	22 (42)	23 (44)	44	5 (11)	19 (43)	20 (46)	8	2 (25)	3 (38)	3 (38)
NSAIDs	78	2 (3)	39 (50)	37 (47)	54	1 (2)	31 (57)	22 (41)	24	1(4)	8 (33)	15 (63)
Cardiovascular agents	14	5 (36)	5 (36)	4 (29)	11	5 (46)	4 (36)	2 (18)	3	0 (0)	1 (33)	2 (67)
Laxatives	73	0 (0)	0 (0)	73 (100)	54	0 (0)	0 (0)	54 (100)	19	0 (0)	0 (0)	19 (100)
Diuretics	20	2 (10)	13 (65)	5 (25)	14	2 (14)	9 (64)	3 (21)	6	0 (0)	4 (67)	2 (33)
Anticoagulants	30	0 (0)	15 (50)	15 (50)	23	0 ()	13 (57)	10 (44)	7	0 (0)	2 (29)	5 (71)
Antidiabetics	12	1 (8)	5 (42)	6 (50)	8	1 (13)	3 (38)	4 (50)	4	0 (0)	2 (50)	2 (50)
Corticosteroids	32	0 (0)	16 (50)	16 (50)	21	0 (0)	10 (48)	11 (52)	11	0 (0)	6 (55)	5 (46)
Antipsychotics	22	5 (23)	12 (55)	5 (23)	16	4 (25)	9 (56)	3 (19)	6	1 (17)	3 (50)	2 (33)
Lipid-lowering agents	14	0 (0)	3 (21)	11 (79)	8	0 (0)	2 (25)	6 (75)	6	0 (0)	1 (17)	5 (83)
Antiasthmatics	7	1 (14)	2 (29)	4 (57)	5	1 (20)	2 (40)	2 (40)	2	0 (0)	0 (0)	2 (100)
Muscle relaxants	0	0 (0)	0 (0)	0 (0)	0	0 (0)	0 (0)	0 (0)	0	0 (0)	0 (0)	0 (0)
Antihistamines	1	0 (0)	1 (100)	0 (0)	1	0 (0)	1 (100)	0 (0)	0	0 (0)	0 (0)	0 (0)
Anticonvulsants	13	0 (0)	7 (54)	6 (46)	8	0 (0)	6 (75)	2 (25)	5	0 (0)	1 (20)	4 (80)
Others	42	2 (5)	8 (19)	32 (76)	33	1 (3)	8 (24)	24 (73)	9	1 (11)	0 (0)	8 (89)

NSAIDs, nonsteroidal anti-inflammatory drugs.

patients) and those younger than 65 (younger patients). The ratio of fatal or life-threatening ADEs among all ADEs for each medication class was also assessed to identify the severity of ADEs for each medication class. All analyses were performed using JMP 10.0 (SAS Institute Inc, Cary, NC) software.

RESULTS

Among 3459 patients included in the JADE study, 1958 (57%) were male, and 62% were 65 years and older. In total, there were 59,439 patient-days, and the median hospital stay was 10 days (interquartile range, 4–19 days).

Overall, 14,435 medications were ordered on admission for the 3459 patients (median, 4; interquartile range, 2–6). Among these, 9356 medications (65%) were prescribed to elderly patients. Electrolytes and fluids were most frequently prescribed on admission (1876 patients, 54%). Sedatives, antibiotics, peptic ulcer drugs, and analgesics were also commonly prescribed on admission (Table 1). The 5 most frequently prescribed medication classes were the same in both elderly and younger patients.

During the study period, we identified 1010 ADEs, among which 74% (746/1010) occurred in elderly patients. Antibiotics were most frequently associated with ADEs among medications prescribed to more than 100 patients, accounting for 36% of all ADEs. Of the 1167 patients who had an antibiotic prescription on admission, 365 antibiotic-related ADEs occurred. The rate of antibiotic-related ADEs was 31 per 100 patients (Table 1). In elderly patients, corticosteroids, anticonvulsants, laxatives, nonsteroidal anti-inflammatory drugs, and antipsychotics were the 5 most frequent classes of prescribed medication following antibiotics. In younger patients, laxatives, lipid-lowering agents, anticonvulsants, corticosteroids, and antipsychotics were the 5 most frequent classes after antibiotics (Table 1).

Forty-six percent of ADEs caused by cardiovascular agents were fatal or life threatening in elderly patients. In contrast, antihypertensives and sedatives were more often associated with fatal or life-threatening ADEs in younger patients (Table 2).

Overall, elderly patients were more likely to have severe ADEs than younger patients. Fatal or life-threatening ADEs accounted for 6.4% and 4.9% in elderly and younger patients, respectively, whereas serious ADEs accounted for 32.7% and 25.0% of ADEs, respectively ($P = 0.0007$, trend test, Fig. 1). Antibiotics were the most common cause of ADEs (36.5/100 patients); however, a low proportion of these ADEs were fatal or life threatening (6 fatal or life-threatening ADEs/100 ADEs). In contrast, cardiovascular agents caused fewer ADEs (2.5 ADEs/100 patients), but the proportion of fatal or life-threatening ADEs was high (46 fatal or life-threatening ADEs/100 ADEs) in elderly patients (Fig. 2A). In younger patients, no medications were categorized into the high frequency group, and the number of medications that caused fatal or life-threatening ADEs was less than those in elderly patients (Fig. 2B).

DISCUSSION

We found that the most common causes of ADEs were antibiotics, corticosteroids, and laxatives and that this ranking was fairly similar in both the elderly and younger patients. In contrast, the most common causes of fatal or life-threatening ADEs differed between elderly and younger patients. Cardiovascular agents and antipsychotics were most strongly associated with fatal or life-threatening ADEs in elderly patients, whereas antihypertensives and sedatives were the most strongly associated in younger patients. Thus, some medication classes caused more ADEs, which tended to be of lower severity, and other classes caused fewer ADEs, but their severity was much higher.

The statistical brief by the Healthcare Cost and Utilization Project reported that the overall rate of ADEs during hospital stays in 32 US states in 2011 was 129 per 10,000 discharges.[10,11] The most commonly identified causes were antibiotics and anti-infective agents, which caused ADEs at a rate of 36.1 per 10,000 discharges. These accounted for 28% of all ADEs, followed by nonspecific ADEs, hormones, and analgesics.[10] In another study, Bates et al[3] reported that analgesics and antibiotics were most often associated with ADEs. Analgesics accounted for 30%, whereas antibiotics accounted for 24% of all ADEs in inpatients. The high frequency of ADEs caused by certain types of medication could reflect the frequent prescription of such medications, which was not taken into account in either report; however, both reports showed a trend wherein antibiotics were the most common medication class associated with ADEs, consistent with our results.

Bates et al[3] also reported that 13% of all ADEs identified in inpatients were fatal or life threatening. Another study by Moore et al[6] showed that fatal ADEs increased 2.7-fold in an 8-year period and that opioid analgesics and antipsychotics were most frequently administered in fatal ADEs. Thus, fatal or life-threatening ADEs were more common in those studies. Not all medications in

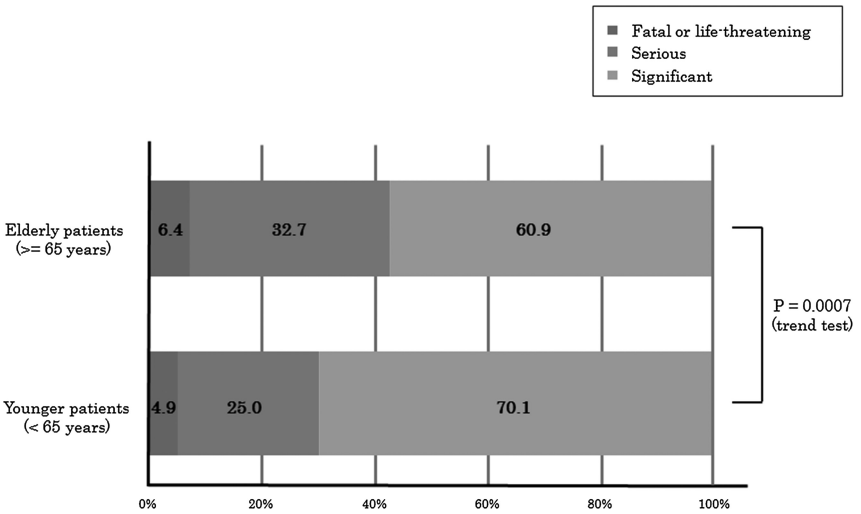

FIGURE 1. Comparison of ADE severity between elderly and younger patients.

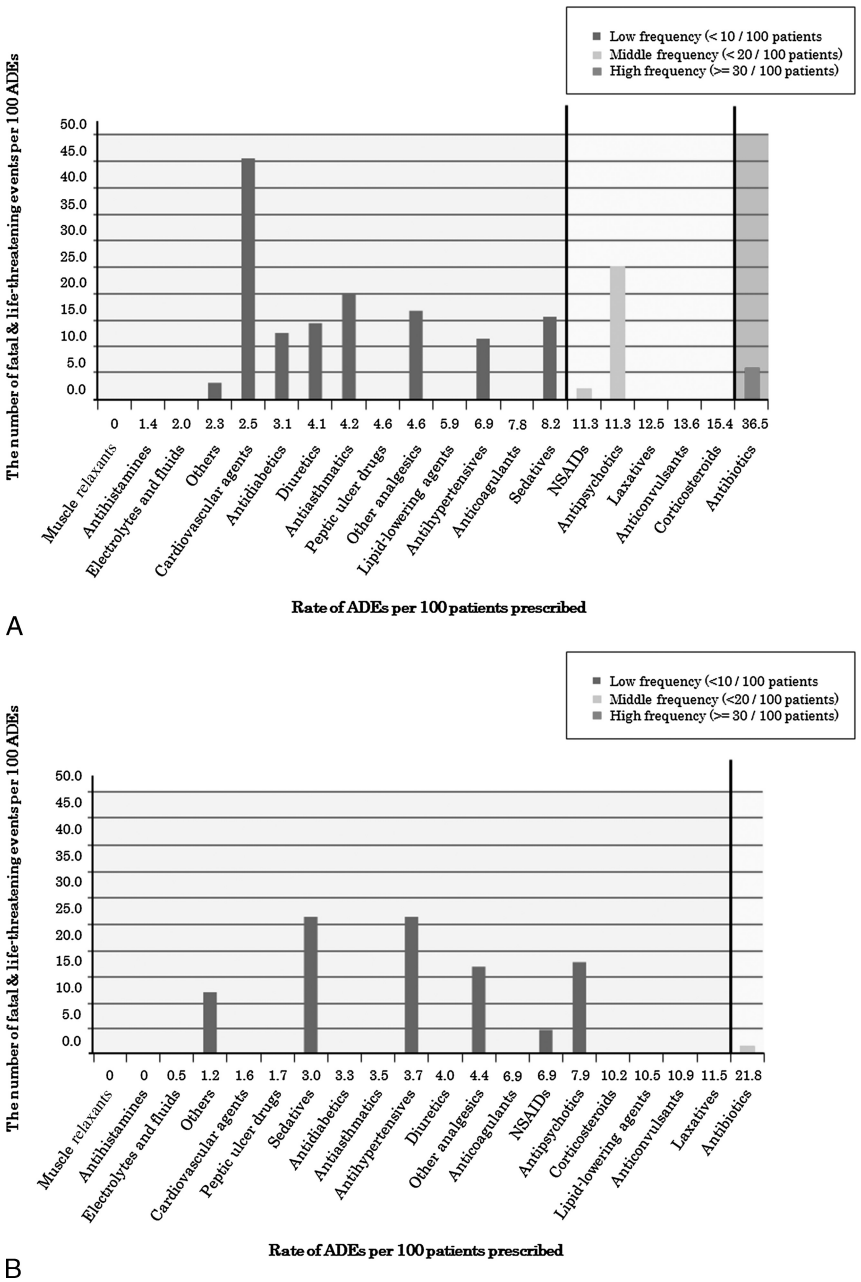

FIGURE 2. Frequency of ADEs and the rate of severe ADEs for each medication class. A, Elderly patients. B, Younger patients.

clinical use have an equal risk or health impact in patients. Moore et al[6] showed that among 467,809 ADEs reported to the US Food and Drug Administration over 8 years, 20% of all medications induced 87% of all ADEs. Our results also show that fatal or life-threatening ADEs were caused by a relatively small number of medications. Therefore, considering both the frequency and severity of ADEs is important to evaluate the risk and impact on inpatients in each medication classes.

Because this study was conducted in a real-world setting, the identified ADEs could reflect actual clinical practice, where patients have multiple comorbidities and are exposed to polypharmacy. In contrast, selected ADEs were reported in premarketing trials or postmarketing surveys, and the medications used were limited.[12–15] A detailed analysis of ADEs in real-world settings could increase the awareness of health care professionals when administering medication use and monitoring ADEs. Appropriate medications could be prescribed by physicians, and more careful and effective monitoring could be performed. Furthermore, our results could have applications for the development of decision support systems to alert health care professionals when prescribing high-risk medications or monitoring patients administered high-risk medications.

Our study has several limitations. First, we estimated the rate of ADEs in each medication class by calculating the number of patients who received each medication class as denominator. Second, some ADEs may not have been noted in the charts and were therefore missed. In addition, some ADEs might be related to multiple medications. However, other robust alternatives to measure

ADEs and determine the medication have not yet been developed; therefore, our methodology to detect ADEs and the medication represents the current standard. Finally, because this study was conducted at urban tertiary care hospitals in Japan, the trend of medication use may differ from other settings.

CONCLUSIONS

We identified the medication classes that are highly associated with ADEs and those that are more likely to result in more severe ADEs. Knowing which medication classes have higher risks for ADEs could help health care professionals make more cautious medication choices and improve monitoring.

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