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Prevalence of hospitalisation caused by adverse drug reactions at an internal medicine ward of a single centre in Japan: a cross-sectional study

Junpei Komagamine, Masaki Kobayashi

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Internal Medicine, National Hospital Organization Tochigi Medical Center, Utsunomiya, Japan

Correspondence to
Dr Junpei Komagamine; junpei0919@yahoo.co.jp

ABSTRACT

Objectives Few studies have investigated the prevalence of adverse drug reactions (ADRs) leading to hospitalisation in Japan. The aim of this study was to determine the prevalence of ADRs leading to hospitalisation and to evaluate the preventability of these ADRs in Japan.

Design A single-centre cross-sectional study using electronic medical records.

Setting Acute care hospital.

Participants All 1545 consecutive hospital admissions to an internal medicine ward due to acute medical illnesses from April 2017 to May 2018. The median patient age was 79 years (IQR 66–87), and the proportion of women was 47.9%.

Outcome measures The primary outcome was the proportion of hospitalisations caused by ADRs among all hospitalisations. All suspected cases of ADRs were independently evaluated by two reviewers, and disagreements were resolved by discussion. The causality assessment for ADRs was performed by using the WHO-Uppsala Monitoring Committee criteria. The contribution of ADRs to hospitalisation and their preventability were evaluated based on the Hallas criteria.

Results Of the 1545 hospitalisations, 153 hospitalisations (9.9%, 95% CI 8.4% to 11.4%) were caused by 200 ADRs. Cardiovascular agents (n=46, 23.0%), antithrombic agents (n=33, 16.5%), psychotropic agents (n=29, 14.5%) and non-steroidal anti-inflammatory drugs (n=24, 12.0%) accounted for approximately two-thirds of all ADRs leading to hospitalisation. Of 153 hospitalisations caused by ADRs, 102 (66.7%) were judged to be preventable.

Conclusions Similar to other countries, one in every ten hospitalisations is caused by ADRs according to data from an internal medicine ward of a Japanese hospital. Most of these hospitalisations are preventable. Some efforts to minimise hospitalisations caused by ADRs are needed.

Strengths and limitations of this study

- ► This is the first study to determine the prevalence of hospitalisations caused by adverse drug reactions (ADRs) and their preventability in an acute care setting in Japan.
- ► The causality and preventability of ADRs were independently evaluated by two investigators using standard methods.
- ► Information on medication history was abstracted from electronic medical records taken by physicians in usual care.

INTRODUCTION

Adverse drug reactions (ADRs) are harmful or unpleasant reactions related to the use or misuse of a medicinal product.[1] ADRs are a major cause of morbidity and impose a burden on healthcare resources because they are common. A past systematic review reported that the prevalence of ADRs leading to hospitalisation was 5.3%,[2] and this prevalence reportedly increased to 10.0% in elderly patients.[3 4] Furthermore, more than 50% of ADRs leading to hospitalisation have been considered preventable.[5] Therefore, an effort to reduce preventable hospitalisations due to ADRs is needed.

Japan is one of the world's most aged societies. Given that preventable ADRs are more frequent in elderly patients,[2] it is important to monitor the prevalence of preventable ADRs in an ageing society. Nonetheless, few studies have ever been conducted to investigate the prevalence of ADRs leading to hospitalisation in Japan. One single-centre study[6] reported that ADRs were identified in 4.9% of hospitalised elderly patients with acute illnesses in Japan. However, this study did not evaluate a causality between hospitalisation and ADRs. Furthermore, no Japanese studies have ever investigated the preventability of ADRs leading to hospitalisation. Thus, our aim was to determine the prevalence of ADRs leading to hospitalisation in an acute care setting and to evaluate the preventability of these ADRs in Japan.

METHODS

Study design and settings

We conducted a single-centre observational study using the electronic medical records of National Hospital Organization Tochigi

Medical Center to determine the prevalence of hospitalisation caused by ADRs among hospitalised patients with acute medical illness. Our hospital is a 350-bed general community hospital in Utsunomiya, Japan, and is one of the two largest acute care hospitals covering approximately 0.5 million people in this area.

Inclusion and exclusion criteria

All consecutive patients hospitalised to the internal medicine ward of our hospital due to acute medical illnesses from April 2017 to May 2018 were included. Patients who were planned to be hospitalised for diagnostic procedures, education or treatment were excluded. We also excluded patients with missing information on regular medications at admission. During the study period, 2007 hospitalisations among 1699 patients occurred. Of those, 1545 hospitalisations in 1358 patients were included in the final analysis (detailed information is shown in online supplementary figure S1 and table S1).

Data collection and screening

Information on age, sex, medications, and final primary and secondary diagnosis for hospitalisation were collected as de-identified data from the electronic medical records of our hospital. For information on prescribed medications, we used a comprehensive medication list documented by pharmacists as usual care. Based on the medication list and the patients' medical history, physical findings and laboratory test results from the electronic medical records, we retrospectively screened the medications that may cause ADRs after discharge from the index hospitalisation. We did not use a list of trigger symptoms[7] for screening. After this screening, 245 medications in 179 hospitalisations were included in the further investigation.

Outcome measures

The primary outcome was the prevalence of hospitalisation caused by ADRs among hospitalised patients with acute illnesses. Based on a previous report,[1] ADRs were defined as appreciably harmful or unpleasant reactions resulting from an intervention associated with the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, alteration of the dosage regimen or withdrawal of the product. However, ADRs related to withdrawal of medications or treatment failure were not included in this study. Intentional drug abuse was also excluded. The secondary outcome was the prevalence of hospitalisation caused by preventable ADRs among hospitalised patients with acute illnesses.

The causality assessment for ADRs was performed using the WHO-Uppsala Monitoring Committee (WHO-UMC)[8] and Naranjo criteria.[9] ADRs were judged to occur if there was a 'certain' or 'probable' causal association between the medication and adverse events based on WHO-UMC criteria. Two investigators (MK and JK) independently reviewed all screened cases using these criteria, and disagreements were resolved by discussions between the two investigators. An agreement rate in assessment of ADRs based on the WHO-UMC and Naranjo criteria was 71.8% (kappa=0.17) and 81.2% (kappa=0.42), respectively. Of 245 screened medications in 179 hospitalisations, 205 medications in 155 hospitalisations were judged to be causative with adverse events (see online supplementary table S2).

Regarding medications judged to be causing ADRs, the two investigators also independently assessed the contribution of the ADR to hospitalisation and the preventability of the ADR based on the Hallas criteria.[10] The cases in which problems due to ADRs were 'dominant' or 'partly contributing' to the hospitalisation were considered to be hospitalisations caused by ADRs. For example, an elderly patient was hospitalised because of influenza and acute heart failure caused by cilostazol. The patient's heart failure symptoms occurred before flu-like symptoms. Although cilostazol contributed to heart failure exacerbation, the major trigger leading to hospitalisation was influenza infection. In this case, the ADR was judged to 'partly contribute' to the hospitalisation.

ADRs were considered to be preventable if the medication-associated ADRs were judged to be 'definitely avoidable' or 'possibly avoidable' based on the Hallas criteria.[10] Hospitalisation caused by multiple medications was judged to be preventable if all associated medications were preventable. An agreement rate in assessment for the contribution and preventability of ADRs caused by each medication was 96.6% and 75.6%, respectively. These evaluations were conducted from December 2018 to February 2019.

Statistical analysis

Approximately 1500 patients were needed to provide a precision of 1% for calculation of the 95% CI of the primary outcome, assuming that the prevalence of hospitalisation caused by ADRs was 4%, which was based on the previous Japanese study for elderly hospitalised patients.[6]

Descriptive statistics were used to summarise the baseline characteristics of the study population. For the primary outcome, the proportion of hospitalisation caused by ADRs in all hospitalisations due to acute illnesses was calculated. The proportion of hospitalisations caused by preventable ADRs in all hospitalisations due to acute illnesses was also calculated. The 95% CIs were calculated for these outcomes. To determine the predictive factors associated with ADRs leading to hospitalisation, multivariable analysis using binary logistic regression was conducted. We examined the association between the primary and secondary outcomes and age, sex and polypharmacy at admission. Polypharmacy was defined as five or more medications based on a past study.[6] These analyses were performed using Stata V.15 (LightStone, Tokyo, Japan) or Excel statistical software package V.2.11 (Bellcurve for Excel; Social Survey Research Information Co., Tokyo, Japan). Statistical significance was defined as a p value<0.05.

Table 1 Characteristics of the 1545 hospitalisations due to acute medical illnesses

Characteristics	Total (n=1545)	Hospitalisation due to ADRs*	
		Yes (n=153)	No (n=1392)
Age (years), median (IQR)	79 (66–87)	83 (71–88)	78 (66–87)
Aged more or 65 years old, n (%)	1195 (77.4)	127 (83.0)	1068 (76.7)
Women, n (%)	740 (47.9)	82 (53.6)	734 (47.3)
Number of regular medications, median (IQR)	5 (2–7)	7 (5–10)	4 (2–7)
Five or more medications, n (%)	808 (52.3)	116 (75.8)	692 (49.7)
Primary diagnosis for hospitalisation†, n (%)			
Acute heart failure	188 (12.2)	20 (13.1)	168 (12.1)
Pneumonia or pneumonitis	122 (7.9)	3 (2.0)	119 (8.6)
Stroke or transient ischaemic attack	94 (6.1)	5 (3.3)	89 (6.4)
Acute coronary syndrome	77 (5.0)	0 (0.0)	77 (5.5)
Gastrointestinal bleeding	76 (4.9)	25 (16.3)	51 (3.7)
Adverse drug events‡	67 (4.3)	65 (42.5)	2 (0.1)
Urinary tract infection	55 (3.6)	3 (2.0)	52 (3.7)
In-hospital death, n (%)	144 (9.3)	11 (7.2)	133 (9.6)

*This is the investigators' defined ADR.
†This presents the most frequent seven reasons for hospital admission.
‡This was the clinical diagnosis by the principal physicians caring for the patients.
ADRs, adverse drug reactions.

Patient involvement

The present study was purely observational in nature, and no active intervention was applied. No patients were involved in determining the research question or outcome measures or in developing plans to design or implement the study. No patients were asked for advice during the interpretation of the results. No plans are in place to disseminate the results of this research to the relevant patient community.

RESULTS

The baseline characteristics of the 1545 hospitalisations due to acute medical illnesses are presented in table 1. Among these cases, the median patient age was 79 years (IQR 66–87), 740 (47.9%) were women and the median number of medications at admission was 5 (IQR 2–7). The most common final clinical diagnoses leading to hospitalisation were acute heart failure (n=188, 12.2%), followed by pneumonia or pneumonitis (n=122, 7.9%), stroke or transient ischaemic attack (n=94, 6.1%), acute coronary syndrome (n=77, 5.0%), gastrointestinal bleeding (n=76, 4.9%) or adverse drug events (n=67, 4.3%).

Of the 205 medications judged to be causative of adverse events, 200 medications were determined to contribute to 153 hospitalisations due to an ADR. The most common categories of medications leading to hospitalisation were cardiovascular agents (n=46, 23.0%), followed by antithrombic agents (n=33, 16.5%), psychotropic agents (n=29, 14.5%) and non-steroidal anti-inflammatory drugs (NSAIDs) (n=24, 12.0%) (table 2). Medications in these four categories accounted for approximately two-thirds of all ADRs leading to hospitalisation.

For the primary outcome, 153 of the 1545 hospitalisations due to acute medical illnesses were judged to be caused by ADRs. Therefore, the proportion of hospitalisations caused by ADRs among all hospitalisations due to acute illnesses was 9.9% (95% CI 8.4% to 11.4%). Of the 153 patients hospitalised due to ADRs, 11 patients (7.2%) died before hospital discharge.

Of the 153 hospitalisations caused by ADRs, 102 (66.7%) were judged to be preventable. Of the 200 medications implicated in ADRs leading to hospitalisation, 137 (68.5%) were judged to be preventable. Of these medications, the most common medication categories were cardiovascular (n=28, 20.4%) and psychotropic (n=28, 20.4%) agents, followed by NSAIDs (n=21, 15.3%). Medications in these three categories accounted for more than half of all preventable ADRs leading to hospitalisation.

Table 3 presents the predictive factors associated with hospitalisations caused by ADRs. Polypharmacy, defined as five or more regular medication use, was the only independent predictive factor for hospitalisations caused by ADRs (ORs 3.17, 95% CI 2.12 to 4.74). Polypharmacy was also the only independent predictive factor associated with preventable hospitalisations caused by ADRs (ORs 3.09, 95% CI 1.90 to 5.02).

DISCUSSION

The present study showed that hospitalisations due to ADRs are common in Japan. However, the prevalence of

Table 2 Most common categories of medications implicated in adverse drug reactions (ADRs) that led to hospitalisations

Categories*	Medications implicated in ADRs		Hospitalisations caused by ADRs†
	Total	Number of preventable cases‡	
All	200 (100.0)	137 (68.5)	153 (100.0)
Cardiovascular agents	46 (23.0)	28 (60.9)	31 (20.3)
Diuretics	23 (11.5)	17 (73.9)	16 (10.5)
Calcium channel blockers	8 (4.0)	4 (50.0)	8 (5.2)
Renin-angiotensin inhibitors	6 (3.0)	1 (16.7)	6 (3.9)
Beta-blocking agents	4 (2.0)	1 (25.0)	4 (2.6)
Digoxin	3 (1.5)	3 (100.0)	3 (2.0)
Others	2 (1.0)	2 (100.0)	2 (1.3)
Antithrombic agents	33 (16.5)	12 (36.4)	30 (19.6)
Antiplatelet agents	19 (9.5)	8 (42.1)	17 (11.1)
Anticoagulant agents	14 (7.0)	4 (28.6)	14 (9.2)
Psychotropic agents	29 (14.5)	28 (96.6)	17 (11.1)
Benzodiazepines	15 (7.5)	15 (100.0)	8 (5.2)
Antipsychotics	12 (6.0)	11 (91.7)	9 (5.9)
Hypnotics	2 (1.0)	2 (100.0)	2 (1.3)
NSAIDs	24 (12.0)	21 (87.5)	23 (15.3)
Herbal medications	13 (6.5)	13 (100.0)	13 (8.5)
Hypoglycaemic agents	10 (5.0)	5 (50.0)	10 (6.5)
Sulfonylureas	4 (2.0)	4 (100.0)	4 (2.6)
Insulins	3 (1.5)	0 (0.0)	3 (2.0)
Others	3 (1.5)	1 (33.3)	3 (2.0)
Antimicrobial agents	10 (5.0)	9 (90.0)	10 (6.5)
Antiepileptic agents	6 (3.0)	5 (83.3)	6 (3.9)
Opioids	5 (2.5)	3 (60.0)	5 (3.3)
Laxatives	4 (2.0)	4 (100.0)	3 (2.0)

Values are given as numbers (percentages) unless stated otherwise.
*These included subcategories of medications representing two or more percentage points of all patients.
†Hospitalisation could be warranted due to more than one medication.
‡The values represent the number of ADRs with the percentage of the total number of ADRs that were preventable among all ADRs within drug categories.
NSAIDs, non-steroidal anti-inflammatory drugs.

Table 3 Univariable and multivariable analyses* for predictive factors of any or the preventable hospitalisations caused by adverse drug events

Variables	Any hospitalisations due to ADRs		Preventable hospitalisations due to ADRs	
	Unadjusted OR (95% CI)	Adjusted OR† (95% CI)	Unadjusted OR (95% CI)	Adjusted OR† (95% CI)
Aged 65 or more years	1.48 (0.95 to 2.30)	0.96 (0.60 to 1.54)	1.30 (0.78 to 2.17)	0.83 (0.48 to 1.44)
Women	1.29 (0.92 to 1.80)	1.22 (0.87 to 1.72)	1.47 (0.98 to 2.21)	1.41 (0.94 to 2.13)
Polypharmacy‡	3.17 (2.16 to 4.66)§	3.17 (2.12 to 4.74)§	3.00 (1.89 to 4.77)§	3.09 (1.90 to 5.02)§

*The threshold for statistical significance was set at p<0.05.
†The variables adjusted for were age, sex and polypharmacy.
‡Polypharmacy was defined as five or more medications.
§Indicate a significant association between selected variables and unplanned admission due to ADRs.
ADRs, adverse drug reactions.

hospitalisation caused by ADRs in the present study seems more frequent than that of the previous Japanese study regarding hospitalised elderly patients.[6] In a previous study,[6] no endocrine drug-related hospitalisations were reported, unlike past studies conducted outside Japan.[4] Moreover, our findings are consistent with those of past studies[2–5 11] showing that approximately 10% of hospitalisations due to acute illnesses were attributed to ADRs. Given that the sample size of the previous Japanese study[6] was smaller than ours, the findings of the present study may reflect a more accurate prevalence of hospitalisations caused by ADRs in Japan.

Cardiovascular agents, antithrombic agents, psychotropic agents and NSAIDs accounted for approximately two-thirds of medications leading to hospitalisation in this study. This finding is similar to that of past studies showing that the most common categories of medications causing hospitalisation included cardiovascular agents, antithrombic agents, psychotropic agents and NSAIDs.[3 4 6 12 13] However, the prevalence of hospitalisations caused by psychotropic agents in this study was higher than that in a past study. It is unclear why psychotropic medication-related hospitalisations were so common in Japan compared with other countries. Although there is no accurate data on a pattern of benzodiazepine use in Japan,[14] consumption of sedative-type benzodiazepines in Japan has been reported to be higher than in other countries.[15] Therefore, it is possible that a higher consumption of benzodiazepines might have resulted in a higher prevalence of hospitalisations caused by psychotropic agents in this study. Our findings suggest that investigation of the pattern and appropriateness of benzodiazepine use in Japan is needed. In this study, 13 (6.5%) of the 200 ADRs leading to hospitalisation were attributed to herbal medications unlike past studies conducted outside Japan.[3 4 12 13] However, our results are similar to those of a previous Japanese study[6] reporting that 3 (7.9%) of 38 medications associated with ADRs were herbal medications. Therefore, this finding may be specific to Japan where herbal medications are often prescribed by physicians.[16] Given that the potentially inappropriate use of traditional Japanese herbal medication among elderly patients may be common in Japan,[17] our findings suggest that a strategy to improve the appropriateness of herbal medication use is needed. Moreover, given that accurate data on the safety of herbal medication use are lacking,[18] monitoring the adverse events of herbal medications is also needed.[19]

Regarding the preventability of hospital admissions caused by ADRs, our findings were also consistent with those of past studies[11 12] showing that more than half of hospitalisations due to ADRs were preventable. However, the preventability of hospitalisations due to ADRs in this study was higher than the estimate of a recent meta-analysis.[20] It is possible that a higher proportion of elderly patients in the present study resulted in a higher prevalence of hospitalisations caused by preventable ADRs because elderly patients were more likely to be hospitalised due to preventable ADRs than young patients.[11] Similar to past studies,[12 20] in the present study, the most common categories of medications associated with preventable ADRs leading to hospitalisation were cardiovascular agents, psychotropic agents and NSAIDs. Therefore, one strategy to minimise hospitalisation due to ADRs may be improving the appropriateness of medication use regarding these three categories. Particularly for the elderly population, implementing potentially inappropriate medication lists, such as Beers' criteria[21] and screening tool of older persons' potentially inappropriate prescriptions (STOPP) criteria,[22] may be useful, because these lists recommend that benzodiazepines and non-cyclooxygenase-selective NSAIDs should be avoided if possible for elderly patients.

In the present study, the number of regular medications was a predictive factor for hospitalisation caused by ADRs, while patient age and sex were not associated with ADRs. A recent systematic review,[4] including 42 articles regarding hospitalisation caused by ADRs in elderly patients, also reported that medication number was a predictive factor for hospitalisations caused by ADRs in all past studies investigating this association, while there were mixed results regarding the associations between hospitalisations due to ADRs and patient age and sex. Therefore, further studies are needed to investigate whether age and sex are predictive factors for hospitalisation due to ADRs.

The proportion of ADRs leading to hospitalisation in this study was higher than the proportion of final clinical diagnoses leading to hospitalisation documented in routine care (9.9% vs 4.3%). Past studies have reported that physicians are often unaware of ADRs in acute care settings,[23–26] although no studies have been conducted in Japan. Therefore, our findings suggest that physicians were not aware of more than half of the ADRs leading to hospitalisation in usual care. However, we did not contact principal physicians caring for patients. Therefore, whether the discrepancy in the prevalence of ADRs leading to hospitalisation between routine care and this research is attributable to physicians' failure to recognise ADRs in usual care remains uncertain. Further studies are needed to investigate the frequency of physicians' failure to recognise ADRs in Japan and the corresponding effects on patient outcomes.

Of the 153 patients hospitalised due to ADRs, 11 patients (7.2%) died during the index hospitalisation, which is similar to the findings of past studies showing that 6%–9% of patients hospitalised due to ADRs died during a hospital stay.[27–29] However, we did not investigate deaths directly caused by ADRs. Therefore, the extent to which ADRs contributed to mortality is unknown. Given the high prevalence of hospitalisations caused by ADRs, further studies are needed to evaluate the effect of ADRs on mortality and morbidity in patients in Japan.

Strengths and weaknesses of the study

To the best of our knowledge, the present study is the first to determine the prevalence of hospitalisations caused

by ADRs and their preventability in Japan. To reduce selection bias and reflect real-world practice, nearly all consecutive hospitalisations due to acute illnesses were included. Furthermore, the causality and preventability of ADRs and the contribution of ADRs to hospitalisation were independently investigated by two investigators based on standard criteria.[8–10]

However, several limitations must be mentioned. First, the present study was limited to a single centre and to patients hospitalised in the internal medicine ward. Therefore, our findings should be confirmed at other wards and hospitals in Japan. Second, we screened ADRs based on information from electronic medical records mainly documented by physicians in usual care. Given that physicians are often unaware of ADRs,[23–26 30] the prevalence of ADRs might have been underestimated. Furthermore, documented medication history and past medical history were sometimes poor. Therefore, some assessments for the preventability of ADRs might be inaccurate. Third, we did not investigate the reasons for the preventability of ADRs. Fourth, we did not systematically screen for medications that may cause adverse events using a list of trigger symptoms; therefore, some ADRs may have been missed. Fifth, no universal gold standard is available to assess the causality of ADRs,[31] although we performed a causality assessment based on the two criteria that were most commonly used in similar previous studies.[4]

CONCLUSIONS

Similar to other countries, the prevalence of hospitalisations caused by ADRs was high among hospitalised internal medicine patients in a Japanese hospital. Most of these hospitalisations might have been preventable. Our findings should be confirmed in other Japanese hospitals.

Contributors JK conceived of and designed this study. JK and MK collected and analysed the data. JK wrote a draft of the main paper. JK and MK discussed the results and interpretations, and were involved in critical revisions of the manuscript. All the authors have read and approved the final version of the manuscript. All the authors had full access to all of the data used in this research. JK assumes responsibility for the integrity and accuracy of the data.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This research was approved by the Medical Ethical Committee of the National Hospital Organization Tochigi Medical Center (No. 30-2). This research was conducted in accordance with the Ethical Guidelines for Epidemiological Research in Japan and the Declaration of Helsinki. The need for individual informed consent was formally waived by the Medical Ethical Committee of the National Hospital Organization Tochigi Medical Center because the de-identified data were collected from medical records without contact with the patients. However, according to the Japanese Ethical Guidelines, we did display an opt-out statement in the waiting room and webpage of the hospital to provide the patients with information about the research and the opportunity to refuse the use of the data.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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