ORIGINAL RESEARCH

Polypharmacy and adverse drug reactions in Japanese elderly taking antihypertensives: a retrospective database study

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Background: The concomitant use of multiple medications by elderly patients with hypertension is a relatively common and growing phenomenon in Japan. This has been attributed to several factors, including treatment guidelines recommending prescription of multiple medications and a continuing increase in the elderly population with multiple comorbidities.

Objective: This study was aimed at investigating the association between polypharmacy, defined as the concomitant use of five or more medications, and risk of adverse drug reaction (ADR) in elderly Japanese hypertensive patients to examine the hypothesis that risk of ADR increases with the administration of an increasing number of co-medications.

Methods: Using a retrospective cohort design, the data regarding all hypertensive patients aged 65 years or older were extracted from the Risk/Benefit Assessment of Drugs – Analysis and Response Council antihypertensive medication database. The data were reviewed for classification of patients into one of three groups according to drug use at the initiation of therapy – a monotherapy group composed of patients who had taken the investigated drug only, a co-medication group composed of patients who had taken the investigated drug and a maximum of three other medications, and a polypharmacy group composed of patients who had taken the investigated drug and four or more other medications – and determination of the number of ADR events experienced. Estimated rate ratios (RRs) and 95% confidence intervals (CIs) were calculated using a Poisson regression model adjusted for drug category and patient age and sex. Various sensitivity analyses were performed to confirm the robustness of the study findings.

Results: Of 61,661 elderly Japanese patients (men, 41.8%; 75 years or older, 35.1%) registered in the database, 2491 patients (4.0%) experienced a total of 3144 ADR events during the study period. The rate of ADR per 10,000 person-days was 2.0 for the monotherapy group, 5.1 for the co-medication group, and 8.6 for the polypharmacy group. After adjusting for age, sex, and initial antihypertensive therapy, the RR was estimated at 2.4 (95% CI, 2.2–2.6) for the co-medication group and 4.3 (95% CI, 3.8–4.8) for the polypharmacy group, when compared with the monotherapy group.

Conclusion: The use of polypharmacy increases the risk of ADR among elderly Japanese patients with hypertension, calling for regular medication review to eliminate the administration of unnecessary co-medications.

Keywords: adverse drug reaction, antihypertensive, elderly, pharmacoepidemiology, polypharmacy

Introduction

Incorrect use of medications, a phenomenon estimated to occur with more than half of all medications currently prescribed, can have dire consequences for patients and health care in general.[1] Such consequences, which include development of antimicrobial

resistance, adverse drug reaction (ADR) events, erroneous prescription of medications, erosion of patient confidence, and waste of resources, have often been attributed to polypharmacy, commonly defined as either the use of multiple medications or the use of a medication without rational indication for its use.[2,3] Cases of polypharmacy are generally described as either minor, defined as concurrent use of two to four medications, or major, defined as concurrent use of five or more medications, to describe the extent of concurrent medication use, but not the appropriateness of the medications prescribed.[4]

Previous studies in elderly populations have not only confirmed that the consequences of polypharmacy include ADR events, drug interactions, and prescription of inappropriate medications, but also observed that ADR events due to polypharmacy may be misdiagnosed as the onset of new symptoms or comorbidities.[2,5–10] This latter phenomenon may in turn lead to increases in the extent of polypharmacy as well as increased medical costs and ultimately, medication errors due to the complexity of the medication regimens.[10] Other studies have found that polypharmacy may lead to poor adherence to medication regimens, unsatisfactory therapeutic outcomes, and lowered quality of life.[5,8]

One of the most common adult diseases worldwide, hypertension has been reported to affect approximately 6.4 million (60%) people of the Japanese population over the age of 65 years.[11] As hypertensive patients are more likely to have comorbid conditions and are required to maintain stringent control of blood pressure, elderly Japanese hypertensive patients are more likely to use multiple medications.[12–19] Based on the hypothesis that administration of relatively low doses of multiple medications results in higher tolerability than administration of relatively high doses of one medication, current clinical guidelines for the treatment of hypertension recommend combination therapies if needed, thus increasing the potential for polypharmacy in hypertensive patients.[15,16]

Despite the potentially dire consequences of polypharmacy, few studies examining the association between polypharmacy and ADR risk in Japanese elderly patients have been conducted. One study of 1289 elderly inpatients in five university hospitals found that among the 9.2% of inpatients experiencing ADR events, the mean number of drugs taken on admission was 5.7, compared to a mean of 5.0 by those who were not experiencing ADR events.[20] Another study of 517 elderly patients with dementia treated at a single hospital found that among the 12.7% of inpatients experiencing ADR events, 15% were taking five or more medications.[21]

However, these studies considered neither the duration of medication use, nor the presence of comorbidities, and included a limited number of medical institutions and clinics, decreasing the ability to generalize the findings to the general Japanese elderly population.

Under the Japanese post-marketing surveillance (PMS) system, data regarding the safety and effectiveness of a drug after it has been introduced into the market are mainly collected through the spontaneous reporting system and drug use investigations (DUIs).[22–24] After a new drug has been marketed for 4 to 10 years, pharmaceutical companies are required to submit the results of PMS studies to conduct what is referred to as a "re-examination" of the drug. To ensure the quality of PMS data utilized for the re-examination, data collection must adhere to a regulation originally entitled "Good Post-Marketing Surveillance Practice" (GPMSP) before being subsequently revised in two regulations entitled "Good Post-Marketing Study Practice" (GPSP) and "Good Vigilance Practice" (GVP) in 2004.[22–24] Under these regulations, doctors who take part in a DUI must register patients newly prescribed the relevant drug during daily medical practice. Usually continuous surveillance and a central registration system are selected to minimize selection bias. Doctors must then record data regarding patient demographic characteristics, medical history, medication use, and disease conditions using a case report form (CRF) prepared by a pharmaceutical company. During a predetermined period for each drug, usually 3 to 6 months, doctors must monitor patients prospectively, recording the results of any laboratory tests conducted and the development of any ADR events. The pharmaceutical company then collects a target number of CRFs, typically 3000 to 10,000, and summarizes the safety and effectiveness data for the re-examination requirement.

After the re-examination has been conducted by a pharmaceutical company, the Risk/Benefit Assessment of Drugs-Analysis and Response (RAD-AR) Council of Japan collects the DUI data examined by the company and pools them with data collected from other companies to construct databases.[25] One current database constructed by the RAD-AR Council is the antihypertensive medication database, which contains data collected from 21 PMS studies conducted by 17 pharmaceutical companies between 1981 and 1999.[26] Defined as the investigated drugs in this study, the antihypertensive medications are categorized as calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs), beta-blockers (BBs), alpha-blockers (ABs), or diuretics. Because the data structure and quality varied among the PMS studies, the RAD-AR Council standardized the data contained in the

database using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes for comorbid conditions;[27] Medical Dictionary for Regulatory Activities (MedDRA) codes for ADR events;[28,29] and drug classification codes for concomitant medications;[30] as well as confirmed the validity of the redefined data by comparing them with the original data and verified their internal consistency.

This database has been used in various pharmacoepidemiological studies in Japan, including studies of the risk of dry cough due to ACEI administration,[31] the effect of concomitant use of CYP3A4 inhibitors and CCBs in terms of ADR incidence,[32] and the effect of nonsteroidal anti-inflammatory drugs in hypertensive patients on antihypertensive therapy.[33] The anonymous database includes separate files containing data regarding patient demographics, medical conditions, medications, and ADR events that can be linked for analyses using a non-identifiable personal number created by the RAD-AR Council.

The current study was aimed at providing safety information for physicians and pharmacists regarding the treatment of elderly hypertensive patients, especially who were exposed to multiple medications. To do so, it examined the association between polypharmacy and ADR risk in elderly Japanese patients using a design and data source that overcame the limitations of previous studies.

Materials and methods
Study design and data source
Using a retrospective cohort design that complied with the administrative rules and regulations of the RAD-AR Council, data regarding approximately 143,000 hypertensive patients were extracted from the antihypertensive medication database, constructed using the PMS data.[25,34] Need for study approval by an institutional review board was waived because only secondary data containing no personal identifiers were extracted and analyzed.

Study subjects
The data regarding all hypertensive patients recorded in the database were reviewed for identifying all patients aged 65 years or older. Any patients whose age or sex was not specified were excluded from further consideration. Patient use of the investigated drug and of concomitant medications, regardless of class, at the initiation of treatment was determined to classify patients into one of three drug use groups: the monotherapy group, defined as patients who had taken the investigated drug only; the co-medication group, defined

as patients who had taken the investigated drug and a maximum of three other medications, including antihypertensive agents; and the polypharmacy group, defined as patients who had taken the investigated drug and four or more other medications.

Variables
To examine the extent to which the patients had experienced ADR events, the outcome of interest, data regarding the date, severity, and intervention required (ie, dosage reduction or discontinuation) were extracted regarding all ADR events that had occurred. Data regarding the duration (in days) from initiation of the investigated drug to the end of follow-up were used to define the study period. Other explanatory variables used in the analyses included the category of the investigated drug (CCB, ACEI, BB, AB, or diuretic), the number of co-medications taken (1, 2 to 4, or 5 or more), patient age (65 to 74 years versus 75 years or older), and patient sex (male versus female).

Statistical analysis
Subject characteristics were described in terms of their frequency. The crude risk of ADR was calculated by dividing the number of ADR events by person-days for each drug use group. Estimated rate ratios (RRs) and 95% confidence intervals (CIs) were calculated using a Poisson regression model adjusted for drug category and patient age and sex.

Various sensitivity analyses were performed to confirm the robustness of the study findings. In the first analysis, only severe ADR events, defined as those that required any actions, such as dosage reduction or discontinuation, were included. In the second analysis, which focused on investigating the long-term effects of polypharmacy, only subjects who had taken the investigated drug for at least 90 days were included. In the third analysis, data regarding the symptoms of "coughing" (MedDRA code: 10011232) or "cough" (MedDRA code: 10011224), which are well-known as ADR events for ACEIs, and thus more likely to be reported by doctors in PMS studies, were excluded to reduce potential reporting bias. In the final analysis, the fact that several patients had begun taking additional medications subsequent to initiation of the study was considered by classifying patients into three groups according to the maximum number of medications that they had taken at any point during the study period, and by such means, the extent of misclassification bias was determined.

All statistical analyses were performed using SAS statistical software, version 9.3 (SAS Institute Inc, Cary,

Results

The process of selecting the study population from the anti-hypertensive medication database is displayed in Figure 1. Of 61,792 patients aged 65 years or older identified, 131 were excluded from the analysis: 112 patients were excluded because the date of medication initiation/end or date of experiencing an ADR event was not recorded; 19 patients were excluded because their sex was not specified. Among the remaining 61,661 patients, 38,888 (63.1%) were classified into the monotherapy group, 19,335 (31.4%) into the co-medication group, and 3438 (5.6%) into the polypharmacy group based on a review of their medication history. The median duration, 25th percentile, and 75th percentile of the follow-up period were 111, 84, and 178 days, respectively.

The characteristics of the study subjects are summarized in Table 1. ACEIs were the most frequently prescribed agents in all three groups, followed by CCBs and BBs. No significant differences in age and sex distribution among the groups were observed.

The risk of ADR according to drug group in person-days is summarized in Table 2. Further, 2491 (4.0%) of the subjects experienced 3144 ADR events, an overall incidence of 3.3 events per 10,000 person-days, and the most frequently experienced ADR events were coughing or cough followed by dizziness. The rate of ADR per 10,000 person-days was 2.0 for the monotherapy group, 5.1 for the co-medication group, and 8.6 for the polypharmacy group. After adjusting for age, sex, and the investigated drug, the RRs for co-medication and polypharmacy groups were estimated at 2.4 (95% CI, 2.2–2.6) and 4.3 (95% CI, 3.8–4.8), respectively, when compared to the monotherapy group.

The results of the sensitivity analysis are summarized in Table 3. As can be observed, when the analysis was restricted to events that required intervention, the risk of ADR increased for both the co-medication and polypharmacy groups compared with the monotherapy group. A similar trend was observed when subjects who had taken the investigated drug for fewer than 90 days were excluded, when symptom of coughing or cough was excluded as an ADR event, and when the maximum number of medications taken was used to classify the patients into drug groups.

Discussion

The primary finding in this investigation of the association between polypharmacy and risk of ADR in elderly Japanese
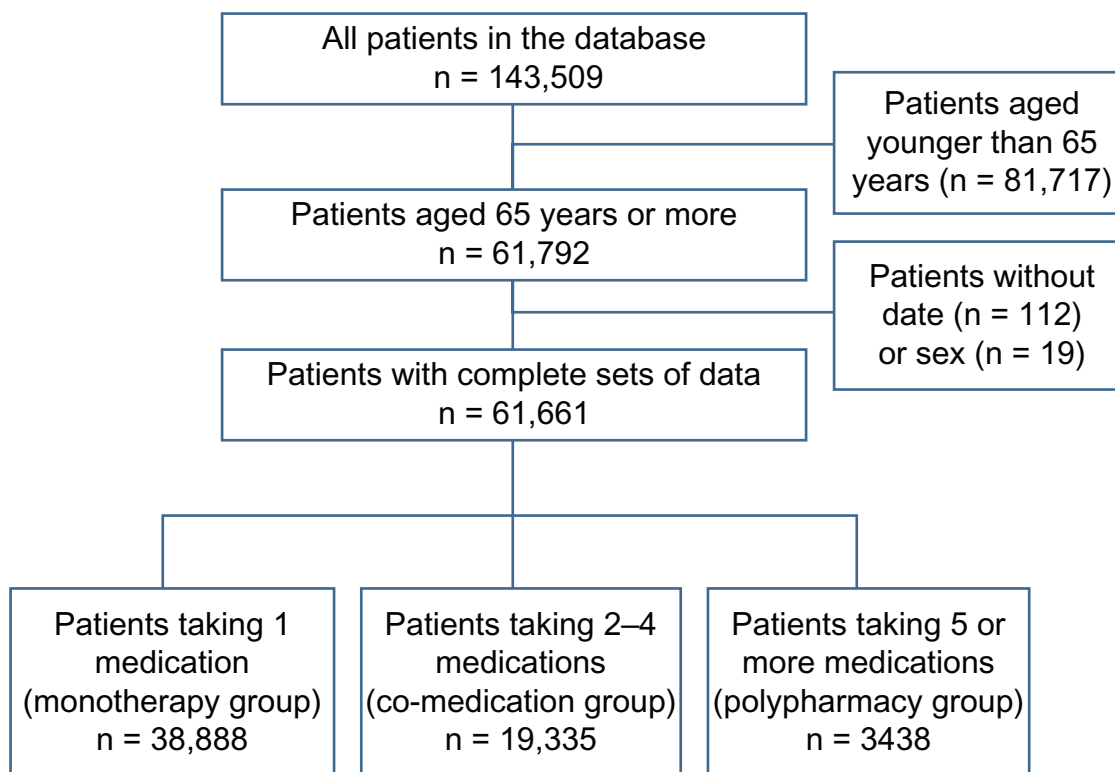

Figure 1 Flowchart of subject selection from the review of patient data in the Risk/Benefit Assessment of Drugs – Analysis and Response Council antihypertensive medication database.

Table 1 Characteristics of study subjects

| | All groups | Drug use group | | |
		Monotherapy n (%)	Co-medication (%)	Polypharmacy (%)
Total	61,661 (100)	38,888 (63.1)	19,335 (31.4)	3438 (5.6)
Age group (years)				
65–74	39,989 (64.9)	25,956 (66.7)	12,069 (62.4)	1964 (57.1)
≥75	21,672 (35.1)	12,932 (33.3)	7266 (37.6)	1474 (42.9)
Sex				
Male	25,791 (41.8)	16,286 (41.9)	7987 (41.3)	1518 (44.2)
Female	35,870 (58.2)	22,602 (58.1)	11,348 (58.7)	1920 (55.8)
Anti-hypertensive drug used				
CCB	13,018 (21.1)	5449 (14.0)	6461 (33.4)	1108 (32.2)
ACEI	24,771 (40.2)	12,747 (32.8)	10,350 (53.5)	1674 (48.7)
BB	16,111 (26.1)	13,720 (35.3)	1908 (9.9)	483 (14.0)
AB	4867 (7.9)	4078 (10.5)	616 (3.2)	173 (5.0)
Diuretic	2894 (4.7)	2894 (7.4)	0 (0.0)	0 (0.0)

Note: Subjects were classified into three groups according to the initial number of medications taken.
Abbreviations: AB, alpha-blocker; ACEI, angiotensin-converting enzyme inhibitor; BB, beta-blocker; CCB, calcium channel blocker.

patients with hypertension was an increasing risk of ADR with an increasing number of medications taken after adjustment for patient characteristics. This finding was confirmed by the results of various sensitivity analyses and is consistent with previous studies that reported a positive association between polypharmacy and the risk of ADR.[2,9,10]

In Japan, so-called automated databases such as claims databases, medical records databases, and cancer registries databases have been developed for use in any type of research. Nevertheless, as only several large databases are currently available, data for the analyses conducted in this study were collected from the RAD-AR Council antihypertensive medication database, which contains the records of approximately 143,000 hypertensive patients.[25] Pharmaceutical companies that release new drugs into the Japanese marketplace are required to conduct PMS studies to collect data regarding the safety and effectiveness of drugs in the course of medical practice that are of sufficiently high quality for use in the re-examinations.[22–24] Even though the post-marketing studies may have possible limitations such as patient selection and reporting bias, in this study, a positive association was identified between ADR risk and number of co-medications.

In accordance with several previous studies, polypharmacy was defined as the use of five or more medications in this study. Such numerical definitions of polypharmacy often do not address the appropriateness of the medications, focusing solely on the extent of their concurrent use.[2,3] The definition, however, is supported with the findings of two previous studies in Japan, which reported that patients who experience ADR events are likely to be taking five or more medications.[20,21] Using the widely accepted definition of polypharmacy, greater risk of ADR was identified in the polypharmacy group than in the monotherapy or co-medication groups in this study.

Further, in accordance with previous pharmacoepidemiology studies, a Poisson regression model was used to estimate the risk of ADR associated with each drug use group. A similar model was used by Ray et al in the evaluation of the risk of sudden cardiac death according to antipsychotic use (ie, current, former, or no use)[35] and by McAfee et al to estimate incidence of drug-induced hospitalization or in-hospital death among patients treated with statins.[36] In the base case analysis, the number of medications being taken at baseline was determined for assigning the subjects into one of

Table 2 Number of person-days, number of ADR events, ADR rate, and estimated rate ratio

| | All groups | Drug use group | | |
		Monotherapy	Co-medication	Polypharmacy
Number of person-days	9,568,650	6,074,669	2,997,958	496,023
Number of ADR events	3144	1196	1519	429
ADR rate per 10,000 person-days	3.3	2.0	5.1	8.6
Estimated rate ratio	–	1.0	2.4	4.3
95% confidence interval	–	–	2.2–2.6	3.8–4.8

Note: ADR rate ratios were estimated using a Poisson regression model adjusted for age, sex, and drug category.
Abbreviation: ADR, adverse drug reaction.

Table 3 Results of sensitivity analyses

	Drug use group		
	Monotherapy	Co-medication	Polypharmacy
Inclusion of severe ADR events only			
Person-days of follow-up	6,074,669	2,997,958	496,023
Number of ADR events	763	930	249
ADR rate per 10,000 person-days	1.3	3.1	5.0
Estimated rate ratio	1	2.6	4.4
95% confidence intervals	–	2.3–2.9	3.8–5.1
Inclusion of only subjects taking investigated drug ≥90 days (n = 42,413)			
Person-days of follow-up	5,284,021	2,658,961	432,305
Number of ADR events	509	676	214
ADR rate per 10,000 person-days	1.0	2.5	5.0
Estimated rate ratio	1	1.9	4.0
95% confidence intervals	–	1.7–2.2	3.4–4.7
Exclusion of coughing or cough as ADR events			
Person-days of follow-up	6,074,669	2,997,958	496,023
Number of ADR events	859	970	325
ADR rate per 10,000 person-days	1.4	3.2	6.6
Estimated rate ratio	1	2.7	5.5
95% confidence intervals	–	2.5–3.0	4.7–6.3
Patient reclassification based on maximum number of medications used			
Person-days of follow-up	5,040,282	3,119,006	1,409,362
Number of ADR events	890	1543	711
ADR rate per 10,000 person-days	1.8	4.9	5.0
Estimated rate ratio	1	2.4	2.9
95% confidence intervals	–	2.2–2.6	2.6–3.2

Note: ADR rate ratios were estimated using a Poisson regression model adjusted for age, sex, and drug category.
Abbreviation: ADR, adverse drug reaction.

the three groups according to the extent of concomitant drug use (results are shown in Table 2). To consider the discrepancy between drug use and actual risk period, sensitivity analysis was conducted after classifying the subjects according to the maximum number of medications taken at any point during the study period rather than the number being taken at initiation of the study period, thereby ensuring that the results were not biased due to misclassification of patients. The result of the analysis confirmed the existence of a positive association between ADR risk and number of co-medications taken.

Due to safety concerns, current clinical guidelines for the treatment of patients with uncontrolled hypertension recommend administration of combination therapies rather than increased doses of one medication.[15,16] The results of this study, however, indicated that administration of multiple medications to elderly hypertensive patients is associated with increased risk of ADR, calling for increased care in the treatment of those patients by this practice. For those patients for whom administration of multiple medications was indicated, several literature reviews have suggested strategies,[2,9,10,37,38] such as conducting medication reviews to identify unnecessary medications including over-the-counter drugs;[39] the development of medication grids that display all medications and administration methods used by each patient in the form of a 7-day schedule to simplify medication regimens;[40] the use of Beers criteria to identify inappropriate prescribing practices;[41] and the development of interdisciplinary teams to perform regular assessments of medication regimens.[42] These efforts can assist in determining the priority of medications used in a current regimen and promote rational use of medications.

The formation of interdisciplinary teams in which health professionals can share patient data to evaluate patient conditions as a whole and select minimally required pharmacotherapies has recently been recommended in Japan.[43] This recommendation reflects recognition that the active contribution of community pharmacists may promote rational use of medications and reduce drug-related problems among the elderly, especially in aging societies.[44] To ensure that elderly patients understand the reasons for and the correct ways of taking medications, and thereby decrease the risk of therapeutic failure as well as ADR, the role of pharmacists should be expanded to the education of patients and the monitoring of appropriate medication use, particularly in cases of polypharmacy. Comprehensive patient management with regular medication review should be conducted

to determine the optimal number of medications and reduce the ADR risk for each patient.

Limitations

Although several sensitivity analyses were performed to consider potential biases, this study had certain limitations that may limit the generalizability of the findings. First, even though PMS studies must be conducted for all drugs prior to re-examination in Japan, the data regarding the results of only 21 PMS studies were contained in the database, as submission of these data was voluntary. Moreover, these data are relatively old, as they were collected from PMS studies conducted between 1981 and 1999, and were collected from few subjects who had taken diuretics and no subjects who had taken angiotensin-receptor blockers (ARBs) or combination drugs, the latter of which are now commonly used in the treatment of hypertensive patients. The RAD-AR Council recently developed a new database that includes the results of five studies of anti-hyperlipidemia drugs and, as of this writing, is preparing to add the results of three more antihypertensive drugs.[45] Further research using data contained in the updated database is thus called for in the future.

Second, the study used PMS data that may itself have limitations due to misclassification of drug use status. Doctors often collect patient data using unreliable and subjective methods, such as by asking patients whether they have taken all of their medications without objectively confirming whether they have truly done so, leading to misclassification and possibly underestimation or overestimation of the risk of ADR. Third, the extent of patient adherence to treatment was not considered, which, particularly in the case of patients who might not have taken medications as prescribed, may have led to the underestimation of the risk of ADR.

Conclusion

Polypharmacy increases the risk of ADR in elderly Japanese patients with hypertension, calling for comprehensive management by regular medication review for determining the optimal number of medications to be prescribed to this patient population. Further studies are required to reduce the risk of drug-related problems in elderly Japanese patients.

Acknowledgments

Disclosure

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