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Association of Hypnotic Drug Use with Fall Incidents in Hospitalized Elderly Patients: A Case-Crossover Study

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We investigated whether use of hypnotic drugs, including benzodiazepine receptor agonists, as well as ramelteon and suvorexant are associated with fall incidents in elderly inpatients aged no less than 75 years, who were hospitalized at an acute care general hospital in Japan, between November 1st, 2016 and October 31st, 2017. Multivariate analysis results were reported as odds ratio (OR) with 95% confidence interval (CI). Following to a case-crossover study protocol, the time windows of the case and the control days were assigned to the day or the days, which are one day or 2–8d before the fall incidents, respectively. In the enrolled 111 patients, the accumulated total available numbers of the cases and the control days were 111 and 554 patient days, respectively. Hypnotic drug use was significantly associated with fall incidents (OR: 2.85, 95% CI: 1.03–7.90, p = 0.04). Especially benzodiazepine receptor agonists (OR: 5.79, 95% CI: 1.52–22.1, p = 0.01) showed statistically significant association with fall incidents. In contrast, neither ramelteon (OR: 7.95, 95% CI: 0.72–87.9, p = 0.09) nor suvorexant (OR: 0.25, 95% CI: 0.06–1.06, p = 0.06) were significantly associated with fall incidents. Thus, benzodiazepine receptor agonists, but not ramelteon or suvorexant, showed significant association with fall incidents. Therefore, special care should be taken especially when benzodiazepine receptor agonists are administered to elderly subjects. In contrast, fall risk may be much less in patients treated with ramelteon or suvorexant. These results could help us to conduct safer drug treatment for insomnia patients aged no less than 75 years.

Key words fall incident; hypnotic drug; benzodiazepine receptor agonist; ramelteon; suvorexant; elderly patient

INTRODUCTION

Epidemiological studies have indicated that approximately 28–35% of elderly subjects aged over 65 years experienced fall incidents annually.1–3 In care facilities, fall incidents were accompanied by bone fracture (approximately 4%) and by other serious injuries (approximately 12%), such as head injury, soft-tissue injury and severe lacerations.4 Furthermore, a multi-year observational study has reported that the fall incidents can be fatal, and hip fractures and head injuries are the most common after fall incidents in older adults.5 In addition, another study reported that approximately 50% of patients, who had fall injury events at home and required hospitalized treatment, discharged to nursing home.6 It is considered that physical and mental burden of these patients would be increased because of the prolonged time periods of staying at medical facility and nursing home outside of one’s own home by fall related trauma. Generally, people aged no less than 75 years with frail condition experience indoor fall incidents more frequently than those aged less than 75 years,7 and therefore, the fall incidents occurred in medical facilities are considered to be quite serious problems in the elderly subjects. Taking account of the fact that approximately 1.5 fall incidents occurred per bed per year,8 fall preventive care for hospitalized patients is one of the most important tasks for health care professionals. A variety of risk factors for fall incidents, including medications, should rigorously be removed.

In elderly subjects, sleep disorder is common,9 and, therefore, hypnotic drugs are widely prescribed. Until recently, benzodiazepine receptor agonists have been frequently used as major drugs for conventional treatment of insomnia; however, many researchers have pointed out that these conventional sedative drugs have several unpleasant side effects, such as residual daytime sleepiness and associated cognitive decline.9,10 as well as various kinds of complex behaviors, such as sleep-related eating disorder and sleep walking, with little or without memory, in the next morning following the drug administration.11 These various side effects could be strongly related to the increased fall risk. Thus, it is indispensable for elderly patients to select appropriate hypnotic drugs to maintain QOL and to improve prognosis. In view of these backgrounds, ramelteon (a melatonin receptor agonist), and suvorexant (an orexin receptor antagonist) have been developed in recent years.12,13 However, there have been no reports focusing on comprehensive analysis of the fall risk associated with hypnotic drugs including newer ones, such as ramelteon or suvorexant. Based upon the above backgrounds, we aimed
to investigate whether use of 3 major hypnotic drugs, namely benzodiazepine receptor agonists, ramelteon, and suvorexant, is actually associated with fall risk in hospitalized elderly patients aged no less than 75 years by a case-crossover study design.

MATERIALS AND METHODS

Setting  This is a retrospective and observational study performed at Kobe City Medical Center General Hospital (Kobe, Japan) which is an acute care hospital with 768 beds accommodating from primary to tertiary medical health care.

Outline of the Study Design  Fall incidents were defined as events in which the body regions such as knees, upper limbs, buttocks and lumbar region accidentally and unintentionally made contact with the lower places such as the floor or the ground. From the fall incident reports of hospitalized patients stored in the hospital, the identification number of the study patients and fall dates were extracted. Personal medical data, such as department, age, sex, and hypnotic drug administration, were recorded from the electronic medical chart. In the ward, patients often complain some sleep problems, which may be derived from various reasons, such as the environmental changes, mental distress caused by clinical conditions and pain derived from the wounded site due to operations or injuries. Therefore, medical doctors often newly add hypnotic drugs to treat these problems. Thus, we selected a case-crossover study design to determine whether initiation of hypnotic drugs could be associated with fall occurrence.

Definition of the Case and the Control Days  Based upon the case-crossover study design,\textsuperscript{14,15} the day immediately before the fall incident was defined as the case day (day-1) as previously described.\textsuperscript{16,17} The control days were defined as the days from 8 to 2 d before the fall incident (from day-8 to day-2) (Fig. 1). To avoid time-dependent changes in the patients’ backgrounds affecting fall incidents, the control days were restricted up to the day-8 (for 7 d). If the patient had multiple fall incidents, only the first fall incident was utilized. Days before hospitalization were excluded from the case or the control days because precise data on drug use were not available.

Delirium Assessment  To assess the possibility of delirium, a delirium screening tool (DST), which has been developed in Japan conforming to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) delirium criteria,\textsuperscript{18} was adopted as the hospital criteria. This tool has 98% sensitivity and 70% specificity to detect delirium, although it takes only 5 min for screening by a nurse. This tool consists of 3 categories (category A; levels of consciousness, arousal, and environmental awareness, category B; changes in cognition, and category C; variations in symptoms), which further have 11 subcategories, by retrospectively reviewing the symptoms of delirium for, at least, the past 24 h. When all of these categories are applicable for study subjects, we judged as delirium.

Patient Selection  Patients with fall incidents were col-

Fig. 1. Schematic Illustration for Definition of the Case and the Control Days

Fig. 2. Flowchart of Patient Enrollment
lected from electronic database recorded between November 1st, 2016 and October 31st, 2017. Among them, patients without the control days during hospitalization, those who died during the hospitalization, those with delirium on either the case or the control days, or those aged less than 75 years were excluded (Fig. 2). Because of the clinical path in this hospital, certain predefined hypnotic drugs, namely ramelteon or suvorexant, should be administrated in patients with delirium for protection against delirium. In addition, patients with delirium are generally at higher risk for fall incidents. Therefore, to avoid the drug selection bias in the risk estimation for fall incidents, patients with delirium have been excluded from this study population.

Data Analysis and Statistical Method Continuous variables were presented as the mean and standard deviation (S.D.), and categorical variables were shown as numbers and percentages. The association between hypnotic drug use and fall risk was assessed by a multivariate conditional logistic regression model, including other drugs than hypnotic drugs such as anti-hypertensives, anti-depressants, anti-psychothetics and opioid analgesics, using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R version 3.3.2 (The R Foundation for Statistical Computing, Vienna, Austria). Multivariate analysis results were reported as odds ratio (OR) with 95% confidence interval (CI). Statistical significance was defined as \( p < 0.05 \).

Ethics Approval Ethics approval for this retrospective study has been obtained from the ethical committee of Kobe City Medical Center General Hospital, and the protocol was conducted in accordance with the provision of the Declaration of Helsinki (as revised in Tokyo 2004). Because this is a retrospective and observational study without any interventions, informed consents from the study patients were not required. Data are presented in a manner that patient identification is impossible.

RESULTS

Patient Characteristics A flow chart of patient enrollment in this study is shown in Fig. 2. Among 434 patients with fall incident reports during the study period, 323 patients, in total, were excluded according to the exclusion criteria. In consequence, 111 patients were enrolled in this study. The mean age was 81.1 years (S.D.: 4.7, range: 75–97 years), and most of the enrolled patients were categorized between the ages of 75 and 89 (95.5%, \( n = 106 \)) (Fig. 3A). Gender distribution showed that 60 (54.1%) patients were male and 51 (45.9%) patients were female, with a male to female ratio of approximately 1.2:1 (Fig. 3B). Fall incident reports were found in 17 departments, and the most prevalent departments were respiratory medicine (14.4%, \( n = 16 \)), gastroenterology (12.6%, \( n = 14 \)) and surgery (9.9%, \( n = 11 \)) (Table 1). Comorbidities of the enrolled patients are shown in Table 2. Many of the study subjects suffered from cancer (24.3%, \( n = 27 \)) or congestive heart failure (10.8%, \( n = 12 \)) (Table 2). The accumulated total available numbers of these patient days in the case and the control days were 111 and 554 patient days, respectively (Table 3). Hypnotic drugs were administrated in 47 (42.3%) and 230 (41.5%) accumulated patient days in the case and the control days, respectively. Benzodiazepine receptor agonists were administrated in 22 (19.8%) and 80 (14.4%) accumulated
Table 2. Major Comorbidities of Study Subjects

| Comorbidities                      | % (n)  |
|-----------------------------------|--------|
| Cancer                            | 24.3 (27) |
| Congestive heart failure          | 10.8 (12) |
| Cerebral vascular accident        | 9.9 (11) |
| Peripheral vascular disease       | 4.5 (5) |
| Metastatic cancer                 | 3.6 (4) |
| Renal disease                     | 3.6 (4) |
| Diabetes                          | 2.7 (3) |
| Peptic ulcer                      | 2.7 (3) |
| Pulmonary disease                 | 1.8 (2) |
| Acute myocardial infarction       | 1.8 (2) |

Variables are expressed as percentages (%) and numbers (n).

Table 3. Proportion of the Hypnotic Drug and Other Drug Use in the Case and the Control Days

| Number of accumulated patient days | Control days (n = 554) | Case day (n = 111) | Total periods (n = 665) |
|-----------------------------------|------------------------|-------------------|------------------------|
| Hypnotic drugs                    | 41.5 (230)             | 42.3 (47)         | 41.7 (277)             |
| Hypnotic drug classes             |                        |                   |                        |
| Benzodiazepine receptor agonists  | 14.4 (80)              | 19.8 (22)         | 15.3 (102)             |
| Ramelteon                         | 26.5 (147)             | 24.3 (27)         | 26.2 (174)             |
| Suvorexant                        | 12.8 (71)              | 7.2 (8)           | 11.9 (79)              |
| Anti-hypertensives                | 56.1 (311)             | 53.2 (59)         | 55.6 (370)             |
| Anti-depressants                  | 6.9 (38)               | 5.4 (6)           | 6.6 (44)               |
| Anti-psychotics                   | 12.6 (70)              | 11.7 (13)         | 12.5 (83)              |
| Opioid analgesics                 | 21.7 (120)             | 19.8 (22)         | 21.4 (142)             |

Variables are expressed as percentages (%) and numbers (n).

patient days in the case and the control days, respectively. Ramelteon were administrated in 27 (24.3%) and 147 (26.5%) accumulated patient days in the case and the control days, respectively. Finally, suvorexant were administrated in 8 (7.2%) and 71 (12.8%) accumulated patient days in the case and the control days, respectively (Table 3). Thus, total hypnotic drugs and benzodiazepine receptor agonists, but not other hypnotic drugs than benzodiazepine receptor agonists, were more prevalently administrated in the case days than in the control days. Similarly, anti-hypertensives, anti-depressants, anti-psychotics, and opioid analgesics were less prevalently prescribed in the case days than in the control days (Table 3).

With regard to the component of benzodiazepine receptor agonists, zolpidem, zopiclone, brotizolam, eszopiclone, nitrazepam, and etizolam were administrated in 28, 22, 16, 14, 14, and 7 accumulated patient days, respectively, in the control days and 9, 3, 5, 4, 2, and 2 accumulated patient days, respectively, in the case days (Fig. 4).

Association between Hypnotic Drug Use and Fall Risk

In enrolled patients, doses of hypnotic drugs were not changed during the case and the control days. Therefore, effects of dose changes of the hypnotic drugs can be ignored. In addition, among the 31 enrolled patients who underwent surgery, one patient underwent it on the case day and two patients were operated on the control days. Other 28 patients were operated on neither the case nor the control days. The average time period from the surgery to the fall incidents was 20.5 ± 16.2 d. Thus, effects of surgery on fall incidents appear to be negligible in this study population.

Multivariate conditional logistic regression analyses showed the statistically significant association between hypnotic drug use and fall risk (OR: 2.85, 95% CI: 1.03–7.90, p = 0.04) (Fig. 5). In contrast, neither anti-hypertensives (OR: 0.90, 95% CI: 0.26–3.09, p = 0.87), anti-depressants (OR: 1.00, 95% CI: 0.10–10.4, p = 1.00), anti-psychotics (OR: 0.99, 95% CI: 0.28–3.56, p = 0.99), nor opioid analgesics (OR: 1.06, 95% CI: 0.33–3.36, p = 0.93) showed statistically significant association with fall incidents (Fig. 5). By classification of hypnotic drugs, furthermore, benzodiazepine receptor agonists (OR: 5.79, 95% CI: 1.52–22.1, p = 0.01) showed statistically significant association with fall risk; however, neither ramelteon (OR: 7.95, 95% CI: 0.72–87.9, p = 0.09), suvorexant (OR: 0.25, 95% CI: 0.06–1.06, p = 0.06), nor anti-hypertensives (OR: 0.89, 95% CI: 0.26–3.07, p = 0.86), anti-depressants (OR: 1.57, 95% CI: 0.14–17.0, p = 0.71), anti-psychotics (OR: 0.78, 95% CI: 0.20–3.10, p = 0.73), nor opioid analgesics (OR: 1.15, 95% CI: 0.35–3.83, p = 0.82) showed statistically significant association with fall incidents (Fig. 6).

Moreover, to explore prolonged sedative effects of these hypnotic drugs on the fall incidents for more than 1 d, we have also carried out the multivariate conditional logistic regression analyses by defining the day-2 as the case day and day-3 to day-8 as the control days (Fig. S1). By this study protocol, the accumulated total available numbers of the case and the control days were 98 and 443 patient days, respectively. Hypnotic drugs were administrated in 229 (42.3%) accumulated patient days, and benzodiazepine receptor agonists, ramelteon and suvorexant were administrated in 79 (14.6%), 147 (27.2%), and 71 (13.1%) accumulated patient days, respectively (Table S1). The multivariate conditional logistic regression analysis revealed that none of the hypnotic drugs showed statistically significant association with fall incidents (Figs. S2 and S3). Thus, prolonged effects of these hypnotic drugs on fall inci-
Distribution in the Length of Continuous Hypnotic Drug Administration

The numbers of continuous hypnotic drug administration during the case and the control days are shown in Fig. 7. A single day administration was the most common in benzodiazepine receptor agonists. In contrast, most of the ramelteon cases were continuous administration throughout the 8-d period. In case of suvorexant, on the other hand, a variety of administration periods from a single day to 8 d were observed. Thus, continuous drug administration was the most prevalent in ramelteon, and the least common in benzodiazepine receptor agonists, indicating the difference in the characteristics of these hypnotic drug use patterns in elderly patients.

DISCUSSION

This study explored, for the first time, the association between fall risk and use of newer hypnotic drugs, such as melatonin receptor agonist and orexin receptor antagonist as well as conventional ones, namely benzodiazepine receptor agonists, by a case-crossover study. We, in this study, first confirmed that hypnotic drug use was significantly associated with fall incidents. Then, the association of each hypnotic drug class use with fall risk was assessed. As we expected, benzodiazepine receptor agonists, but not ramelteon or suvorexant, showed statistically significant association with fall incidents.

Benzodiazepine receptor agonists bind to benzodiazepine-γ-aminobutyric acid, type A (GABAA) receptor-chloride chan-
nel complex in human brain. Most GABAA receptors comprise three types of subunits, namely α-, β- and γ-subunits, and each of them have multiple isoforms, α1–6, β1–3 and γ1–3, respectively. The α1 subunit is thought to be involved in sedative-hypnotic effect, and the both α2, α3, and α5 subunits are responsible for muscle relaxant effects, which can increase fall risk. In fact, the benzodiazepine receptor agonists, so far, have frequently been reported as one of the risk factors associated with fall incidents or fall associated-injuries. Among benzodiazepine receptor agonists, in this study, zolpidem, which has the highest selectivity to the α1 subunit and was supposed to have the least muscle relaxant effects, was most prevalently prescribed (Fig. 4). It appears to be of interest to compare the effects on fall incidents among different benzodiazepine receptor agonists with different duration of the drug actions or different selectivity to benzodiazepine receptor subunits; however, it obviously is impossible to analyze these points statistically in the present study because of the sample size. These points should be clarified in future studies.

On the other hand, ramelteon has much higher affinities than melatonin, a sleep-inducing factor, to both subtypes of melatonin receptors, such as melatonin receptor 1 (MT 1) and melatonin receptor 2 (MT 2). Suvorexant competitively inhibits the orexin, arousal-promoting factor, from binding to both two subtypes of orexin receptors, orexin receptor 1 (OX 1) and orexin receptor 2 (OX 2), resulting in somnolence. The action mechanism of ramelteon and suvorexant, which are not related to the benzodiazepine receptor, suggested us that benzodiazepine-related side effects, including fall incidents, may be infrequent in these hypnotic drugs.

Our study demonstrated that benzodiazepine receptor agonists have significant association with fall risk. In addition to numerous previous reports by other researchers, some case-crossover studies have also demonstrated the association between administration of benzodiazepine receptor agonists and fall or fall-related fractures. These reports are strong evidence supportive of our results. Although there was no significant association between ramelteon use and fall incident, an increasing tendency was observed (p = 0.09). Taking account of this result, we considered the possibility that the fall incidents may have resulted from the carryover effect of benzodiazepine receptor agonists which are, in general, frequently administered at the time when ramelteon begins to be prescribed. However, this was not the case as shown in Figs. S2 and S3. In addition, more than half (54.8%) of the patients administered with ramelteon in the case day were continuously treated by ramelteon from the day-8 (Fig. 7B).

Furthermore, the prevalence of benzodiazepine receptor agonist administration was not significantly different between patients treated with (18.5%, n = 5/27) and without (20.2%, n = 17/84) ramelteon on the case day (p = 1.00, by Fisher’s exact test). Thus, the decisive reason why increasing trend in fall risk with ramelteon was observed remains unclear. Interestingly, unlike benzodiazepine receptor agonists, suvorexant tended to be inversely associated with fall risk although it was statistically insignificant. Elderly patients enrolled in this study commonly suffered from cancers or congestive heart failure; therefore, they might frequently complain insomnia and thus hypnotic drugs might be frequently prescribed. Therefore, this information may provide novel safer options for insomnia treatment in such elderly patients, and may enable elderly patients who have already high fall risk to receive safer treatment as early as possible after hospital admission before the first fall event occurs.

This study has limitations. First, we designed the case-crossover study by defining the case day as one day immediately before fall incidents without the time frame based on the exact time of fall incidents and hypnotic drug administration. Previously published reports of a case-crossover study were performed on the condition that the direct harmful reactions related to hypnotic drugs would not last for more than one day. Therefore, we adapted and modified these study protocols for this study. Specifically, under the condition that the average length of stay in our hospital was 10.4 d in 2017, the time-frame length of each the case and the control days was determined to be 24 h, namely from 0 to 24 o’clock in a day. Second, as a result of the study protocol, accumulated patient numbers in the case and the control days were not so large. However, the great advantage in this case-crossover study design includes that the patient backgrounds are exactly the same between the case and the control days; therefore, relatively small numbers of patients are enough to be statistically analyzed. For this reason, confounders, including patient backgrounds, such as age, gender, past medical history and lifestyles, which do not change in the short-term, are regarded as well matched. Thus, even if the number of study patients is small, analysis accuracy can be higher than usual case-control studies with the same patient numbers. However, it may be necessary to confirm these results in other centers or multiple centers. Finally, considering the feature that the case-crossover study is able to detect association between the factors, but do not necessarily prove the cause and result relationship between them. In addition, the case-crossover study appears to be unable to detect causal factors which did not change during the case and the control days for 8 d at maximum. Furthermore, patient cases that did not have fall incidents during the study period are not included. Therefore, the current study is unable to clarify causal factors responsible for fall incidents in patients treated with ramelteon or suvorexant, although these points appear to be important. These factors may include hypotension, bradycardia, dizziness, impaired cognitive function, sarcopenia, frailty, and other risks for over sedation. Prevention and treatment of these disorders may be useful to reduce fall incidents. However, these points should be elucidated in future studies which include patients without fall incidents during the treatment with ramelteon or suvorexant. In any case, prospective studies with larger numbers of patients would be necessary to confirm the results of this study. In addition, comparison of these data with those in patients aged less than 75 should also be clarified in future studies.

In summary, this is the first study to simultaneously and comprehensively analyze the fall risk of multiple hypnotic drug class, including conventional sedative drugs, such as benzodiazepine receptor agonists, and newer non-sedative drugs, namely ramelteon and suvorexant, in elderly hospitalized patients at an acute care hospital. As a result, we revealed that hypnotic drug use, especially benzodiazepine receptor agonists, was a significant risk factor for fall incidents in hospitalized elderly patients, and that administration of suvorexant may be an alternative safer option for elderly patients. On the basis of these results, the balance of risks and benefits must be carefully considered prior to the administration of
these different classes of hypnotic drugs, and they should be limited to minimum number of prescriptions. Although fall risk of ramelteon and suvorexant in elderly patients should be further examined by further studies with larger numbers of patients and longer observation periods, these results appear to be useful to help medical staff to make safer selections for patients aged no less than 75 years from various kinds of hypnotic drugs in acute care hospitals.

Conflict of Interest  The authors declare no conflict of interest.

Supplementary Materials  The online version of this article contains supplementary materials.

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