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Risk of Falls with Benzodiazepine Receptor Agonists in Combination with Novel hypnotics.

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Abstract

Several risk factors for falls during hospitalization have been reported, of which hypnotics have a major influence. Insomnia is often intractable, and many cases are treated with two or more hypnotics; however, there is concern about the increased risk of falls due to the use of multiple hypnotics. Therefore, we aimed to clarify the effects of combining conventional and new hypnotics on the risk of falls. The impact of the concomitant use of hypnotics on the occurrence of fall events was evaluated retrospectively in patients 20 years of age and older received acute care medicine in a university hospital between January 2013 and August 2022. The survey items included age, sex, drug prescription status, whether a fall accident had occurred, and its circumstances. Of the 47,236 eligible patients, 976 experienced a fall accident during hospitalization (fall rate, 2.07%). Logistic regression analysis of the patient population not taking benzodiazepine receptor agonists showed that age (odds ratio [OR], 1.04), sex (OR, 0.84), and ramelteon use (OR, 3.06) independently contributed to falls. In contrast, in the patient population taking benzodiazepine receptor agonists, logistic regression analysis showed that only age (OR: 1.03) and sex (OR: 0.76) independently contributed to falls. This suggests that ramelteon, suvorexant, and lemborexant, in combination with benzodiazepines, may not increase the risk of falls. Hypnotics with novel mechanisms of action may not increase the risk of fall when combined with benzodiazepine receptor agonists.

Keywords: fall risk, hypnotics, acute care hospitals

Introduction

Falls in hospitalized patients, especially in the elderly, occur at a high frequency [1], leading to prolonged hospitalization, decreased quality of life, and prognosis worsening [2], making falls a problem for which solutions are strongly desired in clinical practice [3,4]. Many reports have shown that drugs affect falls, with hypnotics having a significant effect on falls [5-10]. Benzodiazepine receptor agonists are widely used as hypnotics, but the increased risk of patient falls has become a clinical concern [11-14]. Additionally, benzodiazepine receptor agonists are dependent, making their long-term continuous use problematic.

In recent years, novel hypnotics with different mechanisms, melatonin receptor agonists, and orexin receptor antagonists have been increasingly used. Due to their mechanism of action, they are thought to have a low inhibitory effect on physical activity, and the effect of taking these drugs on the risk of falls is considered small. However, some reports have shown that novel hypnotics increase the risk of falls [11], and the effects of novel hypnotics on the risk of falls are not fully understood.

In addition, an increasing number of patients are switching from benzodiazepine receptor agonists to these novel hypnotics in view of dependence and fall risk, or are combining benzodiazepine receptor agonists with novel hypnotics due to treatment refractoriness [15], however, the impact on fall risk associated with the use of novel hypnotics in these patients has not been clarified.

This study aimed to evaluate the risk of falls associated with the use of a melatonin receptor agonist or orexin receptor antagonist in combination with a benzodiazepine receptor agonist. All inpatients admitted to the Gunma University Hospital over the past 10 years were analyzed.

Methods

Patient cohort

All patients aged ≥ 20 years who were admitted to Gunma University Hospital between January 2013 and August 2022 were included in this study. For patients who were hospitalized multiple times during the study period, only the first hospitalization was included; the second and subsequent hospitalizations were excluded. To control for variations in patients' medical conditions and other factors, patients who were hospitalized for less than 4 days or more than 8 weeks were excluded. Patients who fell within three days of admission were also excluded to exclude the effect of environmental changes due to hospitalization.

Study design

The relationship between the type of medication prescribed and the occurrence of falls during the period of hospitalization was analyzed in a cohort of patients. Patient groups selected according to the above criteria were surveyed for sex, age, history of prescriptions for sleeping pills, and fall records. Inpatient fall records were collected from incident reports submitted by medical staff, and falls were evaluated according to a previous report by Gibson [16]. All drugs prescribed to patients during their hospital stay were electronically extracted from medical records.

The drugs analyzed were the following 28 drugs classified as sleeping pills (Estazolam, Flurazepam, Nitrazepam, Haloxazolam, Triazolam, Flunitrazepam, Brotizolam, Lormetazepam, Oxazolam, Cloxazolam, Diazepam, Fludiazepam, Bromazepam, Medazepam, Lorazepam, Alprazolam, Mexazolam, Tofisopam, Chlordiazepoxide, Ethyl Loflazepate, Quazepam, Rilmazafone, Zopiclone, Zolpidem, Eszopiclone, Ramelteon, Suvorexant, and Lemborexant) by the therapeutic category of drugs defined by the Japanese Ministry of Health and Labor Welfare, which have been used for inpatients at Gunma University Hospital in the past. The following 28 sleeping pills were included in the analysis.

To exclude drugs prescribed as needed but not actually taken, prescriptions of two days or less were not considered. In addition, prescriptions after the occurrence of a fall were excluded from the analysis in cases where a fall occurred. This study was approved by the Gunma University Ethics Review Board for Medical Research Involving Human Subjects (Study No. HS2020-154).

Statistical analysis

Among the sleep medication prescription cases, risk factors for falls were analyzed using multivariate logistic regression analysis, with sex and prescription of each medication as categorical variables and age as a continuous variable. The risk factors for falls for each sleeping medication

were also analyzed using the same technique. All statistical analyses were performed using IBM SPSS Statistics for Windows version 28 (IBM). The significance level was set at $p < 0.05$.

Results

The analysis included 47,236 inpatients, of whom 976 were included as falls (fall rate: 2.07%) (Table. 1). In the subgroup of patients not prescribed benzodiazepine receptor agonists (37,346 patients), multivariate analysis was conducted to examine the impact of age, sex, ramelteon, suvorexant, and lemborexant on falls. The results showed that age (odds ratio [OR]: 1.04), sex (OR: 0.84), and ramelteon (OR: 3.06) independently contributed to falls (Table. 2). In contrast, in patients prescribed benzodiazepine receptor agonists (9,890 patients), only age (odds ratio [OR]: 1.03) and gender (OR: 0.76) were identified as independent factors contributing to falls (Table. 3).

Discussion

The rate of falls in patients who took hypnotics during the study period was similar to previous reports [3,10,17]. An analysis of the risk of falls with ramelteon, suvorexant, and lemvorexant in a patient population not using benzodiazepine receptor agonists showed that ramelteon was associated with a

significantly increased risk of falls. In contrast, no drugs showed a significant difference in the patient population treated with benzodiazepine receptor agonists. The results suggest that suvorexant and lemvorexant do not increase the risk of falls, either alone or in combination with benzodiazepine receptor agonists. Some reports have demonstrated that orexin receptor antagonists are not associated with the risk of falls [12,14], and our results support this finding. Furthermore, these results show that orexin receptor antagonists, even when used in combination with benzodiazepines, do not increase the risk of falls and can be used relatively safely.

Although ramelteon was associated with an increased risk of falls when used alone, it did not increase the risk of falls when used in combination with benzodiazepine receptor agonists. Ramelteon is known to have fewer hypnotic effects than benzodiazepine receptor agonists and orexin receptor antagonists [18]. When used alone, it does not provide adequate sleep, which may have increased the risk of falls due to increased nocturnal activity. However, when used in combination with a benzodiazepine receptor agonist, the agonists may have produced sufficient effects to make the risk of falls comparable to baseline.

This study has some limitations. Firstly, we were unable to adjust for the impact of medications other than hypnotics on falls. Secondly, we could not assess the influence of the dosage and timing of the medication. Thirdly, we did not evaluate the effects of the patient's conditions or disease status, and other treatment interventions. To address these limitations, a more detailed analysis incorporating

additional information is necessary. Additionally, in the group using two types of medications during hospitalization, it has not been confirmed whether the prescriptions for the two drugs overlapped in terms of timing. Therefore, there is a possibility that cases within the group using two medications may include instances where the type of hypnotics was changed during hospitalization, potentially leading to an underestimation of the fall risk associated with co-administration. Verification through future prospective clinical trials is deemed necessary to investigate the potential increase in fall risk associated with the concurrent use of these medications.

Conclusion

This study evaluated the risk of falls when benzodiazepine receptor agonists were combined with melatonin receptor agonists or orexin receptor antagonists in all patients aged 20 years or older admitted to a university hospital in the past 10 years. Concomitant use of a melatonin receptor agonist or orexin receptor antagonist with a benzodiazepine receptor agonist had no effect on the increased risk of falls. The results also suggest that the risk of falls may be high for ramelteon when used alone. To our knowledge, this is the first study to use big data to determine the effect of individual sleep-inducing drugs and concomitant medications on the occurrence of falls. Compared to previous reports, the sample size of this study was much larger, and patient background was controlled to some extent, including adjustment for hospitalization days; therefore, we believe that the results are highly reliable.

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variable		All inpatients	Falls (%)		Non-falls inpatients (%)	
Sex						
	Male	22,943	546	(2.38)	22,397	(97.62)
	Female	24,293	430	(1.77)	23,863	(98.23)
	Total	47,236	976	(2.07)	46,260	(97.93)
Age		61.7±17.2	71.0±13.6		61.5±17.2	
Estazolam		185	16	(8.65)	169	(91.35)
Flurazepam		1	0	(0.00)	1	(100.00)
Nitrazepam		280	13	(4.64)	267	(95.36)
Haloxazolam		1	0	(0.00)	1	(100.00)
Triazolam		559	20	(3.58)	539	(96.42)
Flunitrazepam		329	22	(6.69)	307	(93.31)
Brotizolam		3,431	145	(4.23)	3,286	(95.77)
Lormetazepam		41	1	(2.44)	40	(97.56)
Oxazolam		8	0	(0.00)	8	(100.00)
Cloxazalam		47	2	(4.26)	45	(95.74)
Diazepam		320	23	(7.19)	297	(92.81)
Fludiazepam		6	0	(0.00)	6	(100.00)
Bromazepam		73	0	(0.00)	73	(100.00)
Medazepam		3	0	(0.00)	3	(100.00)
Lorazepam		297	13	(4.38)	284	(95.62)
Alprazolam		320	10	(3.13)	310	(96.88)
Mexazolam		3	0	(0.00)	3	(100.00)
Tofisopam		38	2	(5.26)	36	(94.74)
Chlordiazepoxide		4	0	(0.00)	4	(100.00)
Ethyl Loflazepate		134	7	(5.22)	127	(94.78)
Quazepam		28	2	(7.14)	26	(92.86)
Rilmazafone		83	2	(2.41)	81	(97.59)
Zopiclone		92	4	(4.35)	88	(95.65)
Zolpidem		4,817	140	(2.91)	4,677	(97.09)
Eszopiclone		478	16	(3.35)	462	(96.65)
Ramelteon		292	13	(4.45)	279	(95.55)
Suvorexant		248	11	(4.44)	237	(95.56)
Lemborexant		98	6	(6.12)	92	(93.88)

Table 1

Patient Background for this Study.

variable		All inpatients (% of total)		Falls (% of total)		Non-falls inpatients (% of total)		Multivariate adjusted		p value
								OR	(95% CI)	
Sex										
	Male	18,463	(49.44)	361	(0.97)	18,102	(48.47)			
	Female	18,883	(50.56)	267	(0.71)	18,255	(48.88)	0.84	(0.72-0.99)	< 0.05
	Total	37,346	(100.00)	628	(1.68)	36,718	(98.32)			
Age		61.3±17.5		71.3±13.3		61.1±17.5		1.04	(1.03-1.05)	< 0.05
Ramelteon		349	(0.93)	24	(0.06)	325	(0.87)	3.06	(1.97-4.75)	< 0.05
Suvorexant		378	(1.01)	14	(0.04)	364	(0.97)	1.53	(0.88-2.66)	0.14
Lemborexant		392	(1.05)	11	(0.03)	381	(1.02)	1.26	(0.68-2.33)	0.47

Table 2

Effects of the concomitant use of novel sleep medications on falls in patients not taking benzodiazepine receptor agonists.

variable		All inpatients (% of total)			Falls (% of total)			Non-falls inpatients (% of total)			Multivariate adjusted		p value
											OR	(95% CI)	
Sex													
	Male	4,480	(	45.30)	185	(	1.87)	4,295	(	43.43)			
	Female	5,410	(	54.70)	163	(	1.65)	5,247	(	53.05)	0.76	(0.62-0.95)	< 0.05
	Total	9,890	(	100.00)	348	(	3.52)	9,542	(	96.48)			
Age		63.4±16.0			70.3±14.0			63.1±16.0			1.03	(1.03-1.04)	< 0.05
Ramelteon		292	(	2.95)	13	(	0.13)	279	(	2.82)	1.13	(0.63-2.00)	0.68
Suvorexant		248	(	2.51)	11	(	0.11)	237	(	2.40)	1.19	(0.64-2.21)	0.59
Lemborexant		98	(	0.99)	6	(	0.06)	92	(	0.93)	1.70	(0.73-0.39)	0.22

Table 3

Effects of the concomitant use of novel sleep medications on falls in patients taking benzodiazepine receptor agonists.