Assessment of the Relationship between Hypnotics and Delirium Using the Japanese Adverse Drug Event Report (JADER) Database

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The Japanese Adverse Drug Event Report (JADER) database was used to examine the risk of delirium and the time of its onset with various hypnotics, including 10 benzodiazepines (BZDs), 3 non-benzodiazepines (non-BZDs), 1 melatonin receptor agonist (MRTA), and 1 orexin receptor inhibitor (OXRI). Data entered in the JADER database between April 1, 2004 and February 1, 2016 were analyzed. The index for safety signal detection, the reporting odds ratio (ROR), was the odds ratio for adverse drug reaction reporting. The ROR for each drug was calculated; a signal was considered present if the lower bound of the 95% confidence interval of the ROR was greater than 1. The time to onset of delirium was calculated for drugs for which the number of days from the start of drug administration to delirium onset was reported. During the period examined in the analysis, a total of 621114 adverse drug reaction reports were seen, and the total number of delirium reports was 1417 after redundant cases were excluded. A signal was detected for 5 of the 10 BZDs and all 3 non-BZDs, with no signal for the MRTA and the OXRI. The time of delirium onset varied widely even for drugs classified as being in the same action duration group, and no correlation was seen for delirium onset time. The results of this study suggested that delirium risk varies depending on the hypnotic. Thus, hypnotics can be selected according to their delirium risk.

Key words—The Japanese Adverse Drug Event Report; reporting odds ratio; delirium

INTRODUCTION

Delirium is an acute psychiatric condition with symptoms such as cognitive decline, impaired attention, restlessness, sleep disorder, and disturbed orientation. It is seen frequently in the clinical setting, occurring in approximately 10% of admitted patients and 40% of those aged 70 years or older.1) Prolongation of hospitalization and an increase in mortality have been reported to result from delirium.2,3) Consequently, treatment of the underlying disease and early intervention are necessary. Although delirium is treated through interventions that are adapted to each patient’s background, such as drug therapy, eliminating causal factors, and controlling stress and sleep,4) no definitive treatment guidelines have been established, making prevention important. Direct factors, precipitating factors, and promoting factors have been implicated as playing a role in the cause of delirium.1) Central nervous system (CNS) disease, metabolic disease, alcohol, and drugs have been found to be direct factors; structural brain disorders such as cerebrovascular disorders and decreased cerebral function caused by aging have been found to be precipitating factors; and psychological stress and sleep disorders have been reported as promoting factors. Of these, the use of drugs, a direct factor, has been suggested to have a major effect as a causal factor, with hypnotics in particular acting as a trigger for delirium.5)

Insomnia is a typical sleep disorder with a high prevalence. Between 20% and 25% of adults have insomnia symptoms such as difficult sleep onset, early morning awakening, nocturnal awakening, and difficulty reaching deep sleep. Moreover, insomnia has been reported to have a strong effect on quality of life.6) Hypnotics are highly versatile drugs and are currently prescribed at a frequency of once every 3 months to 4.7% of the Japanese population.7) They are prescribed not only in the field of psychiatry, but also widely in general practice.8) Consequently, they are often taken orally by patients who are at risk of
delirium. In Japan, 4 types of hypnotics have been marketed: benzodiazepines (BZDs), non-benzodiazepines (non-BZDs), melatonin receptor agonists (MRTAs), and orexin receptor inhibitors (OXRIs). An increased risk of delirium has been reported with the use of hypnotics, and it has been suggested that central excitotoxicity due to liberation of dopamine is involved. There have been no reports addressing whether the risk differs between drugs with different pharmacological actions and durations of action. In recent years, it has been shown that the relationship between adverse drug reactions and drugs can be examined using massive databases of real-world adverse drug reactions to calculate a safety signal, the reporting odds ratio (ROR). Adverse drug reaction studies have used the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS), published by the FDA in the United States, and the Japanese Adverse Drug Event Report (JADER) database, published by the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan. Although both databases hold enormous amounts of adverse drug reaction data, the per capita rate of BZD use in Japan is approximately 6-fold higher than in the United States, suggesting that there are regional variations in hypnotic use. Therefore, to obtain results that reflect actual clinical practice in Japan, using the adverse drug reaction reports stored in the JADER database was considered preferable. Consequently, in this study, the JADER database was used to examine the risk of delirium and the time of its onset with the use of various hypnotics.

**METHODS**

**Construction of Database** Data entered in the JADER database between April 1, 2004 and February 1, 2016 were analyzed. The JADER data consists of 4 files: a patient listing table (demo), a drug data table (drug), an adverse drug reaction table (reac), and an underlying disease table (hist). The data tables are divided by ID number. The present analysis examined reports in which “suspect drug” was indicated in the section on drug involvement. Based on the report by Hosomi et al., multiple reports that were registered in the database in duplicate were deleted based on case information, and each case was regarded as one report. Furthermore, the cases with inaccurate date were excluded.

**Analyzed Drugs and Adverse Event Names** All of the drugs examined in the analysis had an indication for insomnia. The 10 BZDs included in the analysis were ultra-short-acting (triazolam), short-acting (rilmazafone, brotizolam, and lormetazepam), intermediate-acting (flunitrazepam, nitrazepam, estazolam, nimetazepam, and quazepam), and long-acting (flurazepam) BZDs. The 3 non-BZDs included were eszopiclone, zopiclone, and zolpidem. The MRTA included was ramelteon, and the OXRI was suvorexant. The adverse event terms used in the JADER database are in conformance with the Medical Dictionary for Regulatory Activities (MedDRA), and the term used to extract patients with delirium was “delirium” (PT 10012218), which is given as the preferred term (PT) in MedDRA 19.0J. Within noninfectious encephalopathy/delirium (SMQ 20000133), delirium was considered to be two items, delirium (PT 10012218) and delirium febrile (PT 10059267). However, none of the drugs related to delirium febrile corresponded to the drugs targeted in this study. Thus, the number of subjects did not change in both SMQ and PT. Therefore, the analysis was conducted using only delirium (PT 10012218), contained in noninfectious encephalopathy / delirium (SMQ 20000133).

**Outcome Item** The index for safety signal detection, the ROR, was the odds ratio for adverse drug reaction reporting. The ROR for each drug was calculated by extracting the adverse drug reaction delirium for individual drugs and classifying adverse drug reactions other than delirium as “other” (Fig. 1). For example, these are explained calculation of triazolam. $n_{21}$ is the number excluding the drugs targeted as “suspect drugs” of delirium. There are seven reports of triazolam as a “suspect drug” of delirium, so if you subtract these from the total number of delirium side effects (1417 cases), $n_{21}$ will be 1410 cases (Table 1). $n_{22}$ is 619512 cases, which is the result of subtracting all side effects (185 cases) other than delirium for triazolam from all side effects (619697 cases) except delirium. The ROR detection criterion was that a signal was considered present if the lower bound of the 95% confidence interval (CI) of the ROR was greater than 1. A designation of “not available” (N/A) was used if there were no reports of adverse drug reactions, and the ROR could therefore not be calculated.

In the analysis of the time of delirium onset, the time to onset was calculated for drugs for which the
Fig. 1. ROR of Drug-induced Delirium in JADER

Table 1. Number of Reports of ROR and Adverse Events Related to Drug-induced Delirium in JADER

<table>
<thead>
<tr>
<th>Classification</th>
<th>Drug</th>
<th>Total Case</th>
<th>Reporting Fraction (%)</th>
<th>ROR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepine (ultra-short-acting)</td>
<td>Triazolam</td>
<td>192</td>
<td>7</td>
<td>3.65</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16.62 (7.80–35.42)</td>
</tr>
<tr>
<td></td>
<td>Rilmazafone</td>
<td>62</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Brotizolam</td>
<td>471</td>
<td>7</td>
<td>1.49</td>
</tr>
<tr>
<td></td>
<td>Lormetazepam</td>
<td>75</td>
<td>2</td>
<td>2.67</td>
</tr>
<tr>
<td></td>
<td>Flunitrazepam</td>
<td>621</td>
<td>8</td>
<td>1.29</td>
</tr>
<tr>
<td></td>
<td>Nitrazepam</td>
<td>207</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Estazolam</td>
<td>108</td>
<td>4</td>
<td>3.70</td>
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<tr>
<td></td>
<td>Nimetazepam</td>
<td>5</td>
<td>0</td>
<td>0</td>
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<tr>
<td></td>
<td>Quazepam</td>
<td>160</td>
<td>1</td>
<td>0.63</td>
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<tr>
<td></td>
<td>Flurazepam</td>
<td>14</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Eszopiclone</td>
<td>44</td>
<td>4</td>
<td>9.09</td>
</tr>
<tr>
<td></td>
<td>Zopiclone</td>
<td>284</td>
<td>6</td>
<td>2.11</td>
</tr>
<tr>
<td></td>
<td>Zolpidem</td>
<td>827</td>
<td>50</td>
<td>6.05</td>
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<tr>
<td></td>
<td>Ramelteon</td>
<td>112</td>
<td>0</td>
<td>0</td>
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<tr>
<td></td>
<td>Suvorexant</td>
<td>86</td>
<td>1</td>
<td>1.16</td>
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<td>Nonbenzodiazepine</td>
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<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Melatonin receptor agonist</td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>Orexin receptor antagonist</td>
<td></td>
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</tbody>
</table>

ROR = \( \frac{\frac{n_{11}}{n_{21}}}{\frac{n_{12}}{n_{22}}} \)

95% CI = \( e^{\ln \text{ROR}} \pm 1.96 \sqrt{\frac{1}{n_{11}} + \frac{1}{n_{12}} + \frac{1}{n_{21}} + \frac{1}{n_{22}}} \)

The number of days from the start of drug administration to delirium onset was reported. The analysis software used was JMP® 9.0.2 (SAS Institute Japan Ltd., Tokyo).

RESULTS

Number of Reports during the Follow-up Period

During the period examined in the analysis, a total of 62114 adverse drug reaction reports were seen, and the total number of delirium reports was 1417 after redundant cases were excluded.

Comparison of the RORs of Delirium Reports for BZDs

The number of delirium reports (proportion of number of delirium reports to the total number of adverse drug reaction reports) and the ROR (95% CI) for ultra-short-acting BZDs were: 7 (3.65%) and 16.62 (95% CI: 7.80 to 35.42), respectively, for triazolam (Table 1); 0 reports for the short-acting BZD rilmazafone, and the ROR was therefore not calculated for rilmazafone; 7 (1.49%) and 6.63 (95% CI: 3.14 to 14.00) for brotizolam; and 2 (2.67%) and 12.0 (95% CI: 2.94 to 48.93) for lormetazepam. Among the intermediate-acting BZDs, the number of reports and ROR were 8 (1.29%) and 5.73 (95% CI: 2.85 to 11.54), respectively, for flunitrazepam; 4 (3.70%) and 16.87 (95% CI: 6.20 to 45.84) for estazolam; and 1 (0.63%) and 2.75 (95% CI: 0.38 to 19.67) for quazepam. There were 0 reports for nitrazepam and nimetazepam. There were 0 reports for the long-acting BZD flurazepam, and the ROR was therefore not calculated. For 5 of the 10 BZDs, the lower bound of the 95% CI of the ROR was greater than 1, meaning that a signal was detected.
Comparison of the RORs of Delirium Reports for non-BZDs  The number of delirium reports with non-BZDs (proportion of number of delirium reports to the total number of adverse drug reaction reports in parentheses) and the ROR (95% CI) were: 4 (9.09%) and 43.85 (95% CI: 15.67 to 122.73), respectively, for eszopiclone; 6 (2.11%) and 9.47 (95% CI: 4.21 to 21.30) for zopiclone; and 50 (6.05%) and 29.14 (95% CI: 21.78 to 38.97) for zolpidem (Table 1). For all 3 non-BZDs, the lower bound of the 95% CI of the ROR was greater than 1, meaning that a signal was detected.

Comparison of the RORs of Delirium Reports for the MRTA and OXRI  There were no reports of delirium with the MRTA ramelteon, and an ROR therefore could not be calculated. With the OXRI suvorexant, there was 1 report of delirium (1.16%) and the ROR was 5.14 (95% CI: 0.72 to 37.00); the lower bound of the 95% CI was less than 1, meaning that a signal was not detected.

Time of Onset Related to Delirium Reports  Next, the time from the first day of administration to delirium onset was examined (Fig. 2). The median time to delirium onset was 43 d for triazolam, 40 d for brotizolam, 649 d for lormetazepam, 11 d for flunitrazepam, 28 d for estazolam, 111 d for eszopiclone, 3 d for zopiclone, and 5 d for zolpidem.

DISCUSSION

Although drugs have previously been reported to trigger delirium, this study focused particularly on frequently prescribed hypnotics and analyzed the relationship between each hypnotic and the risk of delirium. The results showed that a signal was detected for 5 of the 10 BZDs and all 3 non-BZDs. On the other hand, no signal was detected for the MRTA and the OXRI, suggesting that the risk of delirium varies with the drug.

BZDs and non-BZDs bind to the GABA_A receptor and exert their effects by promoting receptor activation. GABA_A receptors consist of 6 α subunits (α1 to α6), 3 β subunits (β1 to β3), and 2 γ subunits (γ1 and γ2), and the combination of these subunits results in a variety of physiological effects. BZDs and non-BZDs inhibit the release of GABA from GABA neurons by binding with the α1 GABA_A receptor, which is a GABA_A receptor with an α1 subunit. This is known to facilitate the release of dopamine by eliminating GABA’s inhibition of dopamine neurons. It has been suggested that increased dopamine is a causal factor in delirium, which implies that α1 GABA_A receptor activation plays a major role in its onset. In the present study, signals were detected with 5 BZDs and the non-BZDs. Moreover, the BZDs are divided by duration of action into 4 types (ultra-short-acting, short-acting, intermediate-acting, and long-acting), and the delirium signal tended to decrease as the duration of action increased. The ultra-short-acting and short-acting types transiently increase inhibition of the central nervous system, and a reflexive release of dopamine has been seen, as compared with the long-acting type, as their effects diminish.
while the inhibition constant (Ki) of eszopiclone for the GABA_A receptor is 50 to 160 nM, the Ki of flunitrazepam is low, 2 to 7 nM, indicating that the binding affinity for the GABA_A receptor weakens as the duration of drug action increases.\textsuperscript{10} This is thought to impede a reflexive increase in dopamine, a tendency that was also seen in the present study. Although the results suggested that the risk of delirium is low with rilmazafone, nitrazepam, nimetazepam, and flurazepam, for which no signal was detected, there were too few adverse drug reaction reports as a whole for these drugs. Hosomi et al.\textsuperscript{18} reported that, when the number of reports is small, the range of the 95% CI increases, making it difficult to see a signal.\textsuperscript{18} Further investigation of these drugs is therefore necessary.

The non-BZDs have little carryover effect the next day and are very safe.\textsuperscript{19} Consequently, they are widely used hypnotics. However, a significant signal was detected for all 3 non-BZDs examined in this study (eszopiclone, zopiclone, and zolpidem), and all 3 showed a stronger signal than the ultra-short-acting BZDs. Of the GABA_A receptors, zopiclone and zolpidem have been reported to exert a particularly strong effect on the \( \alpha_1 \) GABA_A receptor,\textsuperscript{16} and the present results suggest that they may more readily dis-inhibit dopamine and thereby cause delirium than the BZDs.

No significant signal was seen for the MRTA ramelteon. Melatonin is a pineal hormone, and it plays an important role in regulating the sleep-wake rhythm. Ramelteon induces sleep by stimulating the melatonin receptor and increasing the melatonin concentration.\textsuperscript{20} The risk of delirium in preoperative patients has been reported to increase when the melatonin concentration is low and to decrease with prophylactic oral administration of ramelteon.\textsuperscript{21,22} The fact that no signal was seen for ramelteon in the present study also suggested that ramelteon is not involved in the onset of delirium.

As with ramelteon, no significant signal was seen with the OXRI suvorexant. Suvorexant inhibits orexin receptor type 1, which plays a role in anxiety, and orexin receptor type 2, which is involved in maintaining wakefulness. It has anxiolytic and hypnagogic effects and promotes sleep maintenance after sleep onset.\textsuperscript{23} It has been suggested that, because suvorexant exerts a hypnotic effect that is not mediated by the \( \alpha_1 \) GABA_A receptor, it does not cause dopamine dis-inhibition and therefore carries a low risk of delirium. The present results and a variety of other findings indicate that ramelteon and suvorexant carry little risk of delirium. Moreover, ramelteon has been reported not only to be associated with a low risk of delirium, but it may also be linked to delirium prevention. Consequently, these may become typical hypnotics that can be safely used instead of BZD hypnotics in patients at high risk of delirium.

In the analysis of the time of delirium onset, which included drugs for which the number of days from the start of administration to delirium onset had been reported, data were obtained for 3 groups, the ultra-short-acting and intermediate-acting BZDs and the non-BZDs. The time of onset varied widely even for drugs classified as being in the same action duration group, and no correlation was seen for onset time. Moreover, no correlation was seen between time of onset and differences in drug half-life or Ki for the GABA_A receptor. Evidence suggests that the factors involved in the onset of delirium are not only pharmaceutical, but that factors such as environmental changes and organic brain disorders also play a role.\textsuperscript{1} That is, it is highly likely that taking a drug that carries a risk of delirium combined with other risk factors results in delirium onset. It was surmised that this explained the fact that the number of days to delirium onset varied even for drugs of the same type and with the same effects. Consequently, when a patient at high risk of delirium takes a drug that carries a risk of delirium, vigilant monitoring is needed, regardless of the time of oral administration. Pharmacoepidemiological studies using the JADER database are an excellent way to detect trends in the onset of adverse drug reactions, and it is anticipated that this method will be further used in the future. However, its shortcomings include the fact that the JADER database is a spontaneous reporting database, that there is no control group, and that, although the ROR can show the relationship between a drug and delirium, the size of the signal cannot simply be compared with that of other drugs because the total number of adverse drug reaction reports, which is the ROR denominator, varies with the drug. In addition, detection was performed only for the suspect drug in this study, without taking into account factors such as concomitant drugs, duplicate administration of hypnotic drugs, patient characteristics, route of administration, and clinical history. Therefore, the possibility...
that factors other than the drug were involved cannot be ruled out. However, combining adverse drug reaction evaluation and analysis with the results of analysis using the JADER database could lead to the prevention and early detection of adverse drug reactions and to pharmacological management that prevents them from becoming serious.12,13 Although it was previously thought that hypnotics uniformly increase the risk of delirium, the results of this study suggest that the risk varies depending on the hypnotic used. This indicates a basis for selecting a hypnotic according to the delirium risk it carries, and it may be meaningful information that contributes to maintaining good sleep and inhibiting delirium.

Conflict of Interest The authors declare that they have no conflict of interest.

REFERENCES