BPB Reports

Report

Analysis of the Possibility of Drug-Induced Aspiration Pneumonia Due to Anxiolytics by Using the Japanese Adverse Drug Event Report Database

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Received March 6, 2022; Accepted May 2, 2022

With societal aging, the number of patients with aspiration pneumonia is increasing. However, because the relationship between drug use and the development of aspiration pneumonia is not fully understood, improvements in information on the possibility of drug-induced aspiration pneumonia are urgently needed. Hence, in this study, we investigated the relationship between the use of anxiolytics and the development of aspiration pneumonia by using data from the Japan Adverse Drug Event Report (JADER) database. We found that anxiolytics had a signal for the development of aspiration pneumonia with a reporting odds ratio (ROR) of 3.2 (95% confidence interval: 2.5–4.1), and seven of eight anxiolytics for which the development of aspiration pneumonia was reported in the JADER database had a signal as well. Of note, the possibility of the development of aspiration pneumonia was mentioned only in the package inserts of clobazam among the package inserts or risk management plans (RMPs) of these anxiolytics. These results suggest the need for including information on the possibility of aspiration pneumonia development in drug package inserts and RMPs so as to prevent anxiolytic-associated aspiration pneumonia or facilitate its early detection.

Key words aspiration pneumonia, anxiolytics, adverse drug reactions, the Japanese Adverse Drug Event Report database

INTRODUCTION

Given societal aging, the increasing incidence of aspiration pneumonia requires close attention. More than 40,000 people died from aspiration pneumonia in 2020 in Japan, approximately three times the number of deaths from breast cancer and almost the same as those attributable to gastric cancer.[1)] Therefore, identification of the risk factor of aspiration pneumonia is important to prevent the development of aspiration pneumonia. Aspiration pneumonia is understood to be caused by inflammation and lung tissue damage caused by the aspiration of food, bacteria in the oral cavity, or stomach fluid, which is associated with frailty and sarcopenia.[2,3)] Besides older age, sex, dehydration, and dementia have been identified as risk factors for aspiration pneumonia.[4–6)]

Psychopharmaceuticals are known to induce dysphagia,[7,8)] and antipsychotics are reported to increase the risk of aspiration pneumonia.[9)] However, the relationship between the use of anxiolytics and the development of aspiration pneumonia is not sufficiently understood. To alert healthcare professionals about adverse drug reactions (ADRs) by providing them with the relevant information is important for the prevention and early detection of ADRs. Therefore, accumulation of information on the possibility of aspiration pneumonia is expected to be useful for the prevention and early detection of drug-induced aspiration pneumonia. Hence, in this study, we investigated the possibility of anxiolytic-induced aspiration pneumonia by using data from the Japanese Adverse Drug Event Report (JADER) database. Furthermore, we investigated the description of the possibility of aspiration pneumonia in package inserts and risk management plans (RMPs), which are typical drug information sources in Japan.

MATERIALS AND METHODS

Database Source Used in the Analysis Adverse drug event reports in the JADER database were downloaded from the Pharmaceuticals and Medical Devices Agency (PMDA) website (http://www.info.pmda.jp; May 7, 2021). Overall, 678,913 cases reported to the PMDA from the first quarter of 2004 to the fourth quarter of 2020 were included. The JADER data consist of four tables: "Demo," containing the case list; "Drug," containing drugs used in the cases; "Reac," listing ADRs reported in the cases; and "Hist," showing primary diseases in the cases. The "Demo," "Drug," and "Reac" tables were used in this study. Descriptive notations for age (e.g., infant and elderly) are included in the JADER database; "infants" and "the elderly" were calculated as individuals aged less than 10 years and unknown, respectively in this study.

Analysis of the Possibility of Developing Anxiolytic-Induced Aspiration Pneumonia Aspiration pneumonia was detected using the Preferred Term in MedDRA/J Ver. 24.0: "PT10035669/aspiration pneumonia." The association between each drug reported as the cause and the development of aspiration pneu-

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Table 1. The Possibility of Anxiolytic-Induced Aspiration Pneumonia by Anxiolytics

Drug category (ATC code)	Drug number	Reported AP cases	Total cases	ROR	95% CI
Anxiolytics (N05B)	16	61	6,056	3.2	2.5–4.1

AP: aspiration pneumonitis

monia was analyzed using the reporting odds ratio (ROR), a typical signal detection procedure, as described below.

$$ROR = \frac{a/c}{b/d},\ 95\%CI = exp\left\{\log(ROR) \pm 1.96\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}\right\}$$

a: cases that belonged to the group identified as having anxiolytic-induced aspiration pneumonia; b: cases that did not belong to the group but were identified as having aspiration pneumonia; c: cases that belonged to the group and were not identified as having aspiration pneumonia; and d: cases that did not belong to the group and were not identified as having aspiration pneumonia. Detection of a signal for an ADR was defined as a 95% confidence interval (95% CI) lower limit higher than 1.00, according to previous reports. [10]

Anxiolytic drugs were defined using the ATC classification provided by the WHO (https://www.whocc.no/atc_ddd_index/), and the following 16 drugs from among those marketed in Japan were included in the analysis: diazepam, chlordiazepoxide, medazepam, potassium clorazepate, lorazepam, bromazepam, clobazam, alprazolam, fludiazepam, ethyl loflazepate, etizolam, clotiazepam, cloxazolam, tofisopam, hydroxyzine hydrochloride, and hydroxyzine pamoate. The relationship between the development of aspiration pneumonia and individual anxiolytics were analyzed for diazepam, lorazepam, bromazepam, clobazam, alprazolam, ethyl loflazepate, etizolam, and cloxazolam; these were the drugs associated with the development of aspiration pneumonia reported in the dataset used in this study. Descriptions of aspiration pneumonia in package inserts or RMPs (e.g., aspiration pneumonia, deglutition disorder) were investigated using drug brand names (last reference date: February 19, 2022).

RESULTS AND DISCUSSION

The total number of JADER reports was 678,913, and the number of reported aspiration pneumonia cases was 2,200. The ROR of the 16 drugs categorized as anxiolytics based on the ATC classification was 3.2 (95% CI: 2.5–4.1), and the lower limit of the 95% CI was > 1 (Table 1). This result showed that the adverse event signals associated with the development of aspiration pneumonia were related to anxiolytics. The characteristics of the reported cases of anxiolytic-induced aspiration pneumonia are shown in Table 2. We found that male patients tended to report ADRs more frequently than did female patients. This result may be attributed to the fact that aspiration pneumonia is more likely to develop in men than in women.[4] On the other hand, the ages of the patients with anxiolytic-induced aspiration pneumonia reported in the JADER database varied widely. Epidemiological studies have identified older age as a risk factor for the development of aspiration pneumonia.[6] Because the findings of this study indicate that anxiolytic-induced aspiration pneumonia may not be limited to the elderly, further investigation is warranted in this regard. Table 3 shows the ROR and 95% CI for each anxiolytic associated with cases that belonged to the group identified as having aspiration pneumonia. The RORs (with 95% CIs in parentheses) for diazepam, lorazepam, bromazepam, clobazam, alprazolam, ethyl loflazepate, etizolam, and cloxazolam were 2.6 (1.3–5.1), 5.8 (3.1–10.9), 8.5 (5.0–14.4), 10.9 (6.0–20.0), 2.6 (1.3–5.2), 6.3 (3.4–11.8), 2.4 (1.5–4.0), and 3.2 (0.4–22.8), respectively. These results indicate that adverse event signals for the development of aspiration pneumonia were detected among the anxiolytics reported in cases of aspiration pneumonia, except for cloxazolam. All drugs for which a signal for the development of aspiration pneumonia was detected in this

Table 2. Characteristics of the Reported Cases of Anxiolytic-Induced Aspiration Pneumonia

	Number and percentage of reported case	
a) Sex		
Male	33	54.1%
Female	24	39.3%
Unknown	4	6.6%
Overall	61	100.0%
b) Age (years)		
0–9	5	8.2%
10–19	1	1.6%
20–29	9	14.8%
30–39	8	13.1%
40–49	11	18.0%
50–59	8	13.1%
60–69	9	14.8%
70–79	3	4.9%
80+	4	6.6%
Unknown	3	4.9%
Overall	61	100.0%

Table 3. The Possibility of Anxiolytic-Induced Aspiration Pneumonia by Each Anxiolytic

ATC code	Drug	Subcategory	Reported AP cases	Total cases	ROR	95% CI	Mention of the possibility on AP	
							Package insert	RMP
N05BA01	Diazepam	BZD	8	971	2.6	1.3–5.1	NO	N/A
N05BA06	Lorazepam	BZD	10	540	5.8	3.1–10.9	NO	N/A
N05BA08	Bromazepam	BZD	14	525	8.5	5.0–14.4	NO	N/A
N05BA09	Clobazam	BZD	11	322	10.9	6.0–20.0	YES	N/A
N05BA12	Alprazolam	BZD	8	968	2.6	1.3–5.2	NO	N/A
N05BA18	Ethyl loflazepate	BZD	10	499	6.3	3.4–11.8	NO	N/A
N05BA19	Etizolam	BZD	16	2,056	2.4	1.5–4.0	NO	N/A
N05BA22	Cloxazolam	BZD	1	98	3.2	0.4–22.8	NO	N/A

AP: aspiration pneumonitis, RMP: risk management plan, BZD: benzodiazepine derivatives (N05BA), N/A: not applicable

study were benzodiazepines. Benzodiazepines are known to have muscle relaxant effects via the gamma-aminobutyric acid $(GABA)_A$ receptor, and diazepam significantly inhibited swallowing evoked by mechanical, chemical, and electrical stimulation without respiratory depression in anesthetized rats.[11] In addition, the negative effects of benzodiazepines on muscle relaxation (e.g., worsening of myasthenia gravis) are described in the package inserts of the drugs investigated in this study. Though the causes of the development of pneumonia were not distinguished, epidemiological studies have also shown an association between benzodiazepines and the development of pneumonia (e.g., viral pneumonia, pneumococcal pneumonia and aspiration pneumonia).[12] This evidence supports this study's finding that anxiolytics are associated with the development of aspiration pneumonia.

This study has several limitations. First, because the population of patients taking these drugs is unknown, the data accumulated in the JADER database cannot be used to examine the frequency of ADRs. In addition, the effects of anxiolytics other than benzodiazepines (e.g., hydroxyzine hydrochloride) were not examined in detail in this study because of a lack of reports, and the effect of concomitant drugs (e.g., antipsychotics or sleeping pills) were not considered in this study due to the small sample size of cases. Further clinical studies that overcome the above research limitations would be needed for the complete determination of the relationship between anxiolytic usage and the development of aspiration pneumonia. However, drug information on the possibility of aspiration pneumonia development was only listed in the package insert of clobazam and was missing from those of most anxiolytics for which signals were detected in this study. Furthermore, RMPs were not prepared for any of these drugs (Table 3). The findings of this study may highlight the necessity of providing information on aspiration pneumonia caused by anxiolytics to healthcare professionals based on real-world clinical big data. As society ages, the number of patients with aspiration pneumonia is expected to increase further, and there is an urgent need to identify the factors that cause aspiration pneumonia to develop and worsen. The results of this study would indicate the necessity of considering the inclusion of appropriate information on the possibility of aspiration pneumonia development in drug package inserts and RMPs. This would be helpful for alerting healthcare professionals regarding the possibility of anxiolytic-induced aspiration pneumonia.

Conflict of interest The authors declare no conflict of interest.

REFERENCES

1) <https://www.mhlw.go.jp/toukei/saikin/hw/jinkou/geppo/nengai20/dl/h6.pdf>, cited 2/23, 2022.
2) Mandell LA, Niederman MS. Aspiration pneumonia. *N. Engl. J. Med.*, **380**, 651–663 (2019).
3) Okazaki T, Ebihara S, Mori T, Izumi S, Ebihara T. Association between sarcopenia and pneumonia in older people. *Geriatr. Gerontol. Int.*, **20**, 7–13 (2020).
4) Manabe T, Teramoto S, Tamiya N, Okochi J, Hizawa N. Risk factors for aspiration pneumonia in older adults. *PLoS One*, **10**, e0140060 (2015).
5) Ebihara S, Sekiya H, Miyagi M, Ebihara T, Okazaki T. Dysphagia, dystussia, and aspiration pneumonia in elderly people. *J. Thorac. Dis.*, **8**, 632–639 (2016).
6) Suzuki J, Ikeda R, Kato K, Kakuta R, Kobayashi Y, Ohkoshi A, Ishii R, Hirano-Kawamoto A, Ohta J, Kawata R, Kanbayashi T, Hatano M, Shishido T, Miyakura Y, Ishigaki K, Yamauchi Y, Nakazumi M, Endo T, Tozuka H, Kitaya S, Numano Y, Koizumi S, Saito Y, Unuma M, Hashimoto K, Ishida E, Kikuchi T, Kudo T, Watanabe K, Ogura M, Tateda M, Sasaki T, Ohta N, Okazaki T, Katori Y. Characteristics of aspiration pneumonia patients in acute care hospitals: A multicenter, retrospective survey in Northern Japan. *PLoS One*, **16**, e0254261 (2021).
7) Al-Shehri AM. Drug-induced dysphagia. *Ann. Saudi Med.*, **23**, 249–253 (2003).
8) O'Neill JL, Remington TL. Drug-induced esophageal injuries and dysphagia. *Ann. Pharmacother.*, **37**, 1675–1684 (2003).
9) Herzig SJ, LaSalvia MT, Naidus E, Rothbert MB, Zhou W, Gurwitz JH, Marcantonio ER. Antipsychotics and the risk of aspiration pneumonia in individuals hospitalized for nonpsychiatric conditions: A cohort study. *J. Am. Geriatr. Soc.*, **65**, 2580–2586 (2017).
10) Nawa H, Niimura T, Hamano H, Yagi K, Goda M, Zamami Y, Ishizawa K. Evaluation of potential complications of interstitial lung disease associated with antiandrogens using data from databases reporting spontaneous adverse effects. *Front. Pharmacol.*, **12**, 655605 (2021).
11) Tsujimura T, Sakai S, Suzuki T, Ujihara I, Tsuji K, Magara J, Canning BJ, Inoue M. Central inhibition of initiation of swallowing by systemic administration of diazepam and baclofen in anaesthetized rats. *Am. J. Physiol. Gastrointest. Liver Physiol.*, **312**, G498–G507 (2017).
12) Chen TY, Winkelman JW, Mao WC, Liu CL, Hsu CY, Wu CS. The use of benzodiazepine receptor agonists and the risk of hospitalization for pneumonia: A nationwide population-based nested case-control study. *Chest*, **153**, 161–171 (2018).