

What we learned from epidemiological studies on drug-induced pneumonia

Japanese Guideline for Hypertension is for disease mongering

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What we learned from epidemiological studies on drug-induced pneumonia

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It is well known that corticosteroids and cytotoxic anticancer agents cause infections. The labels of non-steroidal anti-inflammatory drugs (NSAIDs) warn that they may conceal signs of infection (fever and inflammation). Many drugs including H2 blockers and proton pump inhibitors (PPI: MedCheckTIP No73 and No74), both of which suppress the secretion of gastric acid, cholesterol lowering agents and angiotensin receptor antagonists (ARB) for hypertension increase infectious diseases.

When we critically appraised the efficacy and safety of diazepam for prevention of febrile seizures (The Informed Prescriber, Jan. 2007), we found that it increased fever (a symptom of infection) by 26% compared to placebo in a randomized controlled trial (RCT). Diazepam is one of the typical benzodiazepines. At that time, there was no study that showed increased pneumonia by benzodiazepine use, but we thought that immunosuppressive action of diazepam was related to increased signs of infection.

In this issue, we examined the relationship between benzodiazepines and community acquired-pneumonia (CAP, a typical infection), and a strong causal relationship was confirmed (p.24). Some other sleeping pills such as svorexant (orexin antagonist: MedCheckTIP No. 74 or English edition No. 9) and ramelteon (melatonin agonist: ibid No. 75) also have immunosuppressive effect and increase infectious diseases.

We have learned the followings from the epidemiological survey which showed strong association between sleeping pills and CAP:
First, drugs that act on the basic mechanism of the body, such as proton pumps and benzodiazepine receptors, have immunosuppressive effects and

increase infectious diseases. Even if the substance is not tested in humans and adverse effects are not known yet, increase of infection can be predicted from its fundamental mechanisms of action.

Secondly, in Japan, a large-scale database system is needed to study harms of drugs. All studies that showed association between benzodiazepines and pneumonia analysed large-scale databases in which the total number of subjects was 17,000 to 240,000, and they used appropriate methods, such as adjusting baseline characteristics to prove the association between benzodiazepines and pneumonia.

We hope that the medical information database "MID - NET" project starting this fiscal year (FY 2018) would work for research on adverse reactions to drugs. However, considering that the project is one of the complement systems for "Conditional Early Approval System", which was implemented in October 2017 by the Manager of the Ministry of Health, Labor and Welfare, it is likely to end up as disappointment.

This is because "Conditional Early Approval System" emphasizes its importance by stating that "An analysis of data using only the persons who used the drug after approval as real-world data requires far fewer participants, and can be completed in short period of time with far smaller cost. This might substitute RCTs, which require a large population, a large amount of money for a long period of time. Poorly designed observational studies could produce results "no association between drugs and adverse events is observed" or "the drug is effective" even if the truth is opposite.

MID-NET system, along with "Conditional Early Approval System", requires strict monitoring.

A new cholesterol lowering agent: **lomitapide is highly toxic**

Fat accumulates in the liver and small intestine

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Hama R., Hamasaki T., Okuyama H., Ogushi Y.

Summary

- Lomitapide (Juxtapid®) is a cholesterol lowering agent with a novel mechanism of action. It was launched in Japan in December 2016 with an indication for homozygous familial hypercholesterolemia (HoFH).
- Lomitapide lowers plasma LDL-cholesterol level by inhibiting triglyceride (TG) transfer to chylomicron and VLDL by inhibiting microsomal triglyceride transfer protein (MTP) in the same way as hepatitis C virus does in the liver cells leading to steatosis of the liver cells. It also inhibits MTP in the intestinal epithelial cells leading to their steatosis.
- Animal toxicity tests showed that one tenth of human dose of lomitapide induced liver cell steatosis and single cell necrosis of liver cells. Liver cancer and intestinal cancer (normally very rare) were also observed by administering one third of human dose of lomitapide in another animal toxicity test (male mice).
- It also causes diarrhea due to poor lipid absorption in the small intestine leading to hemorrhage because absorption of lipophilic vitamins especially vitamin K decreases.
- The efficacy for reduction of mortality from myocardial infarction and from all-cause is unknown, as no randomized controlled trial comparing placebo has been carried out. On the contrary, it is highly toxic carcinogen causing human liver steatosis commonly and small intestinal cancer by about 200 times more than general population.

Conclusion: We strongly recommend against using lomitapide even restricting its use to HoFH.

Keywords:

Lomitapide, homozygous familial hypercholesterolemia, HoFH, non-comparative study, liver steatosis, diarrhea, liver cancer, hemorrhage, intestinal cancer, carcinogenicity.

Introduction

Lomitapide (Juxtapid®) has been approved for an indication of homozygous familial hypercholesterolemia (HoFH) with a condition where "Inadequate effect or poor tolerability with other oral lipid lowering drugs is observed" [1-4].

For HoFH, drug therapy with statins or statins + ezetimibe (Zetia®) or removal of serum LDL-cholesterol (apheresis) has traditionally been performed [5-7]. However, the evidence basis of these treatments has been unknown so far, because randomized controlled

trial (RCT) comparing cholesterol lowering therapy with placebo in patients with HoFH has never been conducted for all-cause mortality as outcome [5-8].

HoFH is associated with a high incidence of myocardial infarction and high mortality not because of high cholesterol level but of other causes, because genetic constitutions for high cholesterol level and other various factors which easily induce atherosclerosis are closely related [8, 9]. The latter include (1) difficulty of utilizing energy (leading to ischemic stress) through cholesterol-carrying lipids by the cells, especially myocardial cells,

(2) prone to inflammation by inducing more TNF- α and other cytokines, (3) increased coagulability, (4) hypersensitivity of vascular endothelium [8, 9].

Therefore, cholesterol lowering therapy for HoFH does not lead to longevity, and it is considered to be only harmful if it is toxic. We will critically examine the results of animal toxicity tests and clinical trials [3-7], which were the basis for the approval of lomitapide.

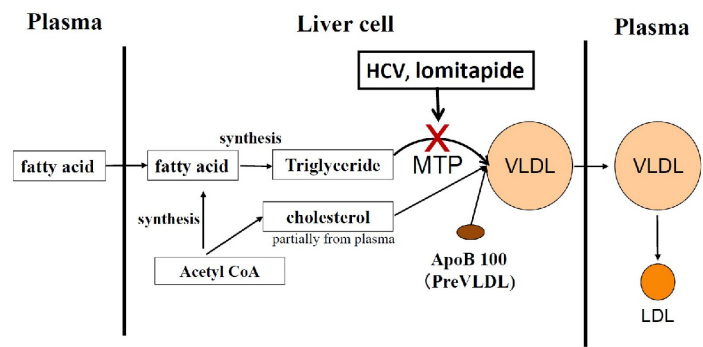
Lomitapide is a poison similar to hepatitis C virus

Within intestinal epithelial cells, lipids are resynthesized to triglycerides (TG), taken up into large particles of fat (chylomicron), secreted and circulated throughout the body. Also in the liver cells, TG is taken up by very low density lipoprotein (VLDL), which is the source of LDL-cholesterol, secreted into the blood and circulated throughout the body. A protein called MTP (microsomal triglyceride transfer protein) plays the role of carrying TG to chylomicrons and VLDL in the intestinal cells and liver cells respectively (Figure. 1).

Lomitapide is a cholesterol lowering agent of novel mechanism of action, which resembles that of hepatitis C virus (HCV). Since HCV inhibits the action of MTP in the liver cells, it induces fatty liver (liver steatosis) [10, 11]. Lomitapide, like HCV, inhibits the function of MTP in liver cells. As a result, liver cells produce less VLDL, and the blood concentration of LDL-cholesterol decreases (Figure. 1). In addition, lomitapide inhibits MTP required for absorption of lipids into the body within intestinal epithelial cells (see Figure. 1, footnote [4]).

Because of this series of actions, TG accumulates in the liver cells and intestinal epithelial cells. In animal toxicity tests, it induced single liver cell necrosis with a tenth of the human dose. As the absorption of lipids in the small intestine decreases, diarrhea frequently occurs and absorption of lipid-soluble vitamins such as vitamins A, D and K (especially vitamin K), decreases, and hemorrhage is easily caused [4].

Figure 1: Role of MTP (microsomal triglyceride transport protein) and its inhibitor

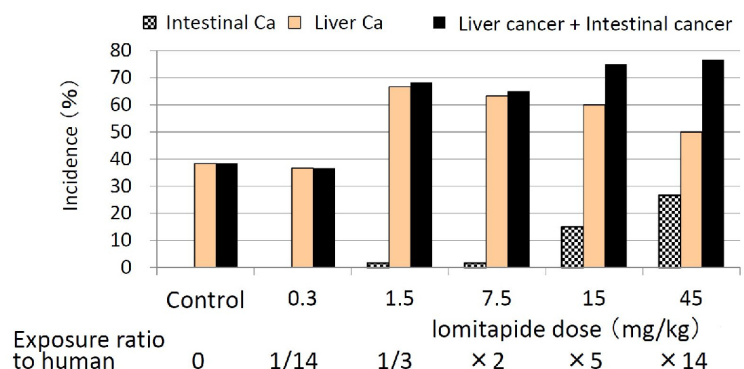


In the liver cells, cholesterol and triglyceride (TG) carried to MTP are added one after another to ApoB (as pre-VLDL). Then, VLDL, which is rich in TG and has very low density, is formed and secreted outside the liver cells. This turns into LDL in the blood. In the intestinal epithelial cells, TG-rich chylomicrons are formed and secreted into the lymphatic vessels in the same manner, and are distributed to the whole body. The core protein of hepatitis C virus (HCV) inhibits MTP in the liver cells and induces fatty liver (liver steatosis). Lomitapide, like HCV, inhibits MTP in the liver cells. In addition, it inhibits MTP in the intestinal epithelial cells, accumulates triglycerides in these cells, and causes cell injuries.

Report of small bowel cancer even in humans

In mice carcinogenicity studies, liver cancer occurred three times more frequently in lomitapide group than in control group with just one third of human dose (p = 0.002). In addition, small intestinal cancer, an extremely

Figure 2: Incidence of cancer of liver and intestine in carcinogenicity study (mice, male)



rare disease, occurred in one animal with one third of the human dose. and occurred in 9 out of 60 animals (15%) with 5 times of the human dose (**Figure 2**). Inhibiting the action of MTP is extremely dangerous because of its potential toxicity and carcinogenicity.

The small intestinal cancer in humans is extremely rare with annual incidence rate only 0.22 to 0.57 persons per 100,000 persons (Western countries) [12]. Lomitapide has been used in 1,173 HoFH patients, and one case (63 years old woman) of ileal cancer has been reported [4]. This result shows that intestinal cancer is 213 times more likely to occur in patients who are treated with lomitapide than in general population ($p < 0.006$).

Results of major clinical trials

In the pivotal clinical trials [4, 5], which served as the basis of the approval, lomitapide 5 mg daily was initially given to 29 HoFH patients, and the dose was gradually increased up to 60 mg. After 26 weeks of treatment, lowered LDL-cholesterol was observed. From 26 weeks onwards until 78 weeks, safety assessment is conducted more frequently and the treatment continued. The median dosage of lomitapide is 40 mg daily.

LDL-cholesterol level fell by 50% at 26 weeks, 44% at 56 weeks, and 38% at 78 weeks, compared with the baseline.

By 26 weeks, six people dropped out. The reasons for dropout were due to 4 adverse events, 3 of which were gastrointestinal disturbances. The most common adverse event was gastrointestinal disturbance. By 26 weeks, 27 (93%) complained of gastrointestinal symptoms.

The amount of fat in the liver was 1.0% at the baseline, and has increased to 8.6% at 26 weeks, which is extremely high. It seems that almost everyone has developed fatty liver in varying degrees. The effect on coronary artery disease is unknown.

In Japan, a similar test [4, 13] was conducted with 9 HoFH patients, and eight of them continued for 52 weeks. The result was similar as the above study [4, 5].

Conclusion

Lomitapide (Juxtapid®) has the effect of "lowering cholesterol", but it causes cell necrosis in the small intestine and liver, and is a poison with carcinogenicity. Lowering cholesterol of persons with homozygous familial hypercholesterolemia (HoFH) provide no benefit, but only harm.

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Japanese Guideline for Hypertension is for disease mongering

Medical checkups create “patients” and shorten their lifespan by “treatment”

Translated from Med Check-TIP (in Japanese) May. 2018;18 (77) :58-60

MedCheckTIP editorial team

Summary

- Following popularization of general health-checks and revision of hypertension guidelines, one in three or four adults and one in two elderly people take antihypertensive medications in Japan today.
- Antihypertensive therapy used to be recommended only for those with sustained systolic blood pressure above 180 mmHg before 2000. Since the revised hypertension guideline in 2000 (HT-GL 2000) lowered the treatment target to 130/85 or lower, the number of "patients with hypertension" has been continuously increasing. Almost one half of people aged 75 years or older now use antihypertensive agents in Japan.
- In Japan's hypertension guideline revised in 2014, the target value was changed to below 140/90 mmHg, admitting that "it was a mistake to set the treatment target at 130/85 mmHg or lower". A randomized controlled trial (RCT) conducted in Japan called JATOS study compared a strict treatment group maintaining systolic blood pressure below 140 mmHg with a mild treatment group maintaining it above 140 mmHg and below 160mmHg. This study found no difference in stroke and myocardial infarction, but the mortality rate tended to be higher in the strict group. In addition, there are many studies which show harmful effects of lowering blood pressure.
- The most widely marketed angiotensin receptor antagonist (ARB) is carcinogenic and increases septic death as well. The criteria for lowering blood pressure should be returned to those before the 2000 guidelines.
- Check the causes of high blood pressure carefully, eliminate stress and sleep debt, and avoid careless antihypertensive therapy.

Keywords:

hypertension, hypertension guidelines, antihypertensives, ARB, carcinogenicity, sepsis, total mortality rate, stress

Introduction

As a result of a systematic review of many randomized controlled studies (RCTs), it was found that general health checkups, subsequent lifestyle changes and medical interventions do not extend the lifespan. According to the review, mortality rate increased in people aged 65 years old and above, and particularly, it increased by 62% in those aged 75 years and above [1]. Hypertension is most frequently detected out in health checkups. If antihypertensive agents shorten life, the impact may be significant. Let's examine the reasons why general health checkup could shorten the lifespan of older people, focusing on hypertension as an example.

Hypertension treatment until the 1990's

Only one RCT showed prolongation of lifespan in which antihypertensive drugs were used in patients with diastolic blood pressure above 115 mmHg [2]. The results of three RCTs [3-5] which compared antihypertensive agents and placebo (or no treatment) on mild hypertension with diastolic blood pressure of 90mmHg to 109 mmHg, published in the 1980's, showed no significant difference in mortality. There was no difference in all-cause mortality by the meta-analysis of these RCTs: the pooled odds ratio (OR) = 0.94 (p = 0.50).

Therefore, until 2000, it was thought that no antihypertensive intervention was needed unless the

diastolic blood pressure was sustained at 95 mmHg or higher (especially 100 mmHg or higher) or the systolic blood pressure was sustained at 170 mmHg to 180 mmHg or higher, and 160/95 mmHg was recommended as the target blood pressure to be achieved [6]. For the elderly people, the target blood pressure was below 180/100 mmHg [7].

Lowering the cut-off blood pressure for intervention and the target blood pressure

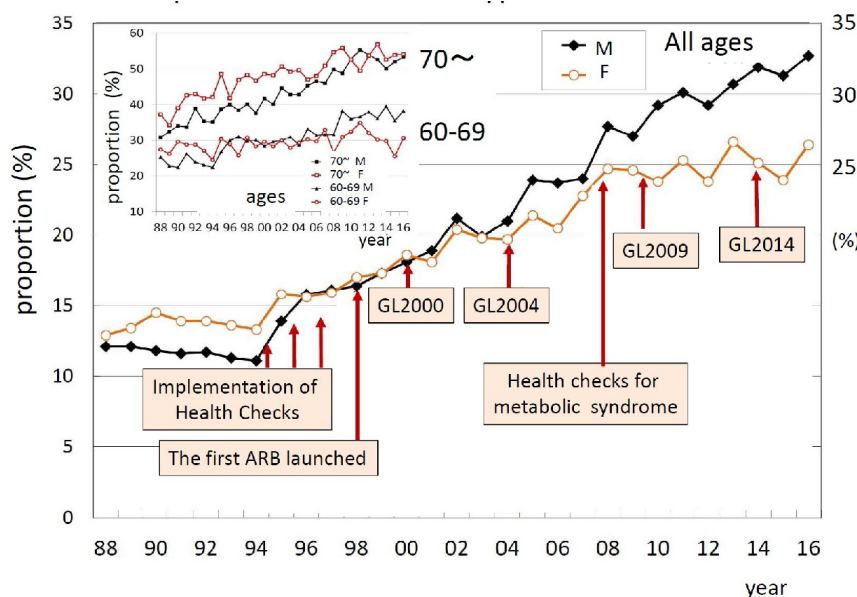
The hypertension guidelines (HT-GL) [8-11] which were frequently revised after 2000 changed this situation completely. They recommend using antihypertensive agents to lower blood pressure very strictly (Table). In particular, strict criteria have been applied to elderly

people since the revision in 2004. The target value was set at lower than 130/85 mmHg and 140/90 mmHg for people under 65 years old and those aged 65 years or older, respectively.

Increased proportion of antihypertensive drug users and health checkup/guidelines

In Japan general health checkups started in 1950s [12,13]. The proportion of antihypertensive drug users was 11 to 13% until 1994, the year in which a stricter policy for general health checkups was implemented[14]. It exceeded 16% during the period of 1995 to 1997 [15](Figure). In 2016, one in three adult men, one in four women, one in two men and women over the age of 70 years were on antihypertensive agents.

Figure: Strengthening health examination and changing ratio of antihypertensive drugs



Data source : National Health and Nutrition Survey (in Japanese)
http://www.mhlw.go.jp/bunya/kenkou/kenkou_eiyou_chousa.html

Table: Changes in the target blood pressure in hypertension treatment

~1999			2000			2004			2009			2014		
age	S	D	age	S	D	age	S	D	age	S	D	age	S	D
<70	<160	<95	<60	<130	<85	<65	<130	<85	<65	<130	<85	<75	<140	<90
			60-69	<140		65-	<140	<90	home	<125	<80	home	<135	<85
70- *a	<180	<100	70-79	<150	<90	75- *b	<140	<90	65- *c	<140	<90	75- *d	<150	<90
			80-	<160		home	<135	<85	home	<145	<85			
*a: aplying JATE study						*b: If more than 160/100, target may be <150/90			*c: If <130/85 is achieved during age <65, milder control is not needed after 65 years old.			*d: If tolerated, <140/90 may be appropriate as for age <75 (home BP < 135/85).		

S : Target systolic blood pressure

D : Target diastolic blood pressure

Among them, angiotensin receptor blockers (ARB), which was first marketed in Japan in 1998, currently have the largest market share. HT-GLs have been revised several times in Japan since 2000, and the cut-off blood pressure for intervention and target of treatment have been lowered by every revision. In addition, "health checkup to find metabolic syndrome" was implemented in 2008. Through these measures, "hypertensive patients" increased very rapidly (Figure) [16-20].

Authorities admitted "There was no evidence supporting the target <130/85"

HT-GL 2014 changed the target for treatment of hypertension from "below 130/85 mmHg", which have been recommended since 2000, to "below 140/90 mmHg". One of the most important reasons was that there had been no evidence supporting the reduction of mortality rate nor cardiovascular disease by lowering blood pressure to below 130/85 mmHg.

In fact, no RCT has proven it as evidence anywhere in the world. In 2015, a RCT named SPRINT was published [21]. In this study, mortality was improved significantly in people with systolic high blood pressure of 139 and BMI averaged 30 with cardiovascular disease and renal impairment whose systolic pressure was lowered to below 120 mmHg as compared with those whose blood pressure was lowered to about 135 mmHg. However, there was a big contradiction that the mortality rate declined despite severe hypotension and acute renal failure needing hospitalization or emergency care increased by 1.7 times and renal impairment increased by 3.5 times ($p < 0.001$ for both). Hence, this study is unreliable.

Mortality may increase even with the target of below 140/90

The target of "below 140/90 mmHg" by GL 2014 is not evidence based, either. There is only one RCT in Japan comparing antihypertensive agents (calcium antagonists) and placebo (JATE study) [16]. The result was that after 3 years, even in the placebo group, the blood pressure dropped from 170 mmHg on average at the beginning to 140 mmHg as in the antihypertensive group. There was no difference in cardiovascular disease incidence in both groups, and malignant tumors were

significantly higher in the antihypertensive group.

In Japan there are two clinical trials [23, 24] comparing the "strict group" whose blood pressure was lowered to below 140/90 mmHg and the group which received less intensive treatment (mild group): JATOS (n=4418) [23] and VALISH (n= 3079) [24].

In the JATOS, there was a difference in achieved blood pressure by about 10 mmHg: 172/89 mmHg at the baseline dropped to 136/75 mmHg in the strict group and 146/78 in the mild group. In VALISH, there was a difference of about 5 mmHg: it dropped from 170/82 before the start to 137/75 mmHg in the strict group and 142/77 mmHg in the mild group.

There was no difference between the strict group and the mild group in the incidence of stroke and myocardial infarction in both RCTs. On the other hand, the number of people who died was bigger in the strict group (n=54) than in the mild group (n=42) after two-year follow-up.

Although it is not a significant difference, it suggests the possibilities that more people may die with strict blood pressure control.

A number of studies show harm of strict control

There are many other studies that show harm of strict control of blood pressure (for details, web supplement).

For example, in the HOT study [25], which was the basis for changing the WHO's Hypertension Treatment Guidelines, the mortality rate was the highest in the lowest blood pressure group although the myocardial infarction decreased.

There are several large cohort studies in Japan. In NIPPON-DATA [26], people who lowered their blood pressure using antihypertensive agents had less ADL (Activity of Daily Life) after 14 years follow-up than those who did not use antihypertensives in all blood pressure groups.

In the Ibaraki prefecture survey [27], people who took antihypertensives and had blood pressure of below 160/95 showed higher mortality rate and higher cancer death rate than those whose blood pressure was higher than 160/95 without antihypertensive treatment.

The PATE study [28] is a RCT conducted in Japan comparing ACE inhibitors and calcium antagonists. As a result of using an antihypertensive agent, the incidence of cardiac disease in people with systolic blood pressure

of 130-139 mmHg, 140-149 mmHg, 150-159 mmHg and 160 or higher did not differ, but it rather increased in those whose blood pressure fell to below 130 mmHg. The incidence of cardiac disease in the people whose blood pressure fell to below 120 mmHg increased significantly than those with blood pressure of 130-139 mmHg. It shows that excessive drop in blood pressure is harmful.

The guidelines neglect the carcinogenicity of ARB

A meta-analysis result of RCTs clearly shows that ARBs, which currently have the largest market share, increase cancer incidence by 11% ($p = 0.001$). When only the trials which are eligible for strict comparison are concerned, it shows 15% increase ($p = 0.0025$) [29]. In addition, the risk of mortality from sepsis increased by 50% ($p = 0.025$) [29]. However, Japanese hypertension guidelines in 2014 ignored this important evidence.

In practice

We recommend people with high blood pressure to find the causes such as stress and sleep debt, and resolve them. Health care workers should give them appropriate guidance and be careful not to thoughtlessly follow the authority-oriented guidelines and not to adversely affect patients with antihypertensives.

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Pneumonia induced by benzodiazepines **Evidence shows causal relations**

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Yasuda Y., Hama R

Summary

- Benzodiazepines (BZD) are commonly used as sleeping pills and/or anxiolytic agents. BZDs generally induce infectious diseases including pneumonia by suppressing the immunity of those who took them.
- The risk of pneumonia is particularly high in the following situations.
1) within 30 days after starting BZD, **2)** ultra-short-acting agents, **3)** high dose (more than usual dosage) and two or more kinds of BZDs, **4)** otherwise healthy persons (0 for Charlson comorbidity index). It is reported that pneumonia caused by BZD leads to an increased mortality rate.
- BZDs are easily prescribed for mild symptoms such as headaches and stiff shoulders. However, they do not cure the symptoms, but only mask them with risk of dependence and addiction. They cause big social problems.
- Especially in elderly people with declined renal, liver and immune functions, not only falls and delirium, but also pneumonia increases. Uncritical use should be prohibited.

Keywords:

benzodiazepine, anxiolytics, hypnotics, pneumonia, infection, immunosuppression, robust association, causality, case-control study, cohort study

Introduction

Benzodiazepine receptor agonist (abbreviated as BZRA: **Note 1**) is used extensively throughout the world, and harm caused by inappropriate use or abuse is an issue .

According to the report of the International Narcotics Control Board (INCB) in 2010 [1], the consumption of BZRAs in Japan is significantly higher than that in other Asian countries. In addition, there is a possibility that inappropriate prescription or abuse might be involved.

Note1: In addition to benzodiazepines (BZD), agents acting on the benzodiazepine receptor (BZR) are also called "nonbenzodiazepines" or "z-drugs". Zolpidem (Ambien) and zopiclone (Imovan) are representative drugs. In this article, these groups of drugs are collectively classified as benzodiazepine receptor agonists (BZRA) or BZDs. Their chemical structures are different, but they basically share the same harmful effects.

BZRAs have many well-known harms such as dizziness, drowsiness, falls, bone fractures, addiction, etc. In this article, we discuss less known harms such as infections, especially pneumonia.

Infectious diseases increase

Although there are various research methods, the most reliable research is the result of meta-analysis, which comprehensively analyzes multiple randomized controlled trials (RCT).

Joya et al. meta-analyzed RCT data, which was the basis of FDA approval, on four sleeping agents (**Note 2**), namely eszopiclone, zaleplon, zolpidem, and ramelteon [2].

The study dealt with the frequency of all infectious diseases. As a result of comparing 8,828 participants in hypnotic drug groups and 4,383 participants in placebo groups who were involved in 36 RCTs, increased risk of infection was observed. The total risk (risk ratio: RR) was

1.44 (p <0.00001).

As a result of the meta-analysis of individual drugs, infections increased about 1.5 times (p <0.00001) for eszopiclone and about 2 times (p = 0.006) for zolpidem.

The **Table 1** summarizes the results of meta-analysis of RCTs reporting the relationship between BZRAs and infectious diseases, and the results of observational study investigating the relationship between BZRAs and pneumonia. There are three kinds of risk levels (OR, RR, HR).

Note2: BZRA except for ramelteon. Ramelteon is a melatonin agonist.

Pneumonia increases

As for the relationship between BZRAs and infection, the relationship with pneumonia has been studied most.

In a cohort case-control study using Taiwan National Health Insurance Research Database, Chen et al.

extracted 12,002 persons who were hospitalized for pneumonia and the same number of persons for control group (4) matched with baseline characteristics (**Note 3**), and examined the relationship between BZD exposure and pneumonia [3].

As a result, the adjusted odds ratio (OR) was 1.86 (p <0.0001) and a significant association was confirmed. In addition, in this study, there was a tendency that the risk increased as the dose of BZD increased. Chen et al. estimated that if two kinds of drugs were used at the dose exceeding the usual dose (DDD: Note 4), incidence of pneumonia increased by 3.5 times (**Figure**).

Note 3: The control group was selected by matching cases and baseline characteristics by using propensity scores.

Note 4: The daily standard dose (routine dose) of medicines defined by the WHO is referred to as DDD (daily defined dose) [11]. DDD for representative drugs include diazepam 10 mg, zolpidem 10 mg, triazolam 0.25 mg, flunitrazepam 1 mg, etc.

Table 1: Risk of infections or pneumonia by benzodiazepines

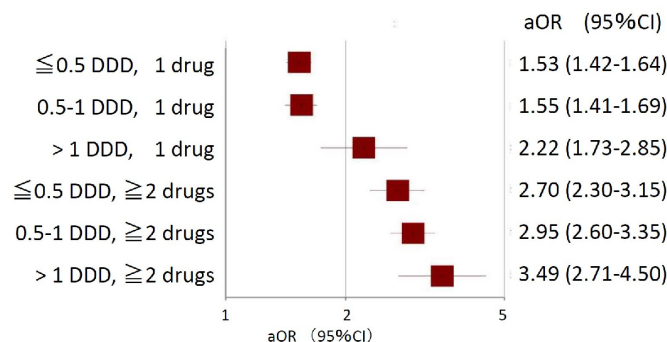
References, year	Methods	Association	Study Sample	Benzodiazepines and increased risk of infection/pneumonia
Joya[2] '09	RCT	Yes	8,828, 4,383	Meta-analysis of 36 RCTs of 4 hypnotics. Infection: RR=1.44
Chen[3] '18	CC	Yes	12,002, 12,002	Pneumonia with all BZRAs: OR=1.86, positive dose-response (Fig1)
Obiora[4] '12	CC	Yes	4,964, 29,697	Pneumonia with BZRAs: OR=1.54, Long term mortality risk: HR=1.32
Jung[5] '16	CC	Yes	51,029, 188,391	Pneumonia risk (use of BZDs within 90days): OR=1.69, Z-drug OR=1.57
Taipale[6] '17	CH	yes	8,501, 8,501	Pneumonia with short term use of BZDs: OR=2.09, Z-drug: OR=1.60
Wang[7] '17	CC	Yes	4,533, 16,388	Pneumonia risk (use of BZDs within 30days): OR=1.65, new use OR=2.47
Vozoris[8] '14	CH	Yes	48,915, 48,915	Older COPD: emergency room visits for COPD or pneumonia:RR 1.92
Almirall[9] '08	CC	No	1,336, 1,326	small sample size, BZDs were analysed as one on 70items: OR=0.94
Dublin [10] '11	CC	No	1,039, 2,022	small sample size, BZDs and opioids were evaluated: OR=1.08

RCT: meta-analysis of randomized controlled trials, CC: case-control study, CH: cohort study

BZRAs, BZDs and Z-drugs : See Note 1. OR: odds ratio, RR: risk ratio, HR: hazard ratio

Patients with Alzheimer disease were the subjects in the Ref.[6], and patients with chronic renal diseases were the subjects in the Ref.[7]

Figure: benzodiazepines and pneumonia: a dose-response (from Ref. 3)



DDD: daily defined dose, aOR: adjusted odds ratio, 95% CI: 95% confidence interval

Obiora et al. conducted a case-control study within cohort using the electronic medical chart of the UK primary care clinic. They extracted 4,964 cases of community pneumonia and 29,697 persons for control group, and examined the association with BZD exposure. They reported that the risk increased by 1.5 times (OR=1.54, $p < 0.0001$) [4].

They also conducted a cohort study in their study. It reported that among 4,964 people who previously suffered from pneumonia, 22% increase was found in mortality within 30 days (HR=1.22, $p=0.004$) and 32% increase was observed in mortality from long-term follow-up (mean follow-up period of 2.8 years) (HR=1.32, <0.001). People without complications are particularly at high risk, and pneumonia and mortality increased 2 to 3 times and about 2 times, respectively. Increased mortality should be taken as a serious outcome.

Jung et al. matched at least gender and age of about 190,000 people as a control with about 50,000 pneumonia patients aged 65 years or older who were members of the Kaiser Permanent Health Organization. They compared the use of BZDs and Z-drugs (see **Note 1**) in the past one year before contracting pneumonia (case control study) [5]. The risk of short-term use (90 days or less) for BZDOR was OR=1.69, and for Z-drugs OR=1.57 ($p < 0.0001$ for both).

Pneumonia also increases in certain disease groups

BZDs also increase the risk of pneumonia even in studies with specific disease groups, such as Alzheimer's disease, chronic obstructive pulmonary disease (COPD) and chronic kidney disease (CKD).

Taipale et al. used Finnish data of about 50,000 Alzheimer's disease patients and selected BZRA non-users whose baseline characteristics were matched 1:1 with those of 8,501 BZRA users to compare the risk of pneumonia in these two groups [6]. Hospitalization or death due to pneumonia increased with the hazard ratio (HR) = 1.22 for the entire BZRA. In the first 30 days of BZRA use, pneumonia risk was the maximum with HR: 2.09, but it was not significant after prolonged use. They say that strong effect is observed in the early stage of the use as sedation effect is remarkable before tolerance develops.

Vozoris NT et al. used a database of 177,355 people

with chronic obstructive pulmonary disease (COPD) over 66 years of age in Province of Ontario, Canada, and compared 48,915 people who newly used BZRA and another 48,915 people in a control group whose baseline characteristics were matched [7]. As a result, the risk ratio (RR) of emergency visits for COPD or pneumonia was 1.92 and significant ($p < 0.0001$).

Wang MT extracted 4,533 pneumonia patients and 16,388 patients who were matched with the former as a control from 36,880 chronic kidney disease patients registered in Taiwan National Health Insurance Database to examine pneumonia risk for using BZD [8]. As a result, the study reported that the odds ratio (OR) was 1.31, and the risk was especially high within 30 days after the start of BZD use with about 2.5 times higher OR (OR = 2.47, $p < 0.0001$).

Reports that were unable to detect associations are small in scale

The reports that suggested the association which we have mentioned above are all large-scale studies involving total 13,000-240,000 persons (**Table 1**). In addition, with a purpose of investigating the relationship between BZRA and pneumonia, control groups whose baseline characteristics were matched were selected, or 4-6 times more patients were selected for control groups to enhance statistical power.

On the other hand, reports by Almirall et al. [9] and Dublin et al. [10], which deny the relationship between benzodiazepines and with pneumonia, are small in scale (about 3000 or less for cases and controls in both studies: **Table 1**) and did not specifically examine the association. Therefore, the results are not reliable.

Mechanism for the induction of infection - especially immunosuppression

It is generally believed that BZDs may cause pneumonia due to aspiration as they have sedative and muscle relaxant actions [4,8]. However, this hypothesis cannot explain the mechanism by which not only pneumonia but all infectious diseases, including urinary tract infection, increase.

BZD receptors are expressed in peripheral blood and immune cells such as leukocyte, and laboratory researches have been conducted on their effect on

Table2 : Effects of BZDs on Immune System (extracted from Ref.12)

Immunologic effects (as GABA _A receptor agonist)	Animals tested
Reduced interleukin, IFN- γ , TNF- α production	mice
Reduced mast cell function	rats
Reduced chemotaxis and phagocytosis	mice, humans
Increased mortality after endotoxin exposure	mice
Inhibition of dendritic cell maturation	mice
reduced interleukin and TNF- α	humans

immune system of animals and humans (Table 2) [7,12]. A mice experiment reported that the function of macrophages was suppressed as BZD stimulated GABA_A receptors, leading to increased pneumococci in the lung and thus increased mortality, but it recovered by using GABA_A receptor antagonist [13].

Examining causality

A robust association between BZRA and increased infection ($p < 0.0001$) is confirmed by the most reliable meta-analysis of RCTs.

Regarding increased pneumonia, a strong association (mostly $p < 0.0001$) with BZRA use before pneumonia was observed in multiple studies (cohort studies and case-control studies) in which bias was excluded as much as possible. Studies with conflicting results were small-scale studies of poor quality. Even with a comprehensive analysis including these poor-quality studies, risk for causing pneumonia with short-term use of BZRA is as high as 1.73 (1.54-1.94), and the P value is as low as < 0.0001 , suggesting a strong relationship. The presence of dose-response relation also supports the strong association. In addition, many animal and human experiments have repeatedly shown that BZDs suppress the function of various immune cells and proliferate bacteria, leading to increased mortality in animals. In this way, the association can be explained by the mechanism of action as well. The causality between the use of BZRA and infectious diseases, particularly pneumonia, is certain. In addition, pneumonia is likely to occur within 30 days or less after the start of the medication. Furthermore, ultra-short acting hypnotics with short half-life showed greater risk.

In practice

Benzodiazepines used as anxiolytic and hypnotic agents are by no means mild drugs. They act on the whole body and decreases immunity, resulting in increased infectious diseases, particularly pneumonia. The risk is high especially for people without complications. Shorter the duration of use is, greater the effect. There is clear dose-dependency, and the causality is certain. Never use them uncritically.

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