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WHO downgrades Tamiflu

Suvorexant : A hypnotic causing cataplexy

Insomnia, Sleep Duration, Harm of hypnotics

PPI causes Pneumonia

CONTENTS （December 2017, Vol. 3, No. 9）

WHO downgrades Tamiflu after reviewing evidence

Translated from the editorial in Med Check-TIP in Japanese Sept 2017 ; 17 (73) : 99

WHO (World Health Organization) reviews their model list of essential medicines every two years.

In the revision launched in June 2017, oseltamivir (Tamiflu) was downgraded in the World Health Organization's essential medicines list (EML) from the "core" to the "complementary" list.

The Expert Committee made the decision for the following reasons:

1) Oseltamivir was included in the essential medicine list (EML) in 2009 and remained in the EML for critically ill patients with influenza.
2) However, there now exists additional evidence indicating its reduced magnitude of effects.
3) Expert committee recommended the listing of oseltamivir be amended and the medicine be moved from the "core" to the "complementary" list,
4) Unless new information supporting the use in seasonal and pandemic outbreaks is provided, the next Expert Committee might consider oseltamivir for deletion.

"Additional evidence" means the results from systematic review and meta-analysis conducted and published by the Cochrane neuraminidase inhibitor research team in April, 2014 and the review results about mortality in the subsequent Health Technology Assessment report.

Evidence from Cochrane team is summarised as follows:

(1)Tamiflu did not reduce hospitalization and pneumonia in patients with influenza.
(2) Tamiflu did not reduce influenza-like illness when used for prophylaxis.
(3) Tamiflu did not reduce death either.
(4) Tamiflu caused psychiatric harm both in treatment trials and in prophylaxis trials. It caused headache, diabetes and renal disease.

The decision of WHO has some limitations. First, neuropsychiatric harm including abnormal behaviours and sudden death is not considered seriously in their decision. Second, they do not take into account that Tamiflu is more hazardous for severely complicated patients or for high-risk influenza patients.

However, it is epoch-making that WHO valued of the results of the systematic review by Cochrane team than those by the pharmaceuticals-funded researches. The latter concluded "Tamiflu has protective efficacy on pneumonia, and it has no neuropsychiatric adverse effects". Moreover, WHO mentioned the possibility of "deletion" in the next revision.

In Japan, it was decided recently that the amount of stockpile should be reduced slightly. This was because no scientific evidence for double dose and/or double duration of Tamiflu use in seriously complicated patients with influenza was found. However, neuraminidase inhibitors are stockpiled for 48 million persons after that decision.

We use 50 times to 1200 times more neuraminidase inhibitors including oseltamivir and laninamivir per capita in Japan than in European countries.

Victims and the bereaved of harms of Tamiflu filed cases for the relief. In the suit, regulators, their witness and the court claim that Tamiflu is totally harmless. They do not accept abnormal behaviours with fatal outcome, sudden death and sequelae as harm of Tamiflu. Consequently, their damages remain unrelieved.

We strongly recommend that in Japan we should consider the Cochrane team's results more seriously and should downgrade the status of oseltamivir and other neuraminidase inhibitors, following the WHO's decision.

New Products

Hypnotic (sleeping pill), suvorexant (brand name Belsomra)

A substance that causes narcolepsy and cataplexy. Is it a "medicine"?

Translated from Med Check-TIP in Japanese Nov 2017 ; 17 (74):124-127

Wada M and Hama R

Summary

• Suvorexant (brand name: Belsomra) is an orexin receptor antagonist which was approved for the treatment of "insomnia" in November, 2014. Clinical trials for this substance reported that participants in the treatment group were able to fall asleep 5.2 minutes quicker and slept 10.7 minutes longer than those in the placebo group.

• Orexin is secreted by the neuron in the brain and is responsible for arousal and various other functions for defense response against stress. It also promotes growth of normal cells and inhibits growth of tumor cells. Hence its antagonists may cause various harms.

•When suvorexant is taken daily, plasma level remains high even during daytime a few days after commencement. In clinical trials, drowsiness, memory impairment, parasomnias (nightmares, sleepwalking etc.), narcolepsy-like symptoms (including cataplexy, hypnagogic hallucination, sleep paralysis) and suicidal ideation increased dose-dependently. In a case of death after drowning during swimming in the sea, cataplexy (emotion-induced paralysis) is strongly suspected as the cause.

• Suvorexant might cause impaired functions of normal cells, inhibition of normal cell growth, immunosuppression, and tumor growth. These possibilities should be continuously monitored. Suvorexant is metabolized by CYP3A (***note 1***). Slow metabolisers are susceptible to more harms, and it is risky to take the substance concomitantly with other medicines which are also metabolized by CYP3A.

Conclusion: Unlike a lack of sleep, insomnia does not cause harm to health. Suvorexant (Belsomra) should not be used because it may cause various harms including those leading to death.

> ***Note 1*** : *One of the subtypes of drug metabolizing enzymes called cytochrome P450. Because its level of activity greatly varies among individuals, blood concentration reaches extremely high and remains high in people with weaker enzymatic activity (slow metaboliser) as compared with people with greater activity (rapid metaboliser). Moreover, when medicines which are metabolized by the same subtype of enzyme are concomitantly used, blood concentrations of both medicines reach high, and their effects persist for a long time.*

Keywords:

hypnotic, insomnia, lack of sleep, sleep debt, suvorexant, Belsomra, orexin, receptor antagonist, sleep latency, total sleep duration, defense, memory impairment, fatigue, sleepwalking, narcolepsy, cataplexy, suicidal ideation, tumor growth, CYP3A

Introduction

In evaluating hypnotics (sleeping pills), it is essential to compare effects of insomnia and effects of hypnotics on health. The reasons are summarized as follows (for more information in detail, refer to the Med-Check TIP in English No9 (this issue p36) [1]).

Insomnia is a subjective complaint that one feels sleep is insufficient, and it is different from having short sleep duration or a lack of sleep (sleep debt). Persons who experience insomnia live longer than those who do not. However, routine use of hypnotics for the treatment of insomnia increases depression, infection, cancer, and even death. A lack of sleep triggers intense stress and promotes aging, leading to various chronic diseases. However, when

optimal sleep duration is secured, stress is lessened and health condition is restored, although insomnia or difficulties in falling asleep is sometimes experienced.

Considering these points, this article examines suvorexant (brand name: Belsomra), an orexin receptor (***note 2***) antagonist.

> ***Note 2*** : *Because orexin is secreted by neurons in the hypothalamus, it is also called "hypocretin". It has two kinds of receptors, and suvorexant inhibit both of them.*

Orexin and its receptor antagonists

Orexin is a chemical substance in the brain which plays an important role in maintaining level of arousal **[2-8]**. In many narcolepsy patients (***note 3***), who feel strong drowsiness and fall asleep even in the daytime, orexin level in cerebrospinal fluid is decreased **[9-11]**. Suvorexant, an orexin receptor antagonist, is believed to induce onset of sleep and maintain it by inhibiting the action of orexin **[2]**. Orexin-producing neurons (orexin neurons) are found in the lateral hypothalamic area and project to the entire central nervous system **[3-7]**.

They are deeply associated with defense response, which is a response against stress **[3,5-7]**. When encountering danger, we must quickly decide whether to "flight or fight" and take an action, and this requires substantial amount of energy **[6,7]**.

Therefore, catecholamine and orexin levels rise in the brain to raise blood pressure, accelerate breathing, raise glucose level, and increase caloric intake. Moreover, while orexin lets normal cells survive and grow, it suppresses growth of tumour cells and eliminate them by promoting apoptosis (programmed natural death of cells) **[8]**. Suvorexant, an orexin receptor antagonist, inhibited the growth of normal ovarian cells in animals used for a chromosomal aberration test **[2]**.

In a carcinogenicity study, adenoma in the thyroid gland and hepatocellular adenoma increased significantly, and in a canine toxicity test, vomiting occurred even at the minimum dose, and reduced albumin and lymphocytes are observed at the medium and high doses **[2]**.

Suvorexant suppresses immunity and cause tumor growth.

> ***Note 3*** : *Narcolepsy is a disease characterized by excessive sleepiness in daytime, nap, sleep paralysis, cataplexy (emotion-induced paralysis), and hypnagogic hallucination [9].*

Pharmacokinetics of suvorexant

The time to maximum blood concentration (Tmax) of suvorexant is 1.5 to 3 hours and its elimination half-life is 10 to 11 hours, and thus high blood concentration remains in the daytime (note 4, Figure 1). Because of these characteristics and its mechanisms of action, carry-over effects were observed on the next day, including various neuropsychiatric adverse reactions mentioned below.

> ***Note 4*** : *The nadir (minimum blood level) after using the medication for 14 days was approximately a half of the maximum blood level on the first day (***Figure 2***, [2])*

Efficacy

Clinical trials in Review Report by the Japanese regulator and Summary Bases of Approval (SBA) are reported by merging a phase II Japanese study and phase III international study (up to 12 months) **[2]**. They compared three groups, namely placebo groups (group P), suvorexant low-dose group (group L) and suvorexant high-dose groups (group H). Participants in group L received 20mg/day (non-elderly persons aged below 65 years old) or 15 mg/day (elderly persons aged 65 years and older), while those in group H received 40 mg/day (non-elderly) or 30mg/day (elderly).

In the efficacy indicators for initiating sleep, such as subjective sleep latency (time to falling asleep) and persistent sleep latency (time to persistent sleep), and in those for maintaining sleep, such as durations of subjective sleep and interrupted sleep, both suvorexant high-dose and low-dose groups (group H and group L) demonstrated superiority over placebo **[2]**. However, when clinical dose (low-dose) was continued for three months, subjective sleep latency was shortened only by 5.2 minutes and subjective sleep duration was prolonged only by 10.7 minutes.

Adverse effects

Carrying-over effects: drowsiness, memory impairment, body sway, fatigue

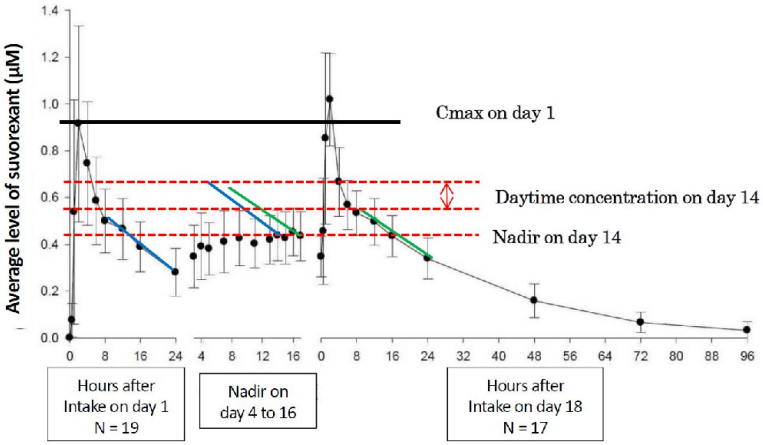
In a cross-over study (phase I) which compared placebo (group P), suvorexant 20 mg (group L) and 40 mg (group H), involving healthy volunteers, on the day after taking the test agent, increased body sway, lowered ability to recall words (memory impairment), and increased cancellation of driving test due to drowsiness were observed dose-dependently. Even those who were able to undergo driving test performed more poorly **[2,11]**.

The figure 2 shows adverse events in the phase II and III studies by groups P, L, and H. Dose-response relationship was found in somnolence ($p<0.0001$), fatigue ($p=0.0027$), and memory impairment among the elderly participants ($p=0.0263$).

1)Parasomnias-related events

Dose-response relationship was also observed in

Figure 1 : Average plasma level of suvorexant in non-Japanese healthy women



Average plasma level of suvorexant in non-Japanese healthy women (n=17-19) who took 40mg of suvorexant before bed time every day and took a single dose of Orth Cyclen (low dose oral contraceptive containing ethinyl estradiol and norgestimate) at day 14.

Comments by MedCheckTIP: It is obvious that nadir on day 14 is equivalent to half of Cmax on day 1. By simulating the concentration curve at 8 ~ 24 hrs after dosing on day 1 or on day 18 , the level of suvorexamt at day time on day 14 is estimated 0.5 to 0.7μM which is equivalent to the level at night on day 1. Hence, it cannot be avoidable for suvorexant users to have insufficient awakening during daytime leading to attention deficit, memory impairment, dizziness and depression.

Moreover, the level shown in the Figure 2 is the average of 17 to 19 persons. The level of suvorexant in the slow metabolisers with extremely low CYP3A activity may increase far more during daytime. Hence narcolepsy with or without cataplexy can occur.

parasomnias-related adverse events, such as abnormal dreams, nightmares, night walking etc. (p=0.0013) (**Figure 2**). Severe parasomnias occurred in a 65 year-old male of the high-dose group. About 2.5 hours after taking the medicine, the patient suddenly got up from the bed, hit his head and face against the wall. Two weeks after terminating the medication, he exhibited moderate sleep walking, and the events were classified as the test product related.

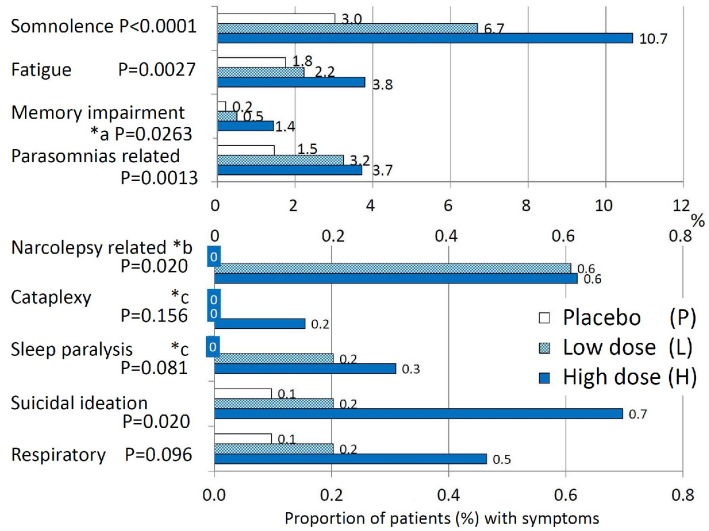
2)Narcolepsy-like symptoms

Narcolepsy-like symptoms include cataplexy (emotion-induced paralysis), hypnagogic/somnolent hallucination, and sleep paralysis. Narcolepsy-related events did not occur in the group P, but they occurred more frequently in both groups L and H. When the below-mentioned two cases, in which cataplexy is highly suspected, were added, dose-response relationship was significant (p=0.020).

Next, each symptom which belongs to narcolepsy-like symptoms is examined. One of the main narcoleptic symptoms is called “cataplexy” or emotion-induced paralysis. When strong emotional stimulation occurs, muscle tone is suddenly lost (the mechanism is explained in the column).

In one case, a 59-year-old male experienced muscle weakness in lower limbs, and it seemed to worsen when he felt excess drowsiness in daytime, and when he laughed or felt other emotional impulses. This case can be considered as cataplexy, although the independent review bord of the clinical trials judged that it could not be categorized as cataplexy because “no functional weakness was confirmed” [2].

Figure 2: Dose-related increase of major adverse events (extracted from [2])



* a: Elderly people * b: Narcolepcy-related events are the percent of patients with at least one symptoms classified with *c or hypnagogic hallucination. P value is the results from Chi² for linear trend.

Narcolepcy-related events and cataplexy are the percent of cases including those in which cataplexy is strongly suspected, such as the case of drowning.

The other case is a 40-year-old woman who drowned during swimming in the sea and died from hypoxic ischemic encephalopathy three days after drowning,

The manufacturer (MSD) explains that she died from hypoxic ischemic encephalopathy three days after drowning, and causal relationship with the test drug has been denied. However, when she experienced near drowning, she must have felt extremely strong emotional impulse that led to cataplexy. It is very likely that because of this, she was not able to swim nor breathe and died. The causal relationship cannot be denied, but strongly suspected.

In a canine toxicity study on several orexin receptor antagonists including suvorexant, when animals are presented with special diet (biscuits wrapped in meat,

beef rolls etc.) after administration of the substances, they exhibited characteristic behavioral changes (transient flexion of the limbs, gait ataxia and recumbency) that suggested cataplexy [2].

Suvorexant may cause cataplexy. However, in its package insert, "narcolepsy" and "cataplexy" are not listed as "side effects". "Suicidal ideation" and "depression-related symptoms", which will be discussed below, are also not included. This is because the manufacturer and the government did not accept that the symptoms of the two trial participants and dogs were cataplexy (***note 5***). Hypnagogic hallucination, somnolent hallucination and sleep paralysis also occurred only in treatment groups.

> ***Note 5*** : *In Summary Bases of approval (SBA) (toxicity study), changes were observed in behavior as well as electroencephalogram, electromyography and electro-oculography. However, because they were not accompanied by characteristics signs of cataplexy which had been reported in literatures, and they were not induced in another food-induced cataplexy tests with dogs, it was concluded that the symptoms of the animals were "not cataplexy, but caused by increased sleep pressure related to pharmacology". Although Review Report stated that "careful examination is necessary..., considering serious risk of narcolepsy and suicide-related events", they were not included in the package insert.*

3)Suicide-related events and depression

As for suicidal ideation, clear dose-response relation was found in the three groups (p=0.0499); 0.1% (P), 0.2% (L) and 0.7% (H) (**Figure 1**). Suicidal ideation is a crucial adverse event related to depression. If suicidal ideation is included in "depression-related events" along with decreased interest, depressed mood, and depression, clear dose-response relation was observed in the three groups (p=0.0077); 0.5% (P), 0.4% (L) and 1.5 % (H) .

In an animal experiment, when animals are administered with orexin in the cerebral ventricle, increased nervous cells were observed in the dentate gyrus (a part of the hippocampus), which is related to recognition, memory and affection, and it acts as an antidepressant. However, when an orexin receptor antagonist was given, this was inhibited [12].

4)Effects on respiratory function

Respiratory function-related events showed dose-dependent increase in the three groups marginally (p=0.096); 0.1% (1 exertional dyspnea in group P), 0.2% (1 dyspnea in group L) and 0.5% (5 dyspnea, 1 hypoxic-ischemic encephalopathy, total 6 cases in group H).

5)Summary of neuropsychiatric adverse reactions

Dose-response relationship was found in somnolence, fatigue, memory impairment, parasomnias, narcolepsy-like symptoms and suicidal ideation. Sleep paralysis also showed tendency for dose-dependent increase. Cataplexy was strongly suspected in two cases in high-dose group. These neuropsychiatric symptoms are adverse reactions to suvorexant (Belsomra). It also causes depression.

One literature explains about orexin nervous system as follows [7]. "Orexin nervous system, whose cell bodies are located in the hypothalamus, is a nervous system that projects to almost all areas of the brain to maintain arousal. It plays an essential role not only in arousal, but also in activating biological functions that control autonomic nerves such as breathing, circulation, body temperature etc. This nervous system is crucial in initiating actions in response to motives such as external stress and appetite. It acts like a master switch for changes in behaviors and autonomic functions associated with sleep and arousal. When it is disrupted, wakeful state cannot be appropriately maintained, and breathing and control of body temperature are impaired. (summary of citation from [7]).

In other words, orexin plays a key role as a master switch for defense response, adjusting almost all organs to such a response. Therefore, when it is inhibited, various peripheral organs may be impaired.

Large individual differences and drug interaction

Suvorexant is metabolized mainly by a drug metabolizing enzyme, CYP3A (***note 1***). In persons whose CYP3A activity is low and metabolism is slow (slow metabolizers), the blood level rises higher and they are more susceptible to harms. However, this is not mentioned in the package insert.

As for drug interaction, when suvorexant was launched in 2014, the package insert contraindicated concomitant use with itraconazole and clarithromycin, which strongly inhibit CYP3A, and gave caution on concomitant use with diltiazem, verapamil and fluconazole[14]. However, only two years later, in 2016, a low-dose formulation, suvorexant 10 mg, was released, and regarding the use of dilitiazem in combination, the package insert mentioned to "consider reducing the dosage to 10 mg once a day". It explains that "this is because increased plasma concentration of the medicine may enhance side effects such as somnolence, fatigue, hypnagogic sleep paralysis, parasomnias and sleep walking", admitting that the medicine might cause narcolepsy-like symptoms. However, it

gives no warning against cataplexy and suicide.

Concomitant use with itraconazole remains contraindicated. However, suvorexant can be used in combination with other CYP3A inhibitors according to the package insert. Acceptance of such concomitant uses is dangerous not only in suvorexant but also in other drugs.

In practice

Reviewing clinical trials revealed that significant dose-response relationship was found in narcolepsy-like symptoms including drowsiness, fatigue, memory impairment, cataplexy (emotion-induced paralysis), and depression-related symptoms including suicidal ideation. The mechanism of action also supports that these adverse reactions may occur. A case of death from drowning during swimming due to suspected cataplexy has also been reported in the clinical trials for application of approval.

Experiencing insomnia itself does not lead to poor health, but using hypnotics including suvorexant would be more harmful to health. Do not prescribe, dispense, nor take suvorexant.

Column

The mechanisms of cataplexy caused by suvorexant: A hypothesis

HAMA, Rokuro

There is no literature that properly describes the mechanisms of cataplexy in narcolepsy patients nor how suvorexant induces cataplexy. However, the following mechanism can be hypothesized [1]. Intense stress promotes activity of glutamic acid, catecholamine and orexin, and activates excitatory nerves. At the same time, in order to prevent overexcitement (exitotoxicity) and ease anxiety or pain, GABA (as endndogenous anxiolytics) and endogenous opioids such as endorphin are activated [2,3]. Stronger the emotional impulse is, stronger the inhibition by GABA may be. However, in narcolepsy patients, whose orexin level is already low, and patients on orexin receptor inhibitors, orexin does not act, and excessive action of GABA induced by strong emotional impulse may cause weakening of muscle tone leading to cataplexy with dyspnea [1].

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Teriparatide (brand name: Forteo, Teribone)

More harm than benefit: Do not use these agents for osteoporosis:

Synopsis from Med Check-TIP in Japanese Nov 2017 ; 17 (74):127-130

Nakanishi T and Hama R

Synopsis

● Teriparatides are products which act in the same way as parathormone (PTH). In Japan, two kinds of teriparatide formulations are approved and marketed now.

One is Forteo, a preparation for daily subcutaneous injection. The other is Teribone, a preparation for weekly subcutaneous injection.

It is reported that mild elevation in PTH can exert an anabolic effect on bone and increase bone tissues. Some clinical trials show that frequency of vertebral fracture decreased to approximately one-third by using these preparations. Frequency of fractures other than vertebra also decreased to approximately two-thirds in clinical trials.

● However, they cause hypercalcemia. This harmful effect is derived from the fundamental pharmacological action of teriparatides as PTH. PTH releases calcium from bones, increases reabsorption of calcium from the kidney, and increases absorption of calcium from the intestinal tract.

Therefore, hypercalcemia is caused by teriparatides as a result of pharmacological action of PTH.

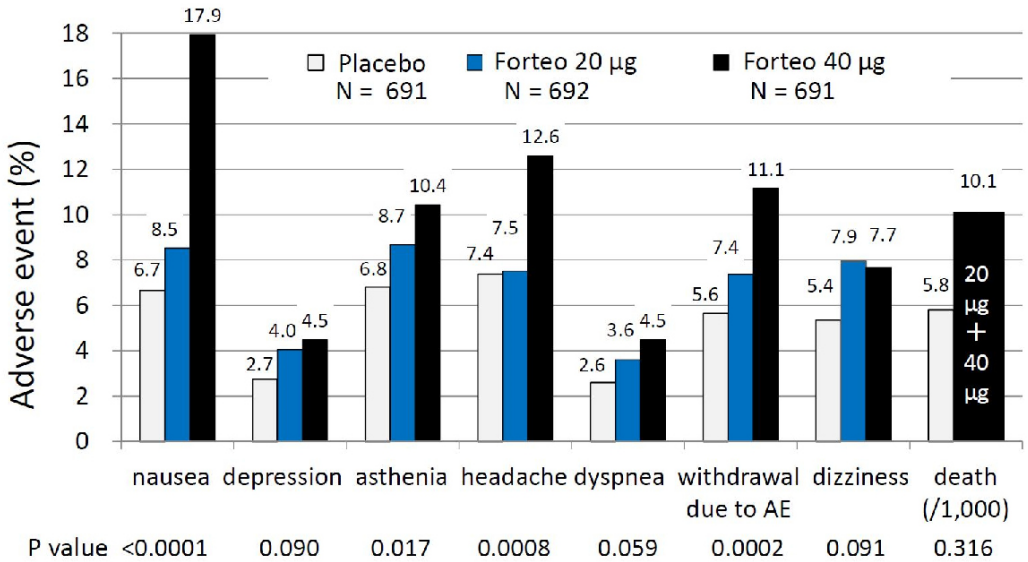
● Also, PTH causes relaxation of the smooth muscle and consequently dilatation of vessels, leading to hypotension, nausea, headache, dizziness and so on. It also affects excitability of nerve cells, causing impotence, depression and dyspnea. Osteosarccoma was reported in animal toxicity studies. Due to these findings, initial clinical trials were suspended prematurely.

The Figure shows dose-related increase of adverse events in two pivotal international clinical trials of Forteo. Nausea, asthenia, headache and withdrawal due to adverse events showed statistically significant dose-response. Depression, dyspnea and dizziness showed marginally significant dose-response.

● In the clinical trials, odds of mortality increased non-significantly by 1.7 times as compared with placebo (**Figure**).

Fig : Adverse events (AE) with dose-dependent increase

(from the two pivotal international clinical trials of Forteo)



● Many spontaneous adverse reaction cases were reported on conscious loss/ syncope and shock after marketing. Especially, circulatory failure/shock, hypotension, unconsciousness/syncope, fever and anaphylaxis were much more frequently reported after using the weekly preparation, Teribon (see **Table**).

The costs exceed 1 million yen (about 8,000 Euros) for one course of treatment (24 months). They are not worth 94 billion yen (about 710 million Euros) of annual drug price in 2015.

CONCLUSIONS: in practice, it is not recommended to use.

Table: Comparison of number and frequency of spontaneous reports in Japan

(Forteo vs Teribone)

Adverse reactions	T. Teribone (weekly)	F. Forteo (daily)	Odds ratio (T vs F)*a	
			OR	95%CI lower limit *b
Death	3	7	0.81	
Heart failure	15	24	1.18	
Myocardial infarction *c	1	6	0.29	
Circulatory failure/shock	36	2	33.96	8.18
Hypotension	70	11	12.01	6.36
Loss of consciousness/syncope	93	33	5.32	3.58
Renal impairment	19	48	0.75	
Hypercalcemia	11	24	0.86	
Seizure	11	25	0.83	
Fevering	27	11	4.63	2.30
Anaphylaxis	14	4	6.60	2.17

*a: The numbers of users were estimated to be 335,000 person-years for Forteo and 177,000 person-years for Teribone. These were calculated by the drug prices and total shipment since launching. We calculated odds ratios for Teribone compared with Forteo based on the estimated numbers of users (person-years).

*b: The lower limits of 95% confidence interval (CI) were shown only in the adverse reactions with significant difference.

*c: We included one case described as "coronary complete occlusion" in the report for Teribone.

Keywords:

Teriparatide, parathormone, PTH, Forteo, Teribone, osteoporosis, vertebral fracture, hypotension, hypercalcemia, high price, spontaneous report, osteosarcoma

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Review

Insomnia, Optimal Sleep Duration and Harm of Sleeping pills

On Essential Points for Evaluating Hypnotics

Translated from Med Check-TIP in Japanese Sept 2017: 17 (73) :110-112

Summary:

●For evaluation of hypnotics (sleeping pills), it is essential to compare effects of insomnia and hypnotics on health.

●Risk of death in persons who experienced insomnia was lower by 10%-19% than that in persons who did not. In other words, the former lived longer. Similar to changes caused by aging, when the participants were forcibly deprived of sleep, their glucose tolerance (sugar processing capacity) and thyroid function deteriorated, and their stress hormone increased. In contrast, when they were allowed to have optimal sleep duration, their conditions were restored.

●Persons who do not experience insomnia usually have deficient sleep, and thus they can fall asleep immediately. However, they maintain high level of stress. On the other hand, persons who usually sleep sufficiently sometimes experience difficulty in falling asleep. Because of that, they tend to feel that they have "insomnia." However, because they usually have adequate sleep duration and have less stress, they remain healthy.

●Risk ratio for death in persons who routinely used hypnotics was higher by 25%-39% than that in persons who did not.

●Incidence of depression was 2.4 times higher in persons on hypnotics as compared with those on placebo. Infection and cancer also increased by 44% and 35%, respectively. The use of hypnotics and anxiolytics may cause traffic accidents, falls, and addiction. When they are discontinued, they may cause withdrawal symptoms as well. These may contribute to increased risk for death.

●Hypnotics and anxiolytics such as benzodiazepines reduce secretion of endogenous anxiolytic substance (GABA) which is secreted as needed at stress. They also down-regulate their receptors, leading to insufficient suppression of excitement when they encounter danger or difficulties. Consequently, they feel excess anxiety, leading to panic disorders and depression. In addition, the medicines also suppress immunity, causing infection and cancer. For assessment of new hypnotics, their effects on receptors and immunity must be examined.

Keywords:

insomnia, optimal sleep duration, sleep latency, sleep debt, hypnotics, risk of death, depression, infection, cancer morbidity, GABA, down-regulation, immunosuppression

Introduction

This issue featured a hypnotic, suvorexant as a "New Product". When considering harm and benefit of hypnotics, it is essential to compare the effects (harm and benefit) of insomnia and effects (harm and benefit) of hypnotics on health.

There are various types of "insomnia", including having difficulty in falling asleep, waking up at the middle of sleep, and waking up too early in the morning. The main feature of insomnia is - person's perception of "not having satisfactory sleep" [1]. It is only a subjective complaint [2]. It is different from short sleep duration or deficient sleep.

In general, insomnia is believed to be harmful to health.

When patients are not satisfied with their sleep, they want to secure enough sleep even by using hypnotics. Furthermore, physicians casually prescribe them. However, is it really true that "insomnia is harmful" and "having adequate sleep by

using hypnotics is beneficial for our health"? This article will examine these questions.

Sleep duration and risk of death

The study conducted in the United States followed over 1 million men and women aged 30 years or older for approximately 5 years **[3]**. The results adjusted by over 30 kinds of risk factors such as smoking and major diseases (hypertension, diabetes etc.) as well as age and sex were reported. Below is the summary of the study **[3]**.

(1) Most people had average of about 8 hours (7.5-8.4 hours) of sleep, followed by about 7 hours (6.5-7.4 hours).

(2) People who slept for 7 hours lived the longest.

(3) About a half of the women and about 70% of the men reported that they never had insomnia.

The Japanese study **[4]** did not examine "insomnia", but it showed similar results regarding (1) and (2).

Does insomnia shorten life expectancy?

In the U.S. study **[3]**, hazard ratio for death was lower by 19% and 13% in women and men who reported insomnia once a month, respectively as compared with those who never did. Even in women and men who reported insomnia 10 times or more a month, hazard ratio for death was lower by 13% and 10%, respectively (**Figure.1**). This means that people with insomnia live longer than those without. While the authors of the study did not give clear explanation about this result which seemingly contradicted with the common view on insomnia, the Med Check No. 13 (Jan. 2014) **[5]** discussed as follows.

(1) Persons who never experience insomnia may actually have a lack of sleep.

(2) Persons who sometimes experience insomnia usually have sufficient sleep for them, and thus tend to live longer.

What happens when one is forcibly deprived of sleep?

Other studies support our views above. One is an experiment involving 11 males in their twenties (***note 1***). In this study, the participants were restricted to sleep only 4 hours a day for 6 days, and then allowed to sleep 12 hours a day for the next 6 days. Their glucose tolerance (***note 2***) worsened when they were deprived of sleep as compared with when they had sufficient sleep ($p<0.02$). Secretion of thyroid-stimulating hormone decreased, and level of stress hormone, cortisol (corticosteroid), increased ($p=0.0001$). Hyperactivity of sympathetic nervous system was observed ($p<0.02$).

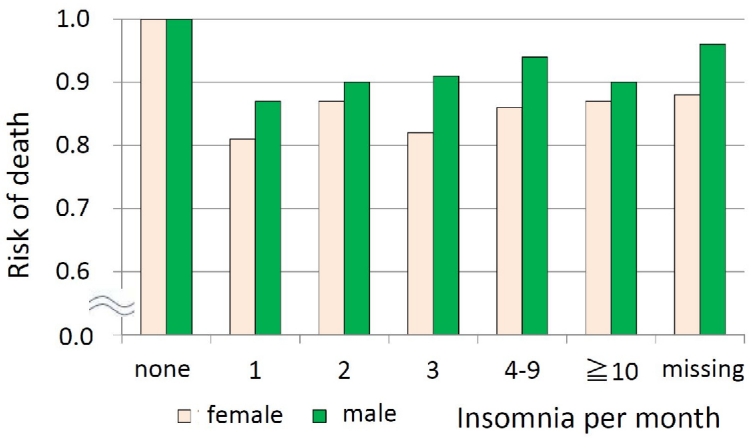
The authors concluded "The effects are similar to those seen in normal ageing and, therefore, sleep debt may increase the severity of age-related chronic disorders." **[6]**.

Another study **[7]** was conducted in Japan to experiment the opposite condition. This study involved 15 healthy men in their twenties. They were allowed to sleep as much as they wished. Their usual sleep duration was 5.8-8.9 hours (average 7.4 hours).

At day 1, they slept for average 10.6 hours. At day 2 and 3, their sleep duration gradually became shorter, and after days 4-9, it stayed at average 8.4 hours. This is considered to be the average optimal sleep duration although it does not apply to all age groups.

After securing optimal sleep duration, their glucose level and cortisol level decreased significantly, and thyroid hormone increased significantly as compared with the

Figure 1: Frequency of insomnia per month and risk of death



Risk of death is expressed as the adjusted hazard ratio compared with "person who never experience insomnia" as the baseline (1.0) [3]

baseline. These changes are totally opposite of those after having deficient sleep. In other words, the participants became healthier and had less stress after the experiment.

Having adequate sleep may sometimes cause difficulty in falling asleep – "Insomnia"

> ***Note 1*** : Lack of sleep = sleep debt. The term, sleep debt is sometimes used in other literatures, but this article uses the term "a lack of sleep" or "deficient sleep".
>
> ***Note 2*** : Test for measuring glucose processing capacity: After taking a certain amount of glucose, changes in glucose level or insulin level are measured. If insulin secretion is insufficient and glucose level rises, poor glucose tolerance is detected.

Sleep latency (time from bedtime to falling asleep) of persons who never experience insomnia tend to be as short as 5-10 minutes. In contrast, people who usually have sufficient sleep may takes 30-40 minutes to fall asleep **[7]**. When it takes long time to fall asleep, one may feel that s/he has "insomnia". People who sometimes experience "insomnia" may have sufficient sleep duration, and thus they have better functions of thyroid and pancreatic β -cells. They may be less prone to chronic diseases, and may tend to be healthy. This may be the reason why they live longer.

Using sleeping pills is as risky as having a major disease

The U.S. study **[3]** proved that the use of hypnotics increased risk ratio for death (**Figure. 2**).

Hazard ratio for death in women and men who took hypnotics everyday increased by 24% and 25%, respectively, as compared with those who never did **[3]**. Another study **[8]** also suggested 39% increase in risk ratio for death when men and women are combined. Large-scale studies using databases reported that risk ratio for death was 4-5-fold higher **[9,10]**. People who complain insomnia would live longer if they do not use hypnotics. However, using hypnotics would shorten their life expectancy rather than improving their health.

Indeed, 25% increase in hazard ratio for death is equivalent to having one major disease. People are tempted to rely on hypnotics, believing that an inability to sleep is unhealthy. However, quite contrarily, the use of hypnotics is more hazardous.

Increased depression, infection and cancer

A meta-analysis of randomized control trials (RCTs) which compared hypnotics and placebo showed that depression occurred 2.1 times more frequently in hypnotic groups than in placebo groups (p=0.0019) **[11]**. As for benzodiazepines, it occurred 2.4 times more frequently (p=0.0092). NNTH was 58.

This means that 1 person out of 58 persons had depression because of the use of hypnotics. One takes hypnotics, thinking that insomnia causes sickness. However, the consequence is totally opposite.

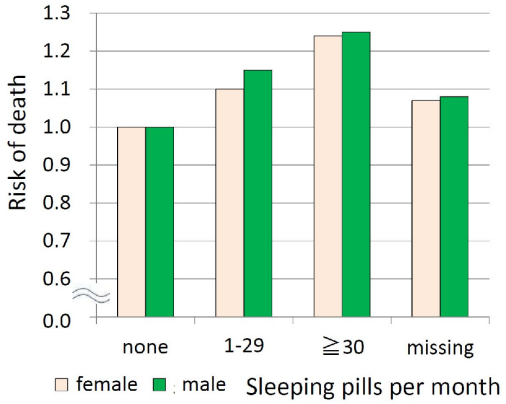
Moreover, the other meta-analyses of RCTs suggested that infection increased by 44% due to using hypnotics (p<0.0001) **[12]**. An epidemiological study using database also showed that cancer increased by 35% **[9]**. In Japan, the leading cause of death is cancer. The lifetime cancer morbidity among Japanese is nearly two-thirds (63%) in men and almost a half (47%) in women **[13]**. If the cancer morbidity increases by 35% with the use of hypnotics, it is a serious harm.

According to the 2014 statistics reported by the International Narcotics Control Board (INCB) **[14]**, the consumption of sleeping and sedative drugs was 67S-DDD/1,000 persons/day in Japan. This is equivalent to that 67/1,000 persons use hypnotics every day. In other words, 1/15 persons use hypnotics (e.g. equivalent to Ambien=zolpidem 10 mg x 1) every day. Considering that mortality increases at least by 20% or more by using hypnotics, such wide use of hypnotics would considerably contribute to increased cancer mortality.

The reason why depression increases with hypnotic use

When an animal encounters danger or a difficulty, sympathetic nervous system (adrenalin) and pituitary-adrenocortical system are activated. At the same time, gamma-aminobutyric acid (GABA), an endogenous anxiolytic substance, is secreted to inhibit overexcitement **[15-16]**. However, when hypnotics or anxiolytics are routinely

Figure 2: Frequency of hypnotic use and risk ratio for death



Risk of death is expressed as the adjusted hazard ratio compared with "person who never experience insomnia" as the baseline (1.0) [3]

used, endogenous secretion of GABA is reduced, and GABA receptors are continuously stimulated, leading to subsequent reduction of receptors (down-regulation). As a result, even daily stress and excitement cannot be coped with, as they cannot be suppressed by reduced endogenous GABA nor medications with reduced receptors. This leads to over-excitement. Then, neuronal cells in the brain are damaged by excitotoxicity, leading to sustained panic disorder and depression.

In addition, a lack of attention by hypnotics or anxiolytics leads to traffic accidents and other types of accidents. Falls at night and bone fractures associated with falls may increase in the elderly people. Addiction and withdrawal symptoms may also be caused **[17]**. These all contribute to increased mortality.

Depending on hypnotics or anxiolytics may simply postpone the problem that we have to face and to resolve. However, those who depend on such medications cannot solve the problem, and the cause of anxiety remains. Hypnotics and anxiolytics even disable them from dealing with the issue effectively and adjusting themselves to real situations. As a result, they may have financial and health problems, and even their life expectancy may be shortened.

The reason why infection and cancer increase

Most of the substances that are essential during vigorous activity, such as adrenalin and corticosteroids, have immunosuppressive effects. GABA, which inhibits overexcitement, is also one of them **[18,19]**.

All immunosuppressive medicines increase infection and cancer. Immunosuppressive effects may also be related to the reason why hypnotics increase infection and cancer.

Furthermore, benzodiazepines are clastogenic and teratogenic, and carcinogenicity was also reported in animals **[10]**.

Conclusion

Securing adequate sleep duration, which might sometimes cause “insomnia”, is needed for healthy and long life. Do not depend on hypnotics. They are hazardous to health as they increase accidents, depression, infection and cancer by paralyzing nerves and suppressing immunity. When evaluating new hypnotics, it is essential to consider their adverse effects on health.

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Pneumonia caused by proton pump inhibitors (PPI): (1)Meta-analysis

Synopsis from MedCheckTIP in Japanese Sept 2017 : 17 (73) :114-115

Keywords:
Proton pump inhibitor, PPI, pneumonia, gastric acid suppression, meta-analysis, peptic ulcer, V-type proton pump, infection

Introduction

Proton pump inhibitors (PPI) exert strong inhibition of gastric acid secretion. They have apparently few immediate adverse reactions, and they are often used for eradication of H. pylori, Gastroesophageal Reflux Disease (GERD), prevention of gastric ulcer in low-dose aspirin users and prevention of stress ulcer in seriously ill patients. They are often used even in elderly persons and the use of PPIs seems excessive in total.

Over use of PPIs

The number of PPI users who were prescribed with equivalent to 8 weeks course of PPI for gastric ulcers was estimated to be 23,600,000 person-courses in 2014. This was calculated from the total amount of shipment of only 5 major brand names of PPIs reported **[1]**. These data support excessive use of PPIs.

Insufficient warning description on PPI labels

There are descriptions and warning of bone fractures and infection with clostridium (C. difficile) in the labels of PPIs as adverse reactions **[2]**. However, the labels of PPIs in Japan do not mention pneumonia at all **[2]**. It is not well known that PPIs inhibit another type of proton pump, V-type proton pump or V-ATPase **[3-5]**.

Epidemiologic studies on PPI and pneumonia

After 2003, a large number of epidemiologic studies which reported the link of PPI use and pneumonia risk have been published. Some of Japanese review papers introduced these studies **[6,7]**. The Guidelines by the American College of Gastroenterology (ACG) mentioned "pneumonia risk of PPI" **[8]**.

A systematic review and meta-analysis were reported in 2015 **[9]**. However, in 2016 an epidemiologic paper with opposite results was published **[10]**, which is criticized in this issue **[11]**. (p42-45)

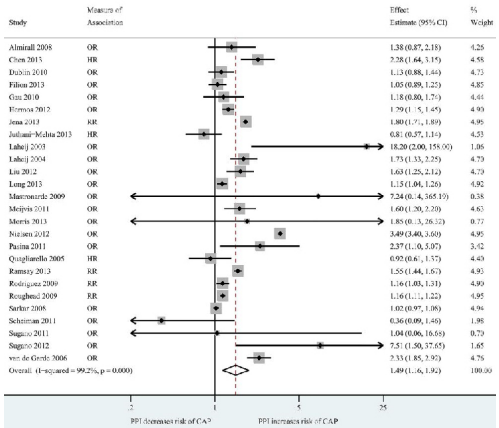
Systematic review and meta-analysis on PPI and pneumonia

The systematic review **[9]** retrieved 33 studies, of which 26 studies were included in the meta-analysis. These 26 studies included 226,769 cases of community acquired pneumonia (CAP) among 6,351,656 participants. A pooled risk of CAP with ambulatory PPI therapy was 1.49 (95% CI: 1.16, 1.92; I2 99.2%).

The risk increased during the first month of therapy (OR 2.10; 95% CI: 1.39, 3.16), regardless of PPI dose or patient age. Among 26 studies, statistically increased risk was reported in 15 studies.

Moreover, even in the studies in which no statistically significant increase in overall risk was observed, statistically significantly increased odds ratio (e.g. 3.8) was reported if the analysis was restricted within one week from the commencement of treatment. Hence, it is true that pneumonia risk is high in the short term.

Figure Meta-analysis results of 26 studies



The paper **[9]** can be accessed for free. Please see the figure on the original paper.

Warnings in prescribing PPIs

The authors of the systematic review **[9]** concluded that outpatient PPI use was associated with a 1.5-fold

increased risk of CAP with the highest risk within the first 30 days after initiation of therapy. They also discussed that providers should be aware of this risk when considering PPI use, especially in cases where alternative regimens may be available or the benefits of PPI use are uncertain **[9]**. These conclusions and discussions are very thoughtful and appropriate.

Mechanism of infections caused by PPI

It is generally believed that secretion of gastric acid is suppressed by PPIs as the mechanisms of pneumonia caused by PPI use. However, more important mechanisms, V-type proton pump (V-ATPase) should be discussed **[3-5]**. PPIs inhibit not only the gastric proton pump but also V-type proton pump which are found in almost all cells in the body, including alveolus type II cells **[12]**, macrophages (including the alveolar macrophages) **[13]**, neutrophils, kidney cells, osteoclasts, testicular cells and plasma membrane of certain neoplastic cells. It plays a very important role in maintaining normal functions of these cells: acidification of urine, bone resorption, appropriate pH maintenance in the immune system cell and sperm maturity.

As for neoplastic cells it helps to invade to other tissus. Inhibition of V-type proton pump may induce decreased surfactant production by type II alveolus cells, impairment of intra-alveolar cleaning by alveolar macrophages, leading to pneumonia. Impaired urinary acidification may also cause urinary infection such as cystitis and/or pyelonephritis. Bone fracture may be induced as the consequence of impaired function of bone metabolism.

In practice

The use of PPIs increases pneumonia especially within one month of treatment. Doctors should explain the harm to their patients, consider the balance of benefit and harm of PPI use and decide whether they should prescribe or not.

When they prescribe, patients should be closely followed-up. The prescription of PPIs should be restricted to six weeks

Table: Summary of systematic review and subgroup analyses.by Lambert et al [9]

Subgroup		number of studies analysed	Pooled effect estimate	95% CI	I^2 (%)	Pvalue
Total		26	1.49	1.16-1.91	99	<0.001
PPI dose *a	High dose	7	1.33	1.05-1.69	34	0.168
	Low dose	8	1.31	1.04-1.66	71	0.001
PPI Duration *b	< 1 month	6	2.10	1.39-3.16	73	0.003
	1-6 months	5	1.51	0.92-2.49	63	0.028
	> 6 months	5	1.37	0.85-2.20	74	0.004
age	＜65 years	7	1.34	1.04-1.71	60	0.020
	≧65 years	11	1.33	1.13-1.58	85	<0.001

*a Dose is categorized as Low for doses <1 defined daily dose, High for doses > 1 defined daily dose
*b Duration refers to duration of time taking PPI prior to community-acquired pneumonia diagnosis
These data are also available in the original paper [9]

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Pneumonia caused by proton pump inhibitor (PPI):
(2) Critical appraisal of a study using prior event rate ratio adjustment method

Translated from MedCheckTIP in Japanese Mov 2017 : 17 (74) :131-132

Summary:

Othman et al. denied the risk of community acquired pneumonia caused by proton pump inhibitors (PPI) based on their study results from both PERR (prior event rate ratio adjustment) method and self-controlled case series study (SCCS) adjusted by prior event rate ratio.

The results are very different from the results obtained by conventional cohort studies, case-control studies and a systematic review and meta-analysis of 26 epidemiologic studies. The reasons of discrepancy between these results are discussed.

It is highly probable that the prior event influenced the prescription of the drug concerned and the important background characteristics (major confounding risk factors) fluctuate very widely between prior to and after the prescription of the drug concerned. In other words, the prior rate ratio adjustment method is misused.

The hazard ratio of pneumonia by the narrow primary care definition was 3.9 (by cohort study) and 2.7 to 3.2 (by SCCS method). These results are consistent with the results from conventional epidemiologic studies and those from the meta-analysis.

It can be concluded that PPIs cause pneumonia.

Keywords:

Proton pump inhibitor (PPI), pneumonia, cohort study, self-control case series, prior event rate adjustment methods, confounder, immunosuppressant

Introduction

This issue reports about pneumonia caused by proton pump inhibitors (PPI) [1] referring to a systematic review and meta-analysis results [2] . On the other hand, Othman et al [3] reported contrary results.

They conclude that the association between the use of PPIs and risk of community acquired pneumonia was likely to be due entirely to confounding factors [3]. In other words, they claimed that the main reason of this discrepancy was derived from entirely insufficient adjustment of the confounder by the past studies.

This article discusses Othman's prior event rate adjustment method and its pitfall, modifying the rapid response [4] to Othman et al [3].

The outline of the Othman article

Othman et al [3] conducted their studies by the following three methods:

(1) Cohort study in which incidence rate ratio (hazard ratio: HR) is calculated by adjusting various confounding risk factors.

(2) The prior event rate ratio adjustment method: crude HR during post period adjusted by crude HR during prior period.

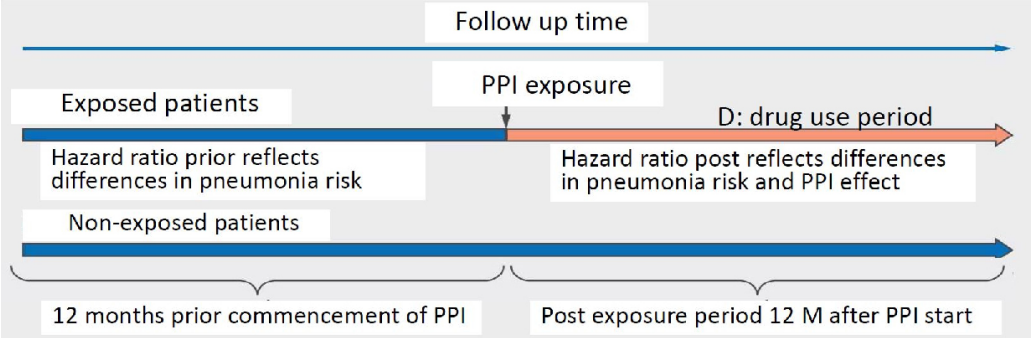
(3) HR by self-control case series method is also adjusted by prior event rate ratio.

(1) The conventional method of cohort study

In their conventional cohort study, "pneumonia" event rate in the PPI prescribed patients (160,000 PPI new users) was compared with that in the 160,000 PPI non-users who were individually matched the exposed patients one to one by age (within 5 years), sex, and year of prescription.

In the Othman's report, event rate ratio (Hazard ratio: HR) was calculated by adjusting various confounding risk factors such as comorbidities, corticosteroid use, immunosuppressant

Figure1: Outlines of cohort study methods by Othman et al



The fundamental method of cohort study is to calculate pneumonia incidence rate ratio (hazard ratio) for drug users compared with non-users with adjustment by various confounding factors (HR-Dadj). Othman et al calculated ratio of post exposure crude hazard ratio (HR-Dcr) to prior exposure crude hazard ratio (HR-Pcr) as prior risk adjusted hazard ratio (HR-Dcr/HR-Pcr). Their patients analysed were exposed to highly immunosuppressive agents that induce pneumonia prior to PPI use and the immunosuppressants might have been stopped after the complication of pneumonia and PPI might have been prescribed in order to prevent stress ulcer in severe septic infections. Adjustment by prior hazard ratio is unnecessary.

use and so on as usually conducted in conventional cohort studies.

Pneumonia risk of PPI use was evident in the conventional cohort methods they reported. HR of pneumonia by the broad primary care definition (Pneumonia 1) was 1.65 (95%CI: 1.53-1.77), while HR of pneumonia by the narrow primary care definition (Pneumonia 2) was 3.87 (95%CI: 2.75-5.44). These results are consistent with the results from other epidemiologic studies and from the meta-analysis of them **[2]**.

(2) The prior event rate ratio adjustment method

The second method of Othman et al. is "the prior event rate ratio adjustment method: PERR method" **[5-7]** which has recently been proposed as a means of reducing the bias that results from residual confounding **[3]**.

The principal benefit claimed is that if crude HR during post period (right half of **Figure 1**) is adjusted by crude HR during prior period (left half of **Figure 1**), all residual confounders may be adjusted. Crude HR means that HR is not adjusted by confounding risk factors.

As a result, HR for pneumonia-1 was reported to be 0.91 (95% CI: 0.83-0.99). This is the results that crude HR 2.06 during post period was divided by the crude HR 2.26 during prior period of PPI prescription. For pneumonia-2, the adjusted HR was 0.82 (95% CI: 0.53-1.20). This is the result that Crude HR 2.82 during post period was divided by crude HR 3.41 during prior period (problem of this method is discussed in the footnotes of **Figure 1** briefly and later precisely).

(3) The self-control case series

The self-controlled case series analysis method is a type of cohort study in which relative risk is based on within person comparisons between exposed and unexposed observation time, so only exposed patients with events can be included. The advantage of this design is that the influence of between person confounding will be eliminated **[3]**.

For pneumonia-1, 48,451 patients were analyzed and 4,461 patients were analyzed for pneumonia-2.

By this method, HR for pneumonia-1 was 1.19 and 1.49 during D1 and D2 period, respectively (see **Figure 2** for D1 and D2). HRs for pneumonia-2 during D1 and D2 period were 2.70 (95%CI: 2.29-3.19) and 3.18 (95%CI:2.93-3.46), respectively. However, HRs were changed to below 1.0 and the results were similar to those obtained by the second method (PERR) (problem of this method is discussed in the footnotes of **Figure 2** briefly and precisely in the following section).

Major reasons for discrepancies lie in the Othman's methods, not in the past studies

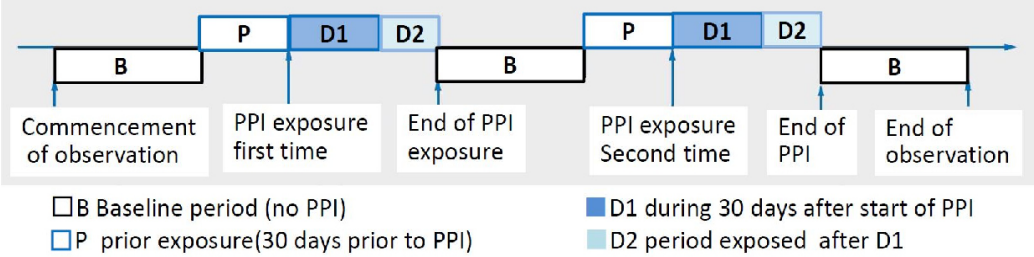
The results by Othman et al **[3]** are very different from the results obtained by the past conventional cohort studies, case-control studies and a systematic review and meta-analysis of 26 epidemiologic studies **[2]**. The reasons of such a discrepancy are discussed **[4]**.

Uddin et al **[7]** discussed that PERR provided more biased estimates than the conventional method when the prior event rate strongly influenced the probability of exposure. Moreover, they discussed that PERR method was sensitive to small violation of one of the key assumptions (i.e. constant effects of confounders in both prior periods and post-periods) **[7]**.

Let us take a look at the situation of pneumonia incidence prior to PPI prescription in the cohort study and self-controlled case series study by Othman et al **[3]**.

PPI-users had more complications than non-users and

Figure 2: Outline of self-controlled case series (SCCS) methods by Othman et al



Original Figure presented by Othman et al is modified in this article for easy understanding. In ordinary SCCS study, pneumonia incidence rate ratio during of PPI exposure (D1, or D1+D2) to that during baseline period (B) is calculated (Hazard ratio: HR-D). On the other hand, Othman reported adjusted HR (HR-D/HR-P) which is adjusted by hazard ratio at P (30 days prior to PPI exposure). During the period P, immunosuppressants might induce pneumonia and the immunosuppressants might have been stopped after the complication of pneumonia, and PPI might have been prescribed in order to prevent stress ulcer in severe septic infections. Adjustment by prior hazard ratio is unnecessary.

included more immunosuppressed patients (10.3 %) than non-users (3.0%): odds ratio = 3.68 (95%CI: 3.56-3.80, p<0.0001).

Immunosuppressed patients were defined according to criteria to contraindicate vaccination **[6]**: in brief; patients with immunosuppressive chemotherapy or radiotherapy, organ transplant patients with immunosuppressive treatment or patients with high dose systemic corticosteroids (2 mg/kg/day of oral prednisolone for at least one week or 1 mg/kg or more for one month).

These immunosuppressants induce pneumonia more frequently than PPI. Hence, pneumonias as prior events may include immunosuppressant-induced pneumonias which may often be very serious and complicated with septic shock with septic-encephalopathy.

After such serious conditions are observed, immunosuppressants are usually stopped or at least the doses are reduced. PPIs are frequently prescribed for prophylaxis of stress-induced peptic ulcer in these situations.

Essential conditions for PERR methods which Uddin et al [5] mentioned are as follows:

(1) Prior events (pneumonias) do not influence the probability of exposure (PPI) and

(2) Confounders (immunosuppressant use) are constant in both prior periods and post-periods.

Hence, both conditions are probably violated in the study by Othman et al **[3]**.

The results from the conventional cohort method (hazard ratio adjusted by various confounding factors including immunosuppressants) and hazard ratio compared with baseline period by SCCS method are the appropriate estimates of PPI risk of pneumonia in the study by Othman et al: adjusted HR for pneumonia (the narrow primary care definition) was 3.73 (95%CI: 2.69 to 5.16) by the conventional cohort methods, and HRs were 2.70 (95%CI: 2.29-3.19) to 3.18 (95% CI: 2.93 to 3.46) by the SCCS method as compared with the baseline period. These results are consistent with the results from the past epidemiologic studies and from meta-analysis by the systematic review **[1]**.

Conclusion

In the study of Othman et al., it is highly probable that the prior event influenced the prescription of the drug concerned and the important background characteristics (major confounding risk factors) fluctuated very widely between prior to and after the prescription of the drug. In other words, the prior rate ratio adjustment method is misuesed. The hazard ratio of pneumonia by the narrow primary care definition was 3.9 (by cohort study), and 2.7 to 3.2 (by SCCS method). These results are consistent with the results from conventional epidemiologic studies and those from the meta-analysis. It can be concluded that PPIs increase (or cause) pneumonia.

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