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Dabigatran (Pradaxa/Prazaxa)

Limited PROBE method undermined the results

Lubiprostone (Amitiza)

Too harmful and expensive for general use as a laxative

CONTENTS （August 2015,Vol. 1, No. 2）

MED CHECK -The Informed Prescriber

Editorial

We want good medicines!

Translated from the editorial in Med Check-TIP (in Japanese) 2015; 15 (May:#59) : 50.

Med Check TIP is a bulletin to evaluate medicinal products: good or bad. We all hope for really helpful medicines that could save lives or alleviate symptoms of disease, while causing little harm. As a bulletin, we really hope to present articles on medicines that work safely with clear-cut benefit. However all articles in this issue on "new products" are associated with problems. It is not our intention to criticise new medicines. Unfortunately negative assessments reflect the reality of pharmaceutical innovation with little therapeutic value since nineties[1].

Dr SUNAHARA, Shigeichi is a pioneer of randomized controlled trials in Japan. He said: "Drugs, being foreign to the human body, only by chance evolve therapeutic value and it is more or less inevitable that they harbor some undesirable effects. To prevent drug-induced suffering, the following 4 caveats are essential: (1) develop a drug with the least possible hazards; (2) collect as detailed information as possible about adverse reactions to the drug even after careful screening; (3) find the safest way of drug administration based on the above-mentioned information and (4) always be alert for unknown risks [2].

The "therapeutic values" expected in such products as dabigatran, lubiprostone and propofol all discussed in this issue, have been found "only by chance". However, dabigatran, for example, has been marketed without taking account of caveats (1) and (2). To be specific, the use of dabigatran is associated with several problems; (1) The limited PROBE method was used in the design of the pivotal clinical trials of dabigatran for approval, (2) Clinical trials for approval were performed without tests to predict hemorrhage). Dabigatran was approved and marketed without information to prevent hemorrhage. The result was deaths due to bleeding that have occurred frequently. (3) Dabigatran was promoted on the basis of misleading information suggesting it is superior to warfarin, the standard treatment. (4) It may be hard to expect that medical professionals are always be alert for unknown harms.

Considering these situations the "Guideline for the Safe use of Drugs and Therapeutics in the Elderly 2015 (draft)" which the Japan Geriatrics Society announced in April 2015 is valuable, recommending against the use of many ineffective and harmful drugs in the elderly. However, the Guideline did not critically evaluate the safety of some classes of drugs used by many people such as antihypertensives, statins and proton pump inhibitors, as we commented in this issue (not published in the English edition).

Recently, the Essential Medicine List (EML) of the World Health Organization (WHO) was revised. The revised EML included some new but very expensive products for the treatment of intractable disease. A typical one is sofosbuvir for hepatitis C, which was also approved in Japan in March 2015. During the development process of sofosbuvir, a homologue showed mitochondrial toxicity and further development was stopped. Would the problem be overcome with sofosbuvir? Further in-depth analysis is essential.

We will examine this new product closely in the next issue of Med Check TIP (No 3). We will also deal with the products in the EML, because we consider many of them to be essential to medical care in Japan also, even though they were introduced into medicine many years ago.

References

1) ISDB Declaration on therapeutic advance in the use of medicines2001: http://www.isdbweb.org/documents/uploads/Declaration/ISDB-decl-english.pdf

2) Sunahara, S. Key note reports In Soda ed. Proceedings of the Kyoto International Conference Against Drug-Induced Sufferings 1979, Excerpta Medica, 1980

Dabigatran: potentially harmful

The safe use is compromised without monitoring and an antagonist
Optimal dose may be lower: Subgroup analysis indicates

Translated and revised based on Med Check TIP (in Japanese) 2015; 15 (May:#59); 51-54.

Abstract:

Dabigatran is a direct thrombin inhibitor. There is an extremely high correlation between aPTT and dabigatran concentrations. However, the manufacturer maintained that any coagulation test as an indicator for assessing the risk of hemorrhage had not been established, and coagulation tests were not performed in the RE-LY study, a pivotal clinical trial for approval. They were not required for the drug approval. The clinical trials conducted without these tests are potentially dangerous and should be reexamined in ethical terms. The RE-LY study was conducted by using the PROBE method which could potentially induce biased management of patients favoring the experimental product. Data from subgroup analysis indicates that an optimal concentration of dabigatran may be lower than the recommended dose to obtain minimal total events (thromboembolic and hemorrhagic). Another issue is that in the event of hemorrhage, no antagonists to dabigatran are available. The testing methods to prevent bleeding should be established by reanalysis of the study data. Developing an antagonist of the drug is also essential. Until these serious limitations have been addressed, it should not be used.

Introduction

Dabigatran (brand name: Prazaxa) is an oral anticoagulant that acts as a direct thrombin antagonist [1]. It was launched in Japan in March, 2011. Recommended usual dase is 150mg b.i.d. It is indicated "to reduce the risk of ischemic stroke and systemic embolism in patients with non-valvular atrial fibrillation." Standard treatment for patients with non-valvular atrial fibrillation is to use warfarin to keep prothrombin time international normalized ratio (PT-INR) appropriately (later explained in detail). Warfarin had long been the only oral anticoagulant until dabigatran was introduced, followed by other oral anticoagulants with similar mechanisms **(note 1)**. These new oral anticoagulants prolong coagulation time concentration-dependently as tested by activated partial thromboplastin time (aPTT), ecarin clotting time (ECT), and thrombin time (TT) mentioned later in detail [1]. However, monitoring by these tests was not required in clinical use of the new oral anticoagulants for their approval [1]. In August 2011, five months after the release of dabigatran, five deaths due to serious bleeding after dabigatran use were reported, and the warning was issued in the form of a blue letter[2]; **(note 2)**.

Immediately after the warning was issued, the Japanese Circulation Society announced an urgent statement. While advocating proper use of the drug, the society has continued to recommend the use of dabigatran [3b]. In the Guidelines for Pharmacotherapy of Atrial Fibrillation revised in June 2013 [4] **(note 3)**, the use of dabigatran in high-risk patients with a CHADS2 score of two or higher is recommended with Level of Evidence B. Dabigatran is listed before any other drugs with Level of Evidence A, including warfarin. Warfarin was listed as the last option despite its high level of evidence. Moreover, an additional note said "new oral anticoagulants are preferable to warfarin if they have an equivalent level of evidence". It seems the revised guideline recommends level-B dabigatran over level-A drugs, including warfarin [4]; **(Suppl. 1)**.

The revised guideline recommends the new drugs, for which a method of monitoring is not established and no neutralizer has been developed, over warfarin, which can be well monitored and has neutralizers. We will examine whether this recommendation is rational, and discuss the most appropriate treatment for the prevention of ischemic stroke and systemic embolism in patients with non-valvular atrial fibrillation.

Note 1: Edoxaban (a brand name：Lixiana, launched in July, 2011), ribaroxaban (brand name xarelto, launched in April, 2012) and apixaban (brand name Eliquis, launched on February, 2013) are on the market now. Of these, only edoxaban is approved for the indication "to treat and reduce risk of recurrence of venous thromboembolism (deep vein thrombosis and pulmonary thromboembolism) and to reduce risk of thromboembolism in patients who received lower limbs orthopedic surgery including the total knee replacement, total hip replacement and hip fracture".

Note 2: According to the package insert revised in July, 2014, "As any monitoring method to assess the anticoagulant activity to prevent bleeding is not established, during administration of the drug, be careful with not only the testing results for blood clotting but also any signs of bleeding or anemia. When these signs were noticed, appropriate measures including immediate stopping the drug and treatment for hemostasis are necessary.

Note 3: "Atrial Fibrillation Treatment Guidelines" were revised in 2013 [4]. It was four years after the 2008 edition (published in November, 2009). Recommendation level A shows superior than B.

Pharmacological action of warfarin

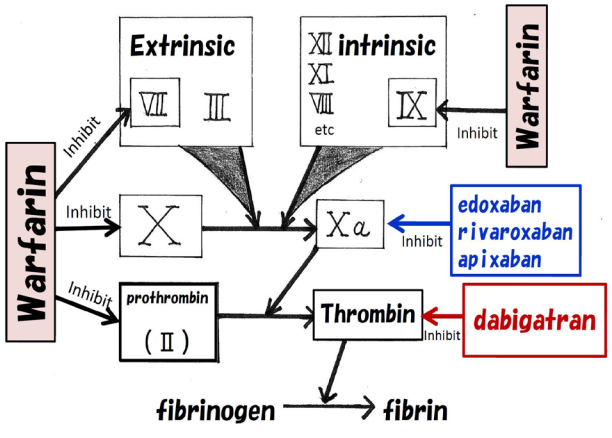
Warfarin is an antagonist of vitamin K. Coagulation Factors II (prothrombin), VII, IX and X, and proteins C and S are synthetized mainly in the liver. These biologically inactive coagulation factors become active form by carboxylation of glutamic acid (Glu) residues of coagulation factors into γ -carboxyglutamic acid (Gla) residues when reduced vitamin K becomes oxidized vitamin K (vitamin K epoxide) by γ -glutamyl carboxylase [5]. **(Suppl. 2)**.

After activating coagulation factors, Vitamin K epoxide is reduced by vitamin K reductase. By inhibiting vitamin reductase, warfarin inhibits vitamin K cycle and activation of vitamin K-dependent coagulation factors II, VII, IX, and X, and works as an anticoagulant [5].

Pharmacological action of dabigatran

The full generic name of dabigatran is "dabigatran etexilate methanesulfonate". It is a prodrug and is rapidly metabolized in the liver. It becomes an active form of dabigatran, which directly inhibits thrombin to inhibit the conversion of fibrinogen into fibrin and blood clotting (**Figure 1**). The bioavailability of dabigatran is as low as 5-6% [1].

Figure 1：Action of oral anticoagulants on coagulation factors

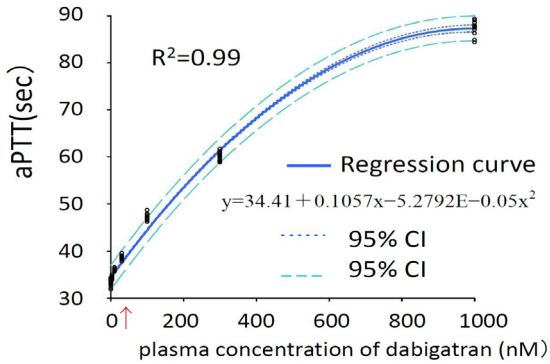


The correlations between plasma concentration (nM) of dabigatran and results of each clotting test are extremely high (R^2=0.99 for aPTT, R^2=1.00 for ECT and R^2=1.00 for thrombin time (TT) (**Figure 2**, **Suppl. 3a** and **3b**, respectively).

The timing of examination and the optimum (safe and effective) test value are still unknown (see section (5) in the following page). However, if an aPTT is prolonged, bleeding time would surely be prolonged (**Figure 3,** see p19) [1a].

In addition, regarding warfarin, consideration is unnecessary for the timing of INR measurement because its elimination half-life is 50-100 hours at the stationary state.

Figure 2: Correlation between concentration of dabigatran and coagulation test results: activated Partial Thromboplastin Time (aPTT)



Major bleeding may increase at more than 38 nM (50 ng/mL) [ref 6]

Pharmacokinetics

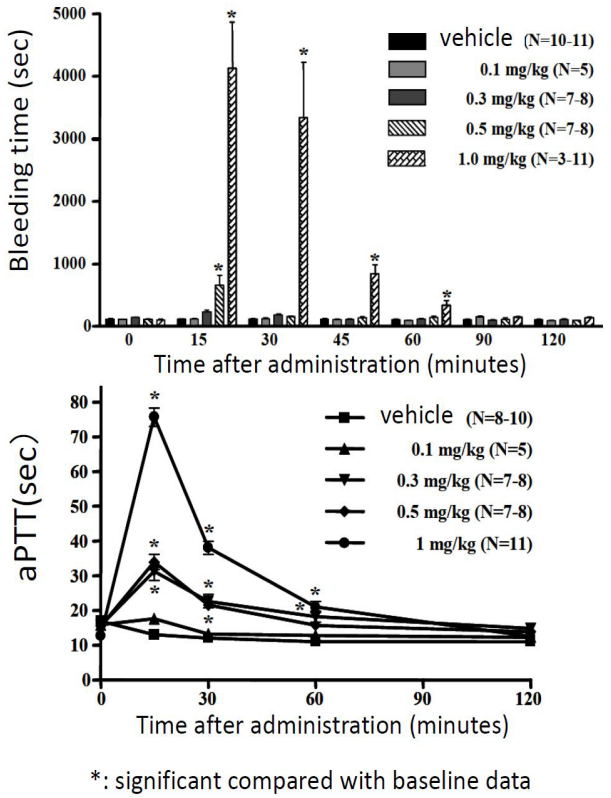
The inter-individual difference of the total blood level of dabigatran is extremely large. Among approximately 30 persons receiving the same dose, the maximum plasma concentration (Cmax) and the area under the curve (AUC) of the highest persons were 30 times (Cmax) and 40 times (AUC) higher respectively than those of the lowest persons [1a]. **Figure 4** (see p19)shows an example. It has also been reported that the maximum difference exceeded 400 times in a clinical trial but the pharmaceutical company failed to report the data [6].

Fasting and postcibal concentrations differ in a single individual, and after repeated use the difference between Cmax and nadir (Cmin) is approximately 3-3.5 times. Because dabigatran is excreted by the kidney, in people with decreased renal function, it easily accumulates, and AUC increases. Interactions also occur frequently.

Result from the RE-LY study

The RE-LY study [7] is a single pivotal randomized controlled study, which provides the evidence base for approval of dabigatran in most countries, including Japan. A total of 18,113 patients with atrial fibrillation were randomly assigned in a non-inferiority trial, using the PROBE (prospective randomized open blinded end-point) method, in which only outcome assessment was blinded, and patients and investigators knew which agents were used during the study period. Dabigatran was used at fixed doses (110 mg or 150 mg, twice a day), but the dose of warfarin was adjusted

Figure 3 : aPTT and bleeding time after dabigatran administration

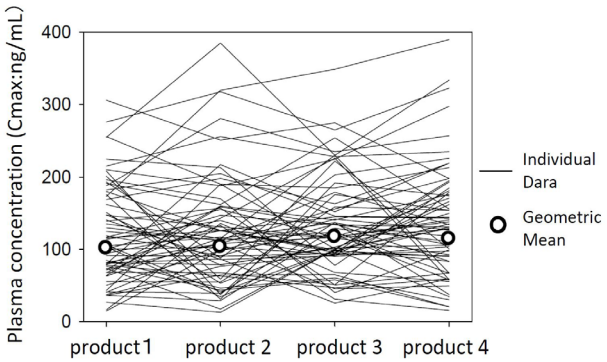


Rats were administered (i.v.) with dabigatran (D). At the time just after injection when plasma concentration may be maximum (15 min.), aPTT and the bleeding time was the most prolonged.

In the 0.3mg/kg or more group, aPTT prolonged more than 30 sec. and bleeding time prolonged compared with control, 0.1mg/kg group and baseline data. 1mg/kg group showed more than 70 sec. of aPTT and more than 4000sec of bleeding time at 15 min. and showed prolonged bleeding time at 60 min. even when aPTT decreased (significantly more than the baseline data).

This may mean that bleeding time is closely related to aPTT and risk of bleeding is well predicted by aPTT.

Figure 4 : Inter-individual difference of plasma concentration (Cmax) of dabigatran



Inter individual difference of plasma concentration (Cmax) for older products (product 1 and 2) and newer products (product 3 and 4). According to the approximate measurement from the graph, ratio of concentration of maximum to that of minimum may be 30. Ratio up to 400 is reported [ref. 6].

based on the test results of PT-INR. The primary outcome was stroke and/or systemic embolism. Serious bleeding was the primary outcome for serious adverse events. The secondary outcomes were stroke, systemic embolism, or death. The median duration of the follow-up period was 2.0 years, and complete follow-up was achieved in 99.9 % of patients, with 20 patients lost to follow-up. All analyses were based on the intention-to-treat principle [7].

The efficacy primary outcome (stroke and systemic embolism) was significantly superior in the dabigatran 150 mg b.i.d group (1.11% per year) than the warfarin group (1.69 % per year, P <0.001). The rate of major bleeding was not significantly different in the dabigatran 150 mg b.i.d group (3.11% per year) compared with the warfarin group (3.36% per year, p=0.31) **(Table-(a))**. These results provided the basis for approval in most countries, including Japan.

However, significantly larger number of participants discontinued the study product in the dabigatran groups than in the warfarin group. The PROBE method may be

Table : Summary of the RE-LY study

events	Warfarin (Wa) N=6022			dabigatran (110mg) N=6015			dabigatran (D150mg) N=6076			D110mg vs Wa OR *a	D110mg vs Wa P *b	D150mg vs Wa OR *a	D150mg vs Wa P *b
	n	%	%/yr	n	%	%/yr	n	%	%/yr				
(a) Outcome events													
Primary outcome *c	199	3.3	1.69	182	3.0	1.53	134	2.2	1.11	0.91	NS	0.66	***
Hemorrhagic stroke	45	0.7	0.38	14	0.2	0.12	12	0.2	0.10	0.31	****	0.26	****
All cause mortality	487	8.1	4.13	446	7.4	3.75	438	7.2	3.64	0.91	NS	0.88	NS
Major bleeding	397	6.6	3.36	322	5.4	2.71	375	6.2	3.11	0.80	**	0.93	NS
Net outcome *d	901	15.0	7.64	844	14.0	7.09	832	13.7	6.91	0.92	NS	0.91	*
Primary+major bleeding	596	9.9	5.1	504	8.4	4.24	509	8.4	4.22	0.83	**	0.83	**
(b) Discontinuation													
Discontinued (1 year)	608	10.2		862	14.5		935	15.5		1.49	****	1.62	****
Discontinued (2 years)	902	16.6		1161	20.7		1211	21.2		1.36	****	1.41	****
(c) Reasons of discontinuation													
patient's decision	375	6.2		440	7.3		474	7.8		1.17	*	1.25	***
outcome events	130	2.2		192	3.2		164	2.7		1.48	***	1.25	NS
serious adverse event	**105**	**1.7**		**163**	**2.7**		**166**	**2.7**		**1.55**	***	**1.57**	***
GI symptoms *e	**38**	**0.6**		**134**	**2.2**		**130**	**2.1**		**3.53**	****	**3.39**	****
GI bleeding	54	0.9		58	1.0		80	1.3		1.08	NS	1.47	*
Others	200	3.3		174	2.9		197	3.2		0.87	NS	0.98	NS

*a : OR: odds ratio *b : p value **** : p<0.0001, *** : p<0.001, ** : p<0.01, * : p<0.05, NS : p>0.05

*c: Primary outcome includes ischemic stroke or systemic embolism.

*d: Net outcome (The net clinical benefit outcome) is the composite outcome including primary outcome, pulmonary embolism, myocardial infarction, death, or major bleeding.

associated with the rate of discontinuation and could have affected the results. We describe limitations of the RE-LY study in the following section.

Limitations of the RE-LY study

(1)Discontinued are 10 times more frequent than those having primary outcome in the dabigatran 150 mg group

The proportions of patients discontinued within one year were 15.5 % , 14.5 % and 10.2 % in 150 mg, 110 mg, and warfarin groups respectively. Odds ratio of discontinuation in the 150 mg group compared with the warfarin group was 1.62 (95% confidence interval (95% CI): 1.45, 1.80, p<0.0001) **(Table-(b))**. The 2-year discontinuation rate was 21.2 % , 20.7% , and 16.6% , respectively. The odds ratio of the 150 mg group compared with the warfarin group was 1.35 (95 % CI: 1.23, 1.48, p<0.0001). The ratio of proportion of patients with discontinuation to the proportion of participants with the primary outcome was 5 times in the warfarin group, and as high as 10 times in the 150 mg group.

(2) Possibility of biased management in favor of the dabigatran

Reasons of discontinuation in the dabigatran 150 mg group and warfarin group include (1) patient's decision (7.8 % vs 6.2 %), (2) serious adverse event (2.7 % vs 1.7 %), (3) gastrointestinal symptoms (2.1 % vs 0.6 %), (4) gastrointestinal bleeding (1.3 % vs 0.9%) **(Table-(c))**. For all reasons except outcome events, dabigatran 150 mg group is significantly higher than the warfarin group. In particular the odds of gastrointestinal symptoms in both dabigatran 150 and dabigatran 110 groups were significantly higher than in the warfarin group (OR: 3.44, 95% CI: 2.39, 4.95, p<0.0001 and 3.59, 95% CI: 2.50, 5.15, p<0.0001).

(3) Double dummy method combined with dummy PT-INR was not used

A double-blind randomized controlled trial (RE-COVER study) of dabigatran for thrombophlebitis was performed by the double dummy method [10]. This was made possible by adopting the following method. In the RE-COVER study, PT-INR values within the possible range as seen in the warfarin group were randomly generated and reported to the participants in the dabigatran group. It is unclear why the same method was not used in the RE-LY study.

(4) No information is available for the proportion of time when warfarin was out of targeted INR range

In four [16, 18,19,20] among five [16-20] randomized controlled trials of warfarin in atrial fibrillation, the proportions of the time when INR was within the target level, lower than the lower limit and higher than the upper limit were reported. However, in the RE-LY study, only information within the target level (64 %) was reported, but no other information, especially proportion of the time higher than the upper limit was not reported.

(5) PROBE method-possibly unreliable due to potential bias

Periodical testing of PT-INR was performed in the warfarin group in the RE-LY study, while no test was performed in the dabigatran groups. In the RE-LY study, the PROBE method was used due to the claim that double blinding was impossible. Hence, participants and investigators could know the identity of the assigned products.

Although the report of RE-LY says that all analyses were based on the intention-to-treat principle [7], it is not known how the higher discontinuation influenced the results of outcomes especially the major hemorrhagic events.

(6) Dabigatran level of 50 ng/mL (38 second for aPTT) is critical to bleed

A plasma level of dabigatran related to bleeding was reported in the subgroup analysis of the RE-LY study [14], and the bleeding frequency was 2-3 % at the optimum level of dabigatran of less than 50ng/mL (32 nM), but 9% at 300 ng/mL and 12 % at over 300 ng/mL [6,14] **(suppl. 4a)**. An aPTT of less than 38 seconds is compatible with the optimal concentrations (less than 50 ng/mL or 32 nM), if we apply the correlation between aPTT and dabigatran concentration as shown in the **Figure 2**.

Further data from the RE-LY study should be disclosed for re-analysis to evaluate what the optimal concentration of dabigatran is to minimize total events of embolism and hemorrhage as shown in **the Supplement 4b** (analysis of total event risk by intensity of anticoagulation [13b]).

(see also An additional analysis using data of the RE-LY from ref [14] entitled "Optimal dose may be lower: Subgroup analysis shows")

Post-marketing surveillance and suit in the United States

Dabigatran was prescribed for 270,000 people in the United States during three months in 2011. Of these, 932 reported serious adverse reactions. Among them, 543 were hospitalized, 25 had sequelae, and 120 died [11]. Approximately one in 300 who took dabigatran got serious adverse reactions, and one in 2,300 who took dabigatran died.

After the marketing of dabigatran began in the United States, many of those who were prescribed dabigatran died, and their families sued the manufacturer, Boehringer Ingelheim Co. (BI Co.). BI Co. announced that they would pay 650 million U. S. dollars (approximately 70 billion yen) to settle the cases in June 2014 [6]. In the suit, internal documents of BI Co. were disclosed. They indicated that if the coagulation tests were used to prevent bleeding, it could have reduced the large number of bleeding accidents [6]. As shown in the previous section, it is reasonable to infer that measurement of aPTTs could prevent substantial proportion of the bleeding accidents.

What is the best outcome for efficacy and safety in anticoagulant use?

The primary outcome should be the long term all-cause mortality, because it is the strongest and the least biased among all the outcomes [22,23]. However, RCTs for the treatment of non-valvular atrial fibrillation did not observe patients for longer than two years. The net clinical benefit outcome (the net outcome) is one of the options for outcome. However this is not reported in the five RCTs for warfarin.

It may be reasonable that proportion of events with ischemic stroke/systemic embolic events + major hemorrhage (abbreviated as "IS/SEE/MH" may be considered as the third best "primary outcome" of anticoagulant therapy [12, 13, 15].

Optimal PT-INR should be the value by which the frequency of "the best primary outcome" becomes the least. For the anticoagulant therapy with warfarin, optimal PT-INR to obtain the least IS/SEE/MH was reported as 1.6-2.6 in Japan [12]. A recently published large-scale investigation,

the J-RHYTHM Registry [13] also confirmed that this (1.6-2.6) of PT-INR was optimal to obtain the least IS/SEE/MH. Yamaguchi et al [24] reported in their randomized controlled trial that low intensity warfarin treatment group (target INR: 1.9 and the range: 1.5 to 2.1) was safer than the conventional-intensity group (target INR:2,5 and the range: 2.2 to 3.5) because of the lower incidence of major hemorrhage with no difference in the incidence rate of ischemic events. According to our re-analysis using the data in Yasaka's paper [12], the least IS/SEE/MH was observed during PT-INR 1.6 to 2.19 [25]. J-RHYTHM Registry [13] showed the least IS/SEE/MH was obtained during PT-INR 1.6 to 1.99 and the next least during 2.0 to 2.59.

These results are consistent with the results from the BAATAF study in which target PT-INR were determined as 1.5 to 2.7 and the PT-INR within the target level was achieved 83 % of duration and the least stroke and major hemorrhagic events were obtained.

In practice: a summary of the treatment of the non-valvular atrial fibrillation

The first-line drug for patients with non-valvular atrial fibrillation is warfarin. The target PT-INR may be 1.6 to 2.19 (less than 2.6). We do not recommend the use of newer oral anticoagulants, including dabigatran, until methods of monitoring and more effective and safer use are established.

If the plasma concentration of dabigatran increases, aPTT, ECT, and thrombin time may be prolonged, and the risk of bleeding may increase (see the next section "Optimal dose may be far lower": an additional analysis using the data from ref [14]).

Optimal dose may be far lower: Subgroup analysis shows

An additional analysis using data of the RE-LY from ref [14]

Summary of subgroup analysis: from ref [14]

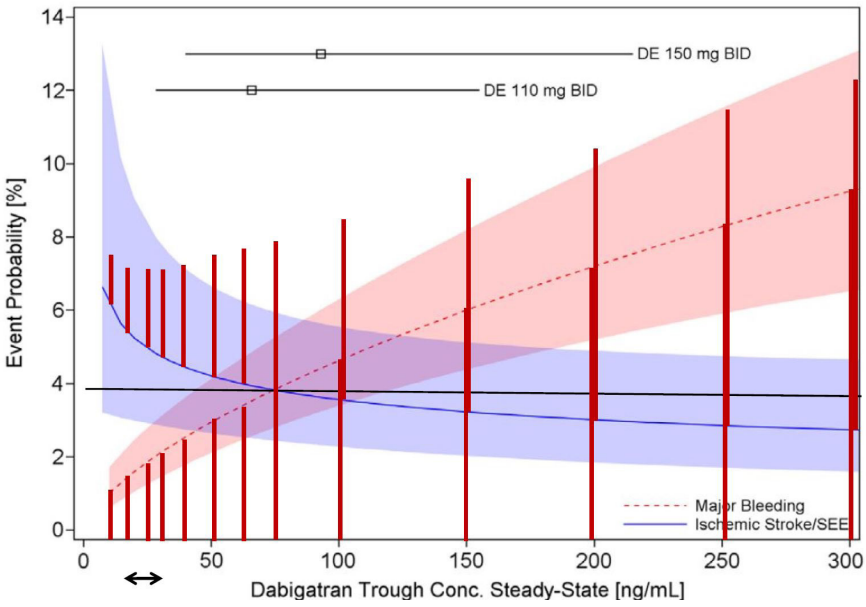
In the subgroup analysis of the RE-LY study, plasma concentrations of dabigatran obtained from 9,183 patients were reported in relation to the clinical outcomes of ischemic stroke/systemic embolism and major bleeding using univariate and multivariate logistic regression and Cox regression models. Among 9,183 patients, 112 ischemic strokes/systemic emboli (1.3 %) and 323 major bleeds (3.8 %) were recorded. A multiple logistic regression model showed that the risk of ischemic events was inversely related to trough dabigatran concentrations (p=0.045), with age and previous stroke (both $p < 0.0001$) as significant covariates. Multiple logistic regression showed major bleeding risk increased with dabigatran exposure ($p < 0.0001$), age ($p < 0.0001$), ASA use ($p < 0.0003$), and diabetes ($p = 0.018$) as significant covariates. The authors concluded that ischemic stroke and bleeding outcomes were correlated with dabigatran plasma concentrations and individual benefit–risk might be improved by tailoring dabigatran dose after considering selected patient characteristics.

Figure 5 is the summary fifure of the results of subgroup analysis showing the risk of ischemic stroke/systemic embolism and major bleeding events for 72-year-old male atrial fibrillation patient with prior stroke and diabetes correlated with the dabigatran plasma trough concentrations.

Assessment by the preferable primary outcome (IS/SEE/MH)

We consider that "ischemic stroke/systemic embolism" and "major bleeding events" (IS/SEE/MH) may be one of the most preferable outcomes. This is estimated by adding the risks of "major bleeding" to the risks of "ischemic stroke/systemic embolism" as indicated by the red vertical line shown in the **Figure 5** (original figure without red vertical lines is shown in the **suppl.5)**.

Figure 5: Dabigatran concentration and risk of "ischemic stroke/systemic embolism + major bleeding events" [red vertical lines are added to the figure in ref 14]



Total risk of "ischemic stroke/systemic embolism + major bleeding events" is estimated by adding the risks of major bleeding on the risks of "ischemic stroke/systemic embolism + major bleeding events" as indicated by the red vertical line shown in the above (Figure 5) .

As we could consider the optimal concentration of dabigatran may be the concentration at which the total risk of "ischemic stroke/systemic embolism + major bleeding events" is the least, it may be about 15 ~ 30 ng/mL (11 ~ 23 nM) from the data in ref [14]. Hence not only 150mg b.i.d but also 110 mg b.i.d. may be far more compared with optimal dose.

The best plasma concentration may be far lower

As we could consider the optimal concentration of dabigatran may be the concentration at which the total risk of IS/SEE/MH is the lowest, it could be simply read approximately 15-30 ng/mL (11-23 nM) for a 72-year old man with history of previous stroke and diabetes from the **Figure 5** (based on the data from the subgroup analysis [14]. The results of optimal concentration of dabigatran for other ages (65, 75 and 85 years) estimated from the data as shown in the figure 1 of the subgroup analysis [14] may not be so different as the results from the 72-year old man with history of previous stroke and diabetes. Hence, not only the plasma concentration obtained by the 150mg b.i.d but also by the 110 mg b.i.d. may be far higher compared with the optimal concentration.

Ongoing dose (110 or 150 mg b.i.d.) may be higher than the optimal

A dose of 110 mg b.i.d. shows about 65 ng/ml of geometric mean of plasma concentration (10 percentile and 90 percentile were 28 and 155 ng/mL respectively). This is 3 times higher than 21 ng/mL if this is an optimal plasma concentration. As for the dose of 150 mg b.i.d, geometric mean of plasma concentration was 91 ng/mL (10 percentile and 90 percentile were 52 and 275 ng/mL respectively).

This is 4 times higher than a possible optimal plasma concentration (21 ng/mL). We do not know what the real optimal dose of dabigatran is, as we could not know what had happened in the discontinued participants. However, according to these data, optimal dose of dabigatran may be far lower than not only 150 mg b.i.d but also 110 mg b.i.d.

Best outcome analysis of warfarin group by PT-INR value is essential

Because IS/SEE/MH may be the preferable outcome to be used to determine the optimal target of PT-INR [12, 13, 15] and because re-analysis of dabigatran groups using IS/SEE/MH as the preferable outcome suggested lower optimal concentration of dabigatran, re-analysis of warfarin group using IS/SEE/MH as the preferable outcome by PT-INR value is essential.

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Dabigatran:

Potentially Harmful

Generic name: dabigatran
Brand name: Pradaxa(US, EU etc)
Prazaxa(Japan)

If you have any questions on this leaflet, please ask your doctor or pharmacist. Please keep medicines out of reach of children.

What is this medicine?

Atrial fibrillation is a common arrhythmia (irregular heart beat). If you have atrial fibrillation, blood easily clots inside the heart, and a fragment of the blood clot travels from the heart to brain or other parts of the body and may plug the blood vessels. Then, you may have stroke (brain vessel obstruction) or embolism in other parts of the body. In order to prevent clotting, a drug called "anticoagulant (or a blood thinner)" is prescribed.

*For this purpose, "warfarin" is the standard drug.
*Dabigatran is a newly approved drug for the same purpose. It is advertised as being very convenient because blood testing is not necessary.
*However, using dabigatran without monitoring is dangerous because excessive action of blood thinners may induce bleeding and make it hard to stop.

*For prediction of excess action of warfarin, a test for monitoring is available. However, the excess action of dabigatran cannot be predicted because no such test is available for the drug. In fact, five death cases due to bleeding were reported and warnings on prescription were issued in August 2011, 5 months after its launch.

Who must avoid dabigatran?

* A person whose kidney function is lowered (including the patients on dialysis).
* A person with ongoing bleeding or who is prone to bleeding
* A person who had gastric ulcer in the past, cerebral hemorrhage within the past six months, or who has other diseases which are likely to cause bleeding
*A person who has epidural (surface of spinal nerve) catheter or whose epidural catheter was extracted within the past 1 hour.
*A person who is using itraconazole, which enhances the effects of dabigatran and is likely to induce bleeding.
*Elderly people. Their renal function is usually decreased, in spite of the apparent normal value of routine kidney function test.

How to use properly?

*We do not explain it in detail, because we do not recommend dabigatran.
*We recommend warfarin instead of dabigatran if you need a drug to prevent blood clotting.
*The reasons are: (1) excess action of warfarin can be detected by a test, but that of dabigatran cannot be, (2) antagonists (drugs to weaken an action of a particular drug) in the case of bleeding is available for warfarin but not available for dabigatran.

Precautions while using dabigatran

*Do not stop dabigatran suddenly, if you are already on the drug without any sign of adverse effects below. An alternative drug is necessary to prevent blood clotting. Discuss with your doctor.
*If you see doctors other than your doctor such as surgeon or dentist etc, while taking this drug, make sure to inform them that you are taking dabigatran. Otherwise, it will very hard to stop bleeding after surgery or tooth extraction. It's very dangerous.
*Your kidney function must be regularly checked because it may be affected by the medication and by other reasons...
*Bleeding may become severe even in the case of slight injury while taking dabigatran. Avoid any intense exercises and dangerous works.

Adverse effects (Side effects)

※ **Stop taking dabigatran and see your doctor or call an ambulance (in the case of serious symptoms),** if you have:

[Bleeding] Bleeding is the most serious reaction.
Definite or possible sign of bleeding are as follows;
Definite: bleeding from nose, skin (under skin), gums, hemosputa, coal tar-like stool, coffee-residue-like vomit, bloody stool and hematuria (red urine).
Sign of cerebral hemorrhage: numbness in hands and feet, slurred speech, losing consciousness and hemiplegia.
Possible sign of abdominal bleeding: nausea, vomiting, diarrhea, discomfort in the stomach and stomachache.

[allergic symptoms] dyspnea (possibility of anaphylaxis and interstitial pneumonia), fever, sore throat and severe urticaria

※ **See your doctor as soon as possible** if you have: yellow skin, any rash and urticaria

■ If you notice any sign of other possible adverse effects (side effects), please ask your doctor or a pharmacist.

Med Check TIP

Lubiprostone (Amitiza)

Too harmful and expensive for general use as a laxative

Translated from Med Check TIP (in Japanese) 2015; 15 (May:#59); 55-57.

Abstract:

Lubiprostone is the most recent laxative to be marketed in the last thirty years, but it is not superior to conventional laxatives in benefits. While the manufacturer emphasizes its specific effect on chloride channel-2 (ClC-2), lubiprostone also has prostaglandin properties. Because both prostaglandin receptors and ClC-2 are widely present in the human body, lubiprostone may cause various adverse reactions. The drug was approved at a time when its prostaglandin properties, including the effect of its active metabolite 15-hydroxyl-lubiprostone, had not been sufficiently investigated. A recent study reported that lubiprostone itself may constrict intestinal circular smooth muscle. Studies with guinea pigs found that lubiprostone increased spontaneous abortion (resorption) at doses as low as one fifth the clinical dose. The mechanism by which the drug induces abortion/resorption can be explained by its effect as a prostaglandin and ClC-2 agonist on the uterine muscle. In addition, dyspnea occurred in 2% to 3% of patients treated with lubiprostone; this is unacceptable for the treatment of constipation. Finally, the drug is very expensive. We conclude that lubiprostone is not appropriate for use as a laxative.

What is lubiprostone?

Lubiprostone is structurally similar to prostone, a bicyclic fatty acid compound derived from prostaglandin E1 (PGE1) [1]. The manufacturer of the drug states that lubiprostone opens a chloride channel-2 (ClC-2) of the small intestinal mucosa, thereby increasing fluid secretion to the lumen, softening the stool, and inducing bowel movements, thus alleviating constipation [2-4]. However, lubiprostone also acts as a prostaglandin analogue [1] (described in detail below) and ClC-2 is present in almost all body cells systemically, including the central nervous system [5]. Hence it may cause adverse reactions systemically.

Lubiprostone (trade name: Amitiza) was approved by the FDA in 2006 for the treatment of chronic idiopathic constipation (CIC) in patients aged 18 years and older [6]. Lubiprostone is now approved for the treatment of CIC and constipation associated with opioids (excluding diphenylheptane opioids such as methadone) in adults [6,7]. Lubiprostone is also indicated for constipation connected with irritable bowel syndrome in women aged 18 years and older. In 2012, lubiprostone was approved as a laxative for CIC in Japan [2]. The recommended dosage of 24 micrograms twice daily is the same as that in the USA [3].

Activation of ClC-2 and function as a prostaglandin

Lubiprostone is claimed to be a specific activator of ClC-2 in the small intestinal mucosa. The Japanese versions of the package insert and interview form for lubiprostone do not mention its prostaglandin effects [3]. The AMITIZA (lubiprostone) official website (www.amitiza.com/) does not mention these either. Only limited information is available regarding the prostaglandin-like effects of lubiprostone, in the Summary Basis of Approval (SBA) and a review of the drug by the Pharmaceuticals and Medical Devices Agency (PMDA) [2]. The SBA [2a] states:

"Effects of lubiprostone on prostaglandin receptors (EP1, EP2, EP3, and FP) were investigated using the longitudinal smooth muscle of the ileum of guinea pigs (for EP1), the circular smooth muscle of the ileum of guinea pigs (for EP2), the seminal duct of guinea pigs (for EP3), and the iris sphincter of beagle dogs (for FP). Lubiprostone was found to cause almost no activation of EP1 and FP, but exerted a weak activation effect on EP2 and EP3. Agonist activity in terms of IC50 of lubiprostone on EP2 and EP3 was less than 1/10 that of misoprostol. These results indicate that agonist activity of lubiprostone on prostaglandin receptors is weak; hence, no clinically significant pharmacological effect is likely to be induced via these receptors."

However, smooth muscle contractility was found to be 20 % in 100 nM lubiprostone compared with 70 % in 100 nM misoprostol. Furthermore, Chan et al. [1] reported that lubiprostone caused the circular smooth muscle of the mouse small intestine to contract at a concentration equal to or higher than 10 nM, and that contraction disappeared when an EP1 antagonist was administered. These results suggest that the prostaglandin-like effect of lubiprostone differs from species to species. This may be interpreted as indicating that inter-individual variation in the prostaglandin-like effect of the drug is very large in humans, making it difficult to predict whether lubiprostone will induce prostaglandin-like effects in any particular individual.

Lubiprostone induces abortion/resorption

The manufacturer notes that although lubiprostone does not induce abortion directly, it can induce fetal

death, abortion, or other fetal abnormalities. The PMDA acknowledges the applicant's explanation, but states that prostaglandin-like effects of the drug cannot be excluded as a cause of harmful influences on the embryo/fetus and reproductive function of parental animals. Therefore, lubiprostone is contraindicated in pregnant or possibly-pregnant women.

Two abortifacient studies using guinea pigs clearly showed that lubiprostone induced abortion [4]. Table 1 extracts the results relating to abortion/resorption from these studies. In Study 1, abortion occurred in 2 of 9 animals and one died microgram/kg). (See **Table 1.**) In Study 2, abortion occurred in 2 of 29 animals (7%) at the minimum dose of 1 microgram/kg (HED = 0.2 microgram/kg). There were no cases of abortion/resorption in 58 animals in the control groups of Studies 1 and 2.

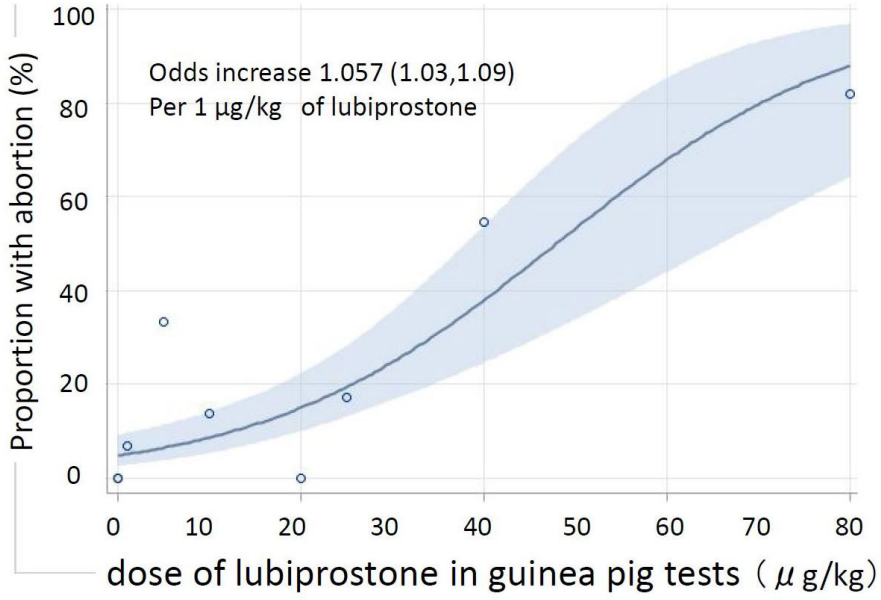
Figure shows the estimated abortion/resorption curve and 95 % confidence interval for the logistic regression analysis of the data from Studies 1 and 2. The odds increase ratio was 1.057 (95% confidence interval: 1.030 to 1.085), which indicates a 5.7 % increase in abortion per 1 microgram/kg dose of lubiprostone.

Table 1: Oral abortion study using guinea pigs (data from FDA [4])

study	dose μg/kg	N	aborted		including late resorption *a		
			n	(%)	N	events (n)	%
1st	0	11	0	0	11	0	0
	5*c	9	2	22	9	3	33
	20	10	0	0	10	0	0
	40	11	4	36	11	6	55
	80	11	6	55	11	9	82
2nd	dose μg/kg	N	aborted (main study)		aborted (main+satelite) *d		
			n	(%)	N	events (n)	%
	0*b	48	0	0	58	0	0
	1*c	24	0	0	29	2	7
	10	24	2	8	29	2	14
	25	24	5	21	29	5	17

*a： Resorption refers to abortion in animals. Late resorption refers to intrauterine death.
*b： 24 animals each were included in the "no treatment" and "only vehicle" control groups.
*c： 5 μg/kg for a guinea pig is equivalent to 1.1 μg/kg for a human (HED=1.1 μg/kg); hence this was approximately the usual daily dose (48 μg/day) for a woman weighing 45 kg. A HED of 1 μg/kg for a guinea pig is far lower than the usual daily dose.
*d： Satellite tests were conducted using 5 guinea pigs in each dose group.
Data of *a and *d were used to perform a logistic regression analysis (see results in Figure 1).

Figure : Dose-response relation between lubiprostone and abortion/resorption: logistic regression analysis and 95% confidence interval (shadow area)



*Logistic regression analysis was performed using the data from Study 1 (including late resorption, which corresponds to human intrauterine death) and Study 2 (including satellite study). The shadow area represents the 95% confidence interval.

in late resorption at the minimum dose of 5 microgram/kg lubiprostone (HED = human equivalent dose = 1.1

ClC-2 exists in uterine muscle, respiratory organs, and central nervous system

The principal activity of ClC-2 is to regulate passive movement of chloride ions. Chloride channels regulate passive movement of inorganic anions (I-, Br-, F-, and others) and organic anions (NO3-, HCO3-, glutamate, aspartic acid, and others); hence they are also called anion channels.

The manufacturer of lubiprostone claims that the drug's main effect is on ClC-2 specifically located in the intestine. However, ClC-2 exists widely in the human body, including in the central and peripheral nervous system, cardiac muscle, epithelial cells, smooth muscle, and exocrine glands. ClC-2 plays an important role in smooth muscle contraction, cardiac contraction, fluid secretion from the epithelium, and regulation of cell volume [5]. Recently, ClC-2 was found to be present in the uterine smooth muscle and it may cause contraction of the uterus [8]. Thus, it is likely that lubiprostone is a "ClC-2 activator," which means that it has pharmacological effects on the whole body.

Lubiprostone-induced abortion/resorption can be explained by the drug's action both as a prostaglandin in the form of an M3 metabolite and/or as a ClC-2 agonist on uterine muscle contraction. Either of these mechanisms can explain lubiprostone's abortifacient effect. Above all, the abortifacient effect of lubiprostone may also occur in humans.

The characteristics of lubiprostone as a prostaglandin suggest that it has properties that dilate blood vessels and affect the function of nerve cells. Due to its antiplatelet and dilatation effects as a prostaglandin, administration of lubiprostone may be harmful for patients who are already using anti-coagulants and/or antiplatelets, particularly the elderly.

Active metabolite (M3) is absorbed and exerts systemic effects

It is claimed that lubiprostone acts locally in the intestine. Although lubiprostone is not detected in the blood, its metabolite (15-hydroxy-lubiprostone: M3), which is as active as lubiprostone, appears in the blood and exerts systemic effects. The mean half-life of M3 at the standard dose of 48 micrograms was found to be 3.91 ± 4.65 hours in two women. The fact that the standard deviation was greater than the mean indicates a large variation among individuals. Moreover, the area below the curve for women was 1.5 times greater than that for men because M3 has a longer half-life in women [2a].

Clinical studies

A PubMed search using the term "lubiprostone/meta analysis"retrieved 4 articles on chronic idiopathic constipation (CIC), 2 articles on irritable bowel syndrome (IBS), and one article on opioid-induced constipation (accessed on April 16, 2015). The result of a meta-analysis of RCTs showed that the risk of failure to respond to therapy were 45.1 % and 66.9 % in the lubiprostone and placebo groups, respectively [9].

The risk ratio of failure to respond to lubiprostone was 0.67 (95 % CI: 0.56, 0.8; NNTB: 4). In a Japanese study, approximately 60% of CIC patients attained defecation within 24 hours and the number of bowel movements increased significantly after lubiprostone administration [2a].

The risk ratio (RR) for adverse events was 1.79 (95 % CI: 1.21, 2.65; NNTH: 4) according to the results of the meta-analysis [9]. In particular, the RRs for diarrhea and vomiting were 4.5 (95% CI: 1.3 to 15.5) and 7.3 (95% CI: 3.8, 14.1), respectively [9].

Regarding adverse reactions, the SBA [2a] reported that when lubiprostone was used at a dosage of 48 microgram/day for 3 to 4 weeks, nausea occurred in 24.4% to 43.8% of cases, headache in 6.7% to 12.5% of cases, dizziness in 5.0% to 9.4% of cases, and diarrhea in 4.2% to 6.7% of cases. For the placebo group, the corresponding figures were 0.0 % to 6.8%, 4.2% to 12.1%, 0.8% to 3.0%, and 0.0% to 1.6%, respectively. Adverse reactions, including laboratory test abnormalities, were reported in 62% of cases in the domestic clinical trials. Major reactions included diarrhea (30 % of cases), nausea (23 %), and dyspnea (1.6 %). The package insert for Amitiza notes that the dose should be reduced for patients with moderate to severe liver abnormality or severe kidney failure. Results of animal experiments point to the risk of fetal abnormality and tumorigenesis. In a foreign study, dyspnea was observed in 3% of patients, and some had to discontinue lubiprostone use because of repeated episodes [10].

Table 2. Meta-analysis results of RCTs of laxatives for chronic idiopathic constipation [ref 9]

laxatives	Number of studies	Number of participants	Failure to respond to therapy (%)		NNTB (95% CI)	RR (95% CI)	NNTH (95% CI)
			Active arm	Placebo arm			
Osmotic	6	676	37.6	68.9	3 (2 - 4)	0.50 (0.39 - 0.63)	--
Stimulant	2	735	42.1	78	3 (2 - 3.5)	0.54 (0.42 - 0.69)	--
total above	7	1411	40.1	73.3	3 (2 - 4)	0.52 (0.46 - 0.60)	3 (2 - 4)
Lubiprostone	3	610	45.1	66.9	4 (3 - 7)	0.67 (0.56 - 0.80)	4 (3 - 6)

*Osmotic laxatives included polyethylene glycol and lactulose; the stimulant laxative was picosulfate.
RR= risk ratio; 95% CI = 95% confidence interval
NNTB = number needed to treat for an additional beneficial outcome; NNTH = number needed to treat for an additional harmful outcome

Comparison of lubiprostone and conventional laxatives

There is no hard data with which to compare lubiprostone and conventional laxatives as no studies have compared the two drugs directly. As shown in **Table 2**, the effect of lubiprostone is similar to that of conventional laxatives. However, adverse reactions, including nausea, headache, and dyspnea, cannot be ignored. In addition, Amitiza is expensive: the standard dosage of 24 micrograms twice daily costs \322.2 per day, whereas the equivalent dosage of magnesia tablets costs only \22.4 per day.

The number of the annual users of magnesium oxide is estimated to be approximately 45 million. Fifteen cases of hypermagnesemia due to magnesium oxide use were reported between August 2008 and April 2005 [11]. Because it is excreted efficiently in urine, magnesium does not accumulate in persons with normal renal function. However, hypermagnesemia may occur in patients with renal failure.

The place of lubiprostone in CIC

Constipation is a condition experienced by many people. The majority do not need to visit a doctor. But if constipation causes discomfort, a medical examination should be performed to check for mechanical obstruction of the intestine. When findings from this examination turn out to be negative, a diagnosis of chronic idiopathic constipation is possible.

Usually, the physician will advise a patient to increase ingestion of dietary fiber—often called bulk laxatives—to increase stool bulk. If bulk laxatives are ineffective, osmotic laxatives may be prescribed, including magnesia for general use and lactulose for patients with liver damage. If these measures fail, then stimulant laxatives such as picosulfate and senna may be tried. For patients taking opioids, it is necessary to use both osmotic laxatives and stimulant laxatives.

Lubiprostone may be included in the category of osmotic laxatives, considering its mechanism of action. It is rather difficult to find a place for lubiprostone in the general approach to CIC treatment described above, because its effect is not superior to that of conventional laxatives and its price is extremely high, to say nothing of its variety of side effects. When all conventional laxatives fail to treat CIC successfully, lubiprostone treatment may be considered for carefully-selected patients, with the exception of women of childbearing age. However, it cannot be recommended for general treatment of CIC.

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Plain Language summary

Lubiprostone: a new product for constipation

Harmful and expensive for general use

It is hard to objectively define “constipation”, because the bowel habits are highly individual. However, it could be called “constipation”, when one has discomfort because of the following conditions: difficulty in passing stools, infrequent stools, and/or small, hard stools. Persons with constipation might also feel the urge to pass stools, but they do not come out.

Normal frequency of bowel movement varies among individuals. It ranges from 3 times a day to around 2 to 3 times a week. When one’s stool is smooth and does not accompany discomfort, it is not constipation even if the frequency of bowel movement is less than once a day. However, it may be often accompanied by some kind of inconvenience and discomfort if one does not have a bowel movement for 3 to 4 days.

While various causes lead to constipation, it is mostly resolved by correcting one’s lifestyle. However, in some cases, other factors may be more the important.

The stomach and intestines are the pipes that always move and send off their contents. Constipation may occur if the contents of the bowels lose much water and become hardened; the bowel movement is extremely decreased; or the intestines are mechanically blocked.

Constipation may also occur if the bowel movements are suppressed by something inside or outside the intestine (e.g., by a cancer), or they are stopped by medicines. The medicines that easily cause constipation include tranquilizers, sleeping pills, antidepressants, calcium antagonists (a drug to lower high blood pressure), painkillers of the stomach and antihistamine in cold remedies or allergic diseases. An anti-diabetic medicine, alpha-glucosidase inhibitors, soften stools, and excessive softening may cause paradoxical constipation. Some changes in life or lifestyle that cause mental strain may induce constipation. Some diseases that impairs oxygen intake, such as advanced emphysema, a chronic severe lung disease, may worsen movement of the bowels and induce constipation.

For the prevention of constipation, the following are important in lifestyle: one should take meals with enough fiber and enough water, avoid enduring defecation desire, and have moderate physical activities. The movement of the bowels becomes most active particularly 10 to 30 minutes after breakfast, which may be the best time to defecate. It is important to habituate bowel movement every day in this time.

If you fail to improve constipation by removing medicines that might caused your constipation and by practicing other preventive measures above, your physician will check for mechanical obstruction of the intestine. When findings from this examination turn out to be negative, the physician may diagnose that you have chronic constipation.

Usually, your physician will advise you to increase ingestion of dietary fiber to increase stool bulk or prescribe a medicine called “bulk laxatives” such as carmellose or Plantago asiatica as an alternative to taking fiber from food.

If bulk laxatives are ineffective, osmotic laxatives, which increase water inside the intestine, may be prescribed, including magnesia for general use, and lactulose for patients with liver damage. If these measures fail, then stimulant laxatives, such as picosulfate and senna, may be tried. For patients taking opioids, it is necessary to use both osmotic laxatives and stimulant laxatives.

Lubiprostone is a very new medicine launched in Japan in 2013. It increases water inside the intestine and may be categorized as an osmotic laxative.

Lubiprostone also seems to have an action as a class of “prostaglandin”, which activates movement of the intestine and uterus. Hence, it may induce abortion if a pregnant woman takes it. It may cause difficulty in breathing in 2 to 4 percent of the persons who take it.

Lubiprostone treatment may be considered for carefully-selected patients, with the exception of women of childbearing age, if all other laxatives failed.

However, it is difficult to find a place for lubiprostone in the general approach to treatment of chronic constipation because it is not superior in efficacy and safety compared with conventional laxatives, and its price is extremely high.

Propofol-induced death in children: at a Univ. Hospital

Contraindicated for mitochondrial toxicity, withdrawal malignant syndrome suspected

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Abstract:

An analytical report on a case of the death of a child involving administration of the contraindicated drug "propofol" was published. The report concluded that "propofol infusion syndrome" was the direct cause of death. It also reported that the contraindicated drug was used at high doses over a long period. As for the underlying cause of this death, the report pointed out that the physicians and pharmacists involved lacked understanding of the characteristics and potential harmful effects of the drug.

In propofol infusion syndrome, continuous administration of the drug for at least 48 hours at high doses rapidly induces cardiac muscle injury that is accompanied by severe metabolic acidosis, rhabdomyolysis, and renal failure, leading to death. Propofol is a mitochondrial toxin. It is used as an ultra-short-acting $GABA_A$ agonist for anesthesia. After administration is discontinued, malignant syndrome may occur because of withdrawal muscle rigidity.

The physicians did not recognize the risk of withdrawal reactions, and the package insert does not mention this risk, which appears to be due to the characteristics of the drug as a mitochondrial toxin and a $GABA_A$ agonist with very rapid elimination half-life. The contents of the package insert for propofol should be revised to include warning of these potential harmful effects.

Introduction

At Tokyo Women's Medical University Hospital, during a five-year period up to 2013, 63 children were administered propofol, a drug that is contraindicated for use with children. 12 of the 63 children died [1a]. One of these was a 2-year-old boy who died in February 2014 due to an overdose of propofol [1b,1c]. The Tokyo Women's Medical University Hospital Third-party Accident Investigation Committee investigated the death of this child and published a report which concluded that the direct cause of the death was propofol infusion syndrome, and not pneumonia [1b].

The report stated that "no purposive medical justification" could be found for administering propofol, a drug that is contraindicated for use with children, at high doses over a long period. The report concluded that this case represented "a lack of understanding of contraindicated medications." The report also highlighted various other issues, including the decision by the central ICU team of physicians in charge of postoperative management to administer propofol to the child, the need for a monitoring system for adverse reactions, lack of appropriate referencing by pharmacists, and poor coordination between the attending physician and ICU physicians.

The investigation focused on the death of the child, whose age was 2 years and 10 months. Propofol was infused for 70 hours. An earlier investigation of the other 11 propofol-related deaths found that the maximum doses administered exceeded 4 mg/kg/h in all cases and 10 mg/kg/h in 5 cases; the usual adult dosage is 0.3-3 mg/kg/h [1].

Propofol is a mitochondrial toxin [2-5]. It has an anesthetic effect as a $GABA_A$ agonist [6-9], and its half-life is extremely short [10]. If the physicians and pharmacists involved in the case described above had known these characteristics, they might not have used the drug. Their lack of knowledge was the fundamental cause of the fatality. This article examines characteristics of propofol that are not mentioned in the report or in the package insert for the drug.

Overview: The course of death and investigation of the cause

The following is a direct quote from the Investigation Committee report [1b].

"Propofol was administered in a 2-year, 10-month old child over a long period: 70 hours and 15 minutes. The total dose administered was 6953.5 mg. (The average dosing rate over the administration period was 8.1 mg/ kg/h, which is 2.7 times higher than the maximum rate recommended for sedation of artificially ventilated adults.) This dosage rate is much higher than the maximum rate of 4 mg/kg/h over 48 hours that has been demonstrated to be safe for infants, according to the literature.

After propofol was discontinued, high fever, increased

CK level, metabolic acidosis, and hyperkalemia were observed, and rhabdomyolysis developed. Regarding the severity of rhabdomyolysis, CK level was 10,036 U/L at resuscitation, and postmortem examination found that the lesion of rhabdomyolysis was not extensive, but only regional.

Therefore, rhabdomyolysis alone could not have been the cause of death. This case followed a unique course: sudden cardiac arrest occurred and marked lactic acidosis developed, followed by hyperkalemia, arrhythmia, and circulatory failure. This led to unsuccessful cardiopulmonary resuscitation and death.

Moreover, since day 2 of the initial dosing, negative T waves had been observed. On day 4, not only negative T waves but also low voltage, a prolonged QRS interval, and ventricular tachycardia were observed, suggesting the possibility of progressive cardiomyopathy. Evidence of cardiomyopathy was not found at autopsy.

However, circulatory failure, which developed suddenly after a short time, was refractory to cardiopulmonary resuscitation, and life support was unsuccessful. Considering this course, it is highly likely that prolonged administration of propofol was directly related to the cause of death. Because the symptoms of rhabdomyolysis, high CK level, arrhythmia, heart failure, and lactic acidosis were observed, it is reasonable to conclude that propofol infusion syndrome was the direct cause of death."

Propofol infusion syndrome and mitochondrial toxin

Propofol was already suspected to be a mitochondrial toxin in 1993 [11].

Two patients with mitochondrial myopathy were administered an anesthetic that contained propofol, and experienced bradycardia (< 50/min). The patients received atropine, administration of propofol was discontinued, and both recovered.

Subsequent studies have identified the direct inhibitory effect of propofol on energy production in the mitochondria as an intracellular mechanism in which propofol infusion syndrome occurs [2-5].

Propofol acts as a mitochondrial toxin by impairing free fatty acid utilization [3,4], reducing cytochrome C oxidase, and impairing coenzyme Q [5] in the mitochondria. The heart is continuously at work and consumes a large amount of energy. It is therefore susceptible to the effect of a mitochondrial toxin, such as propofol, and bradycardia and heart failure are easily induced.

In another case, a preterm baby (580 g) began propofol treatment at an initial dose of 8 mg/kg/h. When the patient's weight reached 1380 g, the dose was increased to 60-80 mg/kg/h infused over 2 hours. After 1 hour, bradycardia (< 100/min), lowered blood pressure (mean arterial blood pressure < 33 mm Hg), and lowered oxygen saturation (85-93%) were observed. Propofol was discontinued after 2 hours, and the patient's condition gradually improved [12]. This case shows that if a higher dose of propofol is infused even for 1 hour in patients, such as premature babies and infants, who have small reserves of glycogen and need to use fatty acid as their source of energy, propofol infusion syndrome may be induced. Concomitant use of catecholamines and/or steroids is also a risk factor [3].

Ultra-short-acting $GABA_A$ agonist: The possibility of withdrawal malignant syndrome

Propofol is a $GABA_A$ agonist [6-9, 13, 14], and its elimination half-life is extremely short.

According to the package insert of diprivan Injection "When single bolus doses of propofol 1.0, 2.0, and 2.5 mg/kg were intravenously administered in 6 healthy Japanese adult males, pharmacokinetics of propofol fit a 3-compartment model, and all blood concentrations decreased in 3 phases. The half-lives of each phase were 2.6 minutes (α -phase), 51.0 minutes (β -phase), and 365 minutes (γ -phase)."

Both the α - and β -phases were shorter than 1 hour, and the γ -phase was as short as 6 hours. Elimination half-lives of triazolam and zolpidem, which are regarded as ultra-short-acting hypnotics, are 2.9 hours and 1.8-2.3 hours respectively, and the half-life of a short-acting hypnotic brotizolam is about 7 hours. Even the γ -phase of the half-life of propofol is shorter than the half-life of brotizolam.

Short-acting benzodiazepines may induce withdrawal catatonia - malignant syndrome. A patient discontinued triazolam and brotizolam for 1 night because he was going to have a blood sample taken for a medical check-up. At about 10 a.m. on the following day, the patient experienced generalized rigidity, and developed catatonia - malignant syndrome with increased CK level [15].

It should be understood that ultra-short-acting propofol may develop dependency in an extremely short time, and may cause malignant syndrome with withdrawal muscle rigidity and fever.

In fact, it has been reported that when propofol was administered for the treatment of typical generalized tonic-clonic status epilepticus, withdrawal convulsions occurred as quickly as after 1-2 days [9]. A 41-year-old woman received propofol for the treatment of status epilepticus, and the condition was well controlled. On the following day, propofol was discontinued, and convulsions recurred after 10 minutes. Because persistent high-frequency coarse rhythmic shaking was observed, the patient was diagnosed with status epilepticus, propofol treatment was resumed, and convulsions subsided. A second trial of propofol withdrawal was performed with an epileptologist at the patient's bedside. Similar convulsive motor activity occurred again, about five minutes after discontinuation of propofol treatment, but the concomitant electroencephalograph (EEG) showed muscle artefact to be without any ictal activity. Propofol treatment was not restarted and the patient was sedated with fentanyl. Based on these findings, the convulsions were considered to have been caused by propofol withdrawal.

In the fatal case of the child in Tokyo Women's Medical University Hospital, although the temporality remains unclear, the report concluded: "After propofol was

discontinued, high fever, increased CK level, metabolic acidosis, and hyperkalemia were observed, and rhabdomyolysis developed." These findings strongly suggest that dependency on propofol developed rapidly, leading to malignant-syndrome-like pathology, including increased CK level and fever caused by withdrawal muscle rigidity.

Proposal

Propofol is a mitochondrial toxin. Its toxicity may appear early in patients with severe conditions who have small glycogen reserves or in patients who are fasting. It is an ultra-short-acting $GABA_A$ antagonist, and may cause withdrawal convulsions or withdrawal catatonia-malignant syndrome that can lead to rhabdomyolysis.

Warnings of these potential harmful effects should be clearly stated in the package insert for propofol.

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Plain Language summary

Anesthetic-induced deaths in children: at a Univ. Hospital

Contraindicated due to heart toxicity
Abstinence syndrome may be suspected

At Tokyo Women's Medical University Hospital, during a five-year period up to 2013, 63 children were administered propofol, an anesthetic drug that is contraindicated for use with children. Of the 63 children 12 died. The third-party to the university hospital published a report focusing on the death of the child, whose age was 2 years and 10 months.

The report concluded from the medical aspects that the direct cause of the death was "propofol infusion syndrome", a sort of toxic syndrome due to the drug. The report stated that "no purposive medical justification" could be found for administering propofol, a drug that is contraindicated for use with children, at high doses over a long period.

The report also concluded from the aspects of the system, that this case represented "a lack of understanding of contraindicated medications" in the medical professionals including attending physicians, central ICU team of physicians, pharmacist. Their poor coordination was also highlighted.

Propofol is a very toxic substance that impairs mitochondria, an indispensable apparatus for respiration and oxygen utilization within a cell. It is especially toxic to heart muscle in infants whose nutritional reserve is scarce because heart muscle usually consumes oxygen to move continuously and requires high energy. The toxicity to mitochondria could induce patient death.

Propofol also acts like an extremely-short-acting sleeping pill, far shorter than a typical short-acting sleeping pills such as triazolam (brand name: Halcion etc.) or zolpidem (brand name: Ambien etc.) or alcohol. Propofol could induce abstinence seizures if it is stopped abruptly, just like after stopping short acting sleeping pills or alcohol. Propofol could induce abstinence seizures/muscle contraction far earlier than the short-acting sleeping pill or alcohol. There is a report that abstinence seizures occurred following discontinuation of the drug after the use for one day. Abstinence seizures or continuous muscle contracture may cause fever or muscle destruction followed by pneumonia, kidney damage and death.

Physicians and pharmacists are not familiar with these facts that propofol is toxic to mitochondria and that abstinence seizure could induce death, because the package insert of propofol for professionals does not describe them.

Warnings of these potentially harmful effects should be clearly stated in the package insert for propofol to prevent use in children.

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