Effects of Tramadol on the International Normalized Ratio of Outpatients Receiving Warfarin: A Prospective Cohort study

นิพนธ์ต้นฉบับ

Original Article

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วารสารไทยเภสัชศาสตร์และวิทยาการสุขภาพ 2560;12(3):133-137.

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Thai Pharmaceutical and Health Science Journal 2017;12(3):133-137.

บทคัดย่อ

วัตถุประสงค์: เพื่อตรวจสอบผลของการใช้ทรามาดอลร่วมกับวาร์ฟารินต่อระดับ INR **วิธีการศึกษา:** การศึกษานี้เป็นแบบ prospective cohort ในผู้ป่วยนอกของโรงพยาบาลกบินทร์บุรี จังหวัดปราจีนบุรี ระหว่างเดือนเมษายน - ตุลาคม พ.ศ. 2558 มีผู้ป่วยเข้าร่วมการวิจัยทั้งหมด 206 ราย ซึ่งจำแนกเป็น 2 กลุ่มได้แก่ กลุ่มที่ไม่ได้ทรามาดอลร่วมกับวาร์ฟาริน 103 ราย และกลุ่มที่ได้รับทรามาดอลร่วมกับวาร์ฟาริน 103 ราย เก็บข้อมูลผู้ป่วยจากระบบคอมพิวเตอร์ของโรงพยาบาลและการสัมภาษณ์ ติดตามการเปลี่ยนแปลงระดับ INR ของผู้ป่วยก่อนและหลังเข้าร่วมการศึกษา มีการวิเคราะห์ความแตกต่างระหว่างกลุ่มผู้ป่วยด้วยสถิติ *t*-test และ chi-square test และแสดงผลค่าความเสี่ยงสัมพัทธ์ (relative risk, RR) **ผลการศึกษา:** เมื่อสิ้นสุดการศึกษาพบว่า ผู้ป่วยในกลุ่มที่ได้รับวาร์ฟารินร่วมกับทรามาดอลมี INR ออกนอกช่วงเป้าหมายมากกว่ากลุ่มที่กลุ่มที่ได้รับวาร์ฟารินอย่างเดียวอย่างมีนัยสำคัญทางสถิติ (47.57% vs. 26.21%; $P < 0.001$) โดยมีความเสี่ยงของ INR ออกนอกช่วงเป้าหมายเป็น 1.61 เท่า (RR = 1.61, 95% CI = 1.16 – 2.22) ไม่พบการเกิดเหตุการณ์ไม่พึงประสงค์จากการใช้วาร์ฟารินในผู้ป่วยทั้งสองกลุ่ม **สรุป:** การใช้ทรามาดอลร่วมกับวาร์ฟารินอาจทำให้ระดับ INR ออกนอกช่วงการรักษาได้ หากจำเป็นต้องใช้ยานี้ร่วมกับวาร์ฟารินควรมีการติดตามระดับ INR ของผู้ป่วยอย่างใกล้ชิด

คำสำคัญ: ทรามาดอล, วาร์ฟาริน, ปฏิกิริยาระหว่างยา, ไอเอ็นอาร์

Abstract

Objective: To examine the effects of tramadol concomitantly used with warfarin on the international normalized ratio (INR) levels. **Method:** This prospective cohort study was conducted in the outpatients who visited Kabinburi Hospital in Prachinburi Province from April to October 2015. Of 206 patients, they were classified into two groups, i.e. 103 patients who did not receive tramadol with warfarin and 103 patients who received both drugs. Patients' data were collected from the hospital's online medical records and interviews. The INR levels of patients were monitored before and after they participated in the study. The differences between the two groups were analyzed using the *t*-test and chi-square test. Moreover, a relative risk (RR) was presented. **Results:** At the end of the study, patients receiving both drugs had the INRs out of the target range more than those receiving no tramadol (47.57% vs. 26.21%; $P < 0.001$). The patients receiving both drugs were 1.61 times more likely to experience the INRs out of the target (RR = 1.61; 95% CI: 1.16 – 2.22). No warfarin-associated adverse events were found in either group. **Conclusion:** The combination use of tramadol and warfarin could cause the out-of-target INR levels. If tramadol is needed, their INR levels should be closely monitored.

Keywords: tramadol, warfarin, drug-drug interaction, INR

Introduction

It is widely known that oral anticoagulants are the primary drugs used in the treatment and prevention of thromboembolism, specifically for outpatients who are diagnosed with atrial fibrillation/flutter or venous thrombo-embolism. One of the most common anticoagulants is warfarin, which can be effectively absorbed into the body.[1] However, it has a narrow therapeutic index and is therefore regarded as a high alert drug. The dosage of warfarin depends on the clinical results of each patient due to the variation in drug response. Nonetheless, it is possible to anticipate the dosage of warfarin given to each patient by monitoring the laboratory test results in accordance with the criteria stipulated by the World Health Organization. For instance, the international normalized ratio (INR), which is calculated by comparing the patient's prothrombin time with the standard prothrombin time of a regular individual.[2]

The expected outcome of warfarin is anticoagulation with the maintenance of the patient's INR level to be in the therapeutic range. If the INR level of the patient falls under the therapeutic range, the patient will have an increased risk of thrombosis. On the other hand, if the INR level of the patient is higher than the therapeutic range, the patient will have a risk of hemorrhagic complication.[3] In addition, drug-drug interactions are regarded as an important factor that has a significant clinical effect on the action of warfarin, such as pharmacodynamic interactions and pharmacokinetic interactions in the process of absorption, distribution, or metabolism that cause changes in the level of warfarin.

Tramadol is classified as a weak opioid and is used to relieve moderate to severe pain. Tramadol is metabolized by cytochromes P450 (CYP) that comprise of CYP2D6 and CYP3A4, as well as by conjugation reactions, N- and O-

demethylation, glucuronidation, and sulfation.[4] As for warfarin, it is metabolized by CYP2C9 (primary metabolism), CYP2C19, CYP2C8, CYP2C18, CYP1A2, and CYP3A4. According to the literature review, many case reports[5-8] found that tramadol caused a significant increase in the INR levels of patients, which is consistent with the nested case control study of Pottegård et al.[9] In addition, the study also found that patients who received tramadol had a higher risk of an increase in INR level than those who did not receive tramadol by 3.1 times (odds ratio = 3.1, 95% CI = 1.9 - 5.2). Nonetheless, the study had some limitations in the aspect of other factors that could affect INR levels such as over consumption of green-leafy vegetables, consumption of nutritional supplements, and concomitant drug use. Moreover, concerning the fact that it was a retrospective study, there could be a selection bias. The mechanism pertaining to the reaction between tramadol and warfarin was not clearly known. Therefore in patients with CYP2D6 polymorphism, metabolism of warfarin with the interaction with tramadol is even harder to predict.[4,5,9]

To examine clinical outcomes as a result of the interaction between tramadol and warfarin in Thai patients, the researchers conducted a prospective cohort study in order to control various factors that could affect INR levels and to determine the reaction time between such two drugs by taking into consideration the changes in the level of INR before and after using tramadol. Specifically the research objective was to examine the relationship between the use of tramadol and the changes in the INR level of patients who were treated with warfarin. We hypothesized that patients who received tramadol in conjunction with warfarin will have INR levels outside the 2 - 3 range more than those who received warfarin with no tramadol.

Methods

This research was a prospective cohort study in order to control other factors that could affect INR levels and to determine the reaction time between the two aforementioned drugs by taking into consideration the changes in the level of INR before and after using tramadol. The study examined outpatients of Kabinburi Hospital in Prachinburi province who were treated with warfarin between April 21, 2015 and October 31, 2015. The selected patients had to be above 20 years of age with the ability to read, write, and communicate. Moreover, the patients had to receive warfarin consecutively for at least 30 days. The INR levels of patients had to be within the 2 - 3 range after having been monitored for at least 3 times before participating in the study. Such criterion was necessary since it had been reported that tramadol can affect the action of warfarin on the first day of co-administration.[5-8] Likewise, such criterion also enabled the effects of tramadol on the changes of INR levels to be monitored more clearly. The INRs of the participating patients were prospectively taken at day 1 and day 7 of the study.

The sample size was calculated using EpiTools software from AusVet Animal Health Services, with the confidence interval of 95% and the statistical power of 80%. The sample comprised of 206 patients, which was divided into 2 groups, the unexposed and exposed groups, of 103 patients each. The unexposed group consisted of patients who solely received warfarin, while the exposed group included patients who received warfarin concomitantly with tramadol.

The data were collected from the medical records of patients on the first day of the study. The patients were monitored for another 7 days after which the patients would meet with their corresponding physicians in order to examine the level of INR. After that, the researcher would conduct an interview with the patients. Information collected through the interview included general information, history of the intake of food, food supplements, herbs or other medications, historical levels of INR, current medications, history of taking tramadol, compliance to the treatment, and other factors. Patients with factors that could potentially affect the INR were excluded. These factors included obvious herb consumptions, over consumption of green-leafy vegetables, consumption of nutritional supplements, and concomitant drug use. In addition, patients taking warfarin of less than 80% of the prescribed dose based on pill count method were also excluded.

The obtained data were analyzed using a software package, namely SPSS Version 16. The statistical significance was determined based on the *P*-value of 0.05. Moreover, descriptive statistics including frequency, percentage, mean, and standard deviation were used simultaneously with inferential statistics. The t-test for independent samples (two-sample t-test) was used in the event of normal distribution. Alternatively, if the data were not normally distributed, the Mann-Whitney U-test would be

used. In addition, differences in the variables were tested at a ratio scale between the two groups of patients. Meanwhile, chi-square test was used to determine the differences between countable variables or between categorical variables. The results were presented as a relative risk (RR) between the exposed group and the non-exposed group.

This study was approved by the Ethic Committee of Naresuan University on April 20, 2015 (IRB No. 041/58).

Results

General information of participating patients

Of 257 patients contacted for study participants, 10 were excluded because of loss of follow-up, while 4, 7, 9, 12, and 9 patients were excluded because of the overconsumption of green-leafy vegetables, consumption of nutritional supplements, consumption of herb, concomitant drugs, and underuse of warfarin (less than 80% of prescribed dose). As a result, a sample of 206 patients were achieved and analyzed accordingly. No adverse events associated with warfarin were found.

Across the sample of 206 patients, there were roughly equal proportions of male (49.02%) and female (50.98%) patients (Table 1). Patients who received warfarin had the mean age of 67.5 ± 14.2 years, while those receiving both warfarin and tramadol had the mean age of 68.4 ± 12.6 years. In the aspect of comorbidity, there were 77 patients (37.38%) with hypertension, 39 (18.93%) with hyperlipidemia, 24 (11.65%) with diabetes mellitus, 11 (5.34%) with heart failure, and 59 (28.64%) with other diseases. The participating patients had been treated with warfarin for an average of 2.8 ± 2.1 years. In addition, indications for warfarin consisted of atrial fibrillation, heart valve disease, deep vein thrombosis, pulmonary embolism, and other conditions, which accounted for 119 (59.21%), 29 (14.08%), 22 (10.68%), 15 (7.28%), and 25 (12.14%) patients, respectively (Table 1).

Average INR levels

This research monitored the INR level of each patient for a total of 4 times. Upon the completion of the research, the unexposed group had the average INR level of 2.60 ± 0.45 which was lower than that in the exposed group (3.10 ± 0.83), with a statistical significance (*P*-value < 0.001) (Table 2).

Table 1 General characteristics of the patients (N = 206).

Characteristics	N (%) by groups		*P*-value
	Unexposed Group (N = 103)	Exposed Group (N = 103)	
Gender*			0.6777
- Male	52 (50.49)	49 (47.57)	
- Female	51 (49.51)	54 (52.43)	
Age (year)#	67.5 ± 14.2	68.4 ± 12.6	0.6264
History of allergies*			0.2435
- Yes	8 (7.77)	12 (11.65)	
- No	95 (02.23)	91 (88.35)	
Chronic diseases*			
- Hypertension	36 (33.64)	41 (39.81)	0.2020
- Hyperlipidemia	18 (16.82)	21 (20.39)	0.4365
- Diabetes Mellitus	10 (9.35)	14 (13.59)	0.3124
- Heart failure	8 (7.48)	3 (2.91)	0.2698
- Others	35 (32.71)	24 (23.30)	0.0912
Average number of years of warfarin use#	2.7 ± 1.9	2.9 ± 2.3	0.4693
Warfarin indications*			
- Atrial fibrillation	58 (54.72)	61 (58.65)	0.3424
- Heart valve disease	18 (16.98)	11 (10.58)	0.2260
- Deep vein thrombosis	13 (12.26)	9 (8.65)	0.2978
- Pulmonary embolism	7 (6.60)	8 (7.70)	0.6514
- Others	10 (9.43)	15 (14.42)	0.1421

* chi-square test for categorical data for statistical analysis
# two-sample t-test continuous data for statistical analysis

Table 2 Changes in the INR levels (N = 206).

Time of INR monitoring	Average level of INR		*P*-Value*
	Unexposed group (N = 103)	Exposed group (N = 103)	
Historical value (1st time)	2.51 ± 0.32	2.54 ± 0.36	0.10
Historical value (2nd time)	2.43 ± 0.30	2.42 ± 0.31	0.79
Prior to the study (Day 1)	2.50 ± 0.42	2.50 ± 0.48	0.74
After the study (Day 7)	2.60 ± 0.45	3.10 ± 0.83	< 0.001

* Two-sample t-test was used in the statistical analysis

INR out of target range

At the end of the study, 49 of 103 patients in the exposed group had their INR out of the target range (47.57%). As expected, only 27 of 103 patients in the unexposed group (26.21%) experienced an out-of-range INR. This difference was found statistically significant (*P*-value = 0.002). In terms of relative risk, patients using warfarin and tramadol was 1.61 times more likely to have the INR out of target compared with those receiving warfarin only (RR = 1.61, 95% CI = 1.16 – 2.22).

Table 3 Relative risk of out-of-range INR among patients receiving warfarin plus compared with those receiving warfarin (N = 206).

Groups	INR out of 2 – 3 range, N (%)	
	Yes	No
Exposed group	49 (47.57%)	54 (52.43%)
Unexposed group	27 (26.21%)	76 (73.79%)

RR = 1.61, 95% CI = 1.16 – 2.22, P-value = 0.002.

Tramadol doses that may cause INR level out of the 2 – 3 range

It was found that the average dose of tramadol among patients that had INR level outside the 2 - 3 range was 355.0 ± 20.0 mg/week. On the contrary, among those patients with INR within the 2 – 3 range, their average dose of warfarin was 205.0 ± 11.5 mg/week. The difference between the aforementioned doses of tramadol was statistically significant (*P*-value < 0.001).

Discussions and Conclusion

Our study found that the use of tramadol in conjunction with warfarin caused the level of INR to be out of range. Patients who received warfarin with tramadol had 1.61 times higher chance of having out-of-range INR levels than patients who did not take tramadol (RR = 1.61, 95% CI = 1.16 – 2.22). Such difference was statistically significant at a *P*-value of 0.002. Our finding was in accordance with the research conducted by Anton Pottegård et al. in 2014.[10] They conducted a descriptive research in 513 patients who were able to control their INR levels. The results indicated that the use of tramadol concomitantly with tramadol caused the level of INR to increase by more than 4 times and up to 1.80 incidents per person per year at the 95% confidence interval of 1.53 – 2.10.

Since the interaction between tramadol and warfarin has not yet been clearly identified, the recommendation to manage the administrations of the two drugs has not been issued. Therefore we recommended the weekly dose of tramadol to be no more than 350 milligrams in the event that it is necessary for patients to receive tramadol concomitantly with warfarin. We also suggest that it is significant to closely observe the side effects of warfarin. In case of abnormal symptoms, the patients should visit the doctor immediately.

The limitations of this research encompassed the fact that patients also received concomitant medications other than tramadol. This could confound the results. Moreover, concerning the lack of clarity on the reaction between tramadol and warfarin, it was uncertain whether tramadol actually caused the changes in the INR level of patients who were treated with warfarin. Accordingly, it is significant to study the mechanism pertaining to the reaction between tramadol and warfarin in future researches.

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Editorial note
Manuscript received in original form on April 22, 2017;
accepted in final form on June 13, 2017