สาเหตุและการจัดการปัญหาของการเกิดพิษจากการใช้ยาวาร์ฟาริน ณ โรงพยาบาลป่าซาง จังหวัดลำพูน ประเทศไทย

ปรีชญา ตาใจ[1*] อภิรุจี อินตาวงศ์[2] ธีธัช ใบเนียม[2] ยุพิน นำปูนศักดิ์[3] อาทิตย์ จันทร์ตา[3]

[1] คณะเภสัชศาสตร์ มหาวิทยาลัยพายัพ จังหวัดเชียงใหม่ 50000

[2] คณะเภสัชศาสตร์ มหาวิทยาลัยพายัพ จังหวัดเชียงใหม่ 50000

[3] ฝ่ายเภสัชกรรม โรงพยาบาลป่าซาง จังหวัดลำพูน 51120

บทคัดย่อ

การศึกษานี้มีวัตถุประสงค์เพื่อรวบรวมสาเหตุและการจัดการกับปัญหาที่เกิดจากพิษของยาวาร์ฟาริน ในผู้ป่วยนอกที่รับการรักษา ณ คลินิกวาร์ฟาริน โรงพยาบาลป่าซาง จังหวัดลำพูน ประเทศไทย เป็นการศึกษาเชิงพรรณนาแบบย้อนหลังในผู้ป่วยที่มีค่า International Normalized Ratio (INR) >3.0 และ 3.5 ในผู้ป่วยที่ได้รับการเปลี่ยนลิ้นหัวใจเทียมชนิดโลหะ ระหว่างวันที่ 1 มกราคม ถึง 31 ธันวาคม 2561 ผู้ป่วย 138 คน เข้ารับการรักษาจำนวน 267 ครั้ง พบความชุกของการเกิดพิษจากยาวาร์ฟารินร้อยละ 18.6 (267/1,434) หาสาเหตุได้ถึงร้อยละ 96.3 (257/267) สาเหตุที่พบบ่อยที่สุด คือ ภาวะหรือโรคที่เหนี่ยวนำทำให้เกิดพิษจากยาวาร์ฟาริน ร้อยละ 57.1 (237/415) และการเกิดอันตรกิริยาจากการใช้ยาอื่นร่วมกับยาวาร์ฟาริน ร้อยละ 36.6 (152/415) พบผู้ป่วยเกิดภาวะเลือดออกชนิดรุนแรงร้อยละ 3.7 (10/267) และการจัดการกับการเกิดพิษจากยาวาร์ฟารินขึ้นกับระดับ INR และความรุนแรงของการเกิดภาวะเลือดออก พบว่าแพทย์ให้การรักษาการเกิดพิษจากยาวาร์ฟารินตามคำแนะนำจากหลายการศึกษา มากถึงเกือบ 100% (266/267) และพบว่าระดับ INR กลับเข้าสู่ช่วงของการรักษาในผู้ป่วยทุกคน (100%, 267/267) การเกิดพิษจากยาวาร์ฟารินพบได้บ่อย และควรได้รับการดูแลโดยสหสาขาวิชาชีพเพื่อป้องกันการเกิดพิษจากยาวาร์ฟารินอย่างมีประสิทธิภาพ

คำสำคัญ: ยาต้านการแข็งตัวของเลือด วาร์ฟาริน การเกิดพิษ ภาวะเลือดออก การรักษา

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[*] **ผู้รับผิดชอบบทความ**

ปรีชญา ตาใจ

คณะเภสัชศาสตร์ มหาวิทยาลัยพายัพ จังหวัดเชียงใหม่ 50000

Email: tapreechaya@gmail.com

Warfarin Toxicity: Causes and Management in Pasang Hospital, Lamphun Province, Thailand

Preechaya Tajai[1*] Aphirujee Intawong[2] Teetat Bainiam[2] Yupin Nampoonsak[3] Atit chanta[3]

[1] Faculty of Pharmacy Payap University Chiang Mai 50000, Thailand.

[2] Faculty of Pharmacy Payap University Chiang Mai 50000, Thailand.

[3] Pharmacy department, Pasang hospital, Lamphun 51120, Thailand.

Abstract

This study aims to determine the causes and management of warfarin toxicity in outpatients who visited an anticoagulation clinic at Pasang Hospital, Lamphun, Thailand. This is a retrospective review of all outpatients who visited the anticoagulation clinic at Pasang Hospital between 1 January to 31 December 2018 with an international normalized ratio (INR) >3.0 and 3.5 in patients who have undergone mechanical mitral valve replacement. During the study period, 267 increased INR measurements (138 patients) met the inclusion criteria for warfarin toxicity. The prevalence of warfarin toxicity was 18.6% (267/1,434). The causes of warfarin toxicity were identified and addressed in 96.3% (257/267) of patients. Where the causes were identified, 57.1% (237/415) were due to drug-disease interaction and unstable underlying disease, and 36.6% (152/415) were due to drug-drug interaction. Major bleeding occurred in 3.7% (10/267) of patients. The management of patients who presented with warfarin toxicity depended on the degree of INR elevation and the severity of bleeding. Physicians' adherence to the recommendations from published literatures was almost 100% (266/267) of patients. The INR value decreased in all patients (100%, 267/267) after the intervention given. In conclusion, warfarin toxicity is quite common and is best managed by a multidisciplinary team in order to prevent warfarin toxicity effectively.

Keywords: Anticoagulant, Warfarin, Toxicity, Bleeding, Treatment

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[*] Corresponding author

Preechaya Tajai

Faculty of Pharmacy Payap University Chiang Mai 50000, Thailand

Email: tapreechaya@gmail.com

Introduction

Warfarin is a widely used oral anticoagulant indicated for the prevention and treatment of pulmonary embolism, venous thrombosis, myocardial infarction, and atrial fibrillation[1, 2]. Warfarin therapy is challenging because it has a narrow therapeutic window[1]. The data which was collected by the pharmacists showed that the therapeutic international normalised ratio (INR) outcome was achieved in only 52.65% of patients who visited Pasang Hospital, Lamphun, Thailand (unpublished data). Moreover, various factors have been reported to affect the response to warfarin therapy such as old age, disease states, poor adherence, and drug-drug interaction[3, 4]. Warfarin therapy requires close monitoring due to complications, especially clotting and bleeding[5].

Bleeding complications with a high INR is associated with an excess mortality especially in patients with an INR of ⩾3.0[6-8]. The increased risk of death was significant in patients who reached INR levels of >3.0 after an increase in anticoagulant dose. The expected number of deaths associated with an increased INR were at least 500 in the study[6]. Several literatures supported a direct relationship between increased INR and risk of bleeding[9, 10]. Risk factors in developing warfarin toxicity are dosing errors, drug-drug interactions, acute illnesses (diarrhea, cardiac failure, hepatic impairment, fever) and dietary changes influencing vitamin K intake[1, 11, 12]. Some studies indicated diarrhea as the factor associated with an increased response to warfarin by decreasing the absorption of dietary vitamin K[12]. Cardiac failure and hepatic impairment were important factors associated with an increased response to warfarin due to the reduction of warfarin metabolism and synthesis of vitamin K dependent clotting factors[12]. Moreover, some studies suggested that fever and febrile illness were associated with an increased response to warfarin by increased clearance of vitamin K dependent clotting factors, decreased dietary vitamin K intake, or decreased metabolism of warfarin[12]. Management of warfarin toxicity depends on the degree of INR elevation with or without bleeding, and the severity of bleeding. Patients with an elevated INR (4.5-10.0) and no evidence of bleeding can be managed by withholding warfarin and close monitoring[1, 11, 13-16]. Vitamin K is considered in patients presented with minor bleeding while the presence of major bleeding requires vitamin K in conjunction with fresh frozen plasma (FFP) or 4-factor prothrombin complex concentrate (PCC)[1, 11, 13-16].

In Thailand, some studies evaluated the prevalence of warfarin adverse drug reactions (ADRs) and the factors associated

with these ADRs. The study showed that ADRs were found in 46.55 events/100 patient-years including prolonged INR, bruising and hematuria[10]. Another study revealed the causes of warfarin supratherapeutic INR values (INR >3 and 3.5 in mechanical mitral valve replacement) which were dose adjustment, patient's adherence, drug-drug and drug-disease interaction. The management of supratherapeutic INR values were appropriate. However, some management was considered improper such as suboptimal management in major bleeding events[17]. In support of previous data, our study focused on the causes and management of warfarin toxicity in Thai healthcare facilities. Therefore, this study aimed to determine the causes and management of warfarin toxicity in outpatients who visited an anticoagulation clinic at Pasang Hospital, Lamphun, Thailand.

Materials and Methods

Study design, setting and data collection

This study was a retrospective review which was carried out at the anticoagulation clinic, Pasang Hospital, Lamphun, Thailand. The study population consisted of outpatients who were prescribed warfarin and had been taking warfarin for at least 6 months. Eligible patients were those presented with warfarin toxicity, as defined by INR value greater than 3.0 and 3.5 in patients who have undergone mechanical mitral valve replacement[16]. Patients visited the anticoagulation clinic at Pasang Hospital, with warfarin toxicity during a one-year period from 1 January 2018 to 31 December 2018. No sample size was calculated. All patients who met the inclusion criteria and identified during the study period were eligible. Inclusion criteria were as follows: 1) Patients had been taking warfarin for at least 6 months; 2) Patients visited the anticoagulation clinic, Pasang Hospital; and 3) Patients presented with warfarin toxicity (INR >3 and 3.5 in mechanical mitral valve replacement). Exclusion criteria were as follows: 1) Patients with an elevated INR who did not use warfarin; and 2) Patients who were clinically unstable during the study period. Patients who visited the anticoagulation clinic more than once during the study period were recorded separately for each event.

The characteristics of patients, INR measurements[18], complications of bleeding, presumed causes and management of warfarin toxicity were collected from a medical chart recorded by physicians and pharmacists. HOSxP (hospital information system), including Electronic health record (EHR) was used to identify patients with increased INR and

reviewed medical data, laboratory measurements, and prescription data. The presence of bleeding, including signs and sites of bleeding, were recorded by the physicians. Bleeding was classified as major and non-major bleeding (minor bleeding and no bleeding). Major bleeding was regarded as life-threatening bleeding, bleeding requiring blood transfusion, bleeding in body cavity or bleeding that required anticoagulation withdrawal[6, 7]. The presumed causes of warfarin toxicity (such as changes in clinical disease status, drug interaction) and the management were evaluated by physicians and pharmacists.

Statistical analysis

Descriptive statistics were used to calculate baseline characteristics of the patients, INR measurements, complications of bleeding, causes of warfarin toxicity and the management. Data was shown as number (%) of patients and mean ± SD.

Table 1. Baseline characteristics of the patients, anticoagulant indication and INR

Characteristics	Number of patients (%)
Gender[a]	
- Male	62 (44.9)
- Female	76 (55.1)
Mean age (years ± SD)[a]	68±11
Indications for anticoagulation[b]	
- Atrial fibrillation	175 (65.5)
- Multiple indications (stroke with AF)	50 (18.7)
- Heart valve replacement	11 (4.1)
- Embolism (DVT, PE)	8 (3.1)
- Myocardial infarction	5 (1.9)
- Stroke	4 (1.5)
- Others	14 (5.2)
Baseline INR (target INR without warfarin toxicity)[b]	
- INR 2.0-3.0	250 (93.6)
- INR 2.5-3.5 (in a patient with a mechanical heart valve)	17 (6.4)
Mean supratherapeutic INR (range)[b]	3.8 (3.01-8.7)
- INR 3.1-5.0	249 (93.3)
- INR >5.0	18 (6.7)

[a]n=138

[b]n= 267

Results

During the study period, 267 increased INR measurements (138 patients) were identified and met the inclusion criteria for warfarin toxicity. One patient could be presented with more than one events of warfarin toxicity during the study period and each event was recorded. For clarity this study will refer to the 267 events of warfarin toxicity as patients.

Fifty five percent (76/138) of patients were female and 45% (62/138) were male. The average age was 68±11 years (range 33-89 years). The most common indications for warfarin prescription were atrial fibrillation (AF) (65.5%, 175/267), multiple indications (stroke with AF) (18.7%, 50/267), heart valve replacements (4.1%, 11/267) and embolism including deep-vein thrombosis (DVT) and pulmonary embolism (PE) (3.1%, 8/267). The average INR was 3.8±0.8 (range 3.01-8.7). The INR was between 3.1-5.0 in 93.3% (249/267) of patients, and greater than 5.0 in 6.7% (18/267) of patients (see Table 1).

Table 2. Suspected reasons for elevated INR (n=267)

Suspected reasons for elevated INR	Number of patients (%)
Cause not identified/not documented	10 (3.7)
Cause identified	257 (96.3)
Cause of warfarin toxicity[a,b]	
- Drug-disease interaction	237 (57.1)
- Drug-drug interaction	152 (36.6)
- Drug-food interaction (including alcohol consumption)	10 (2.4)
- Poor compliance	9 (2.2)
- Drug-herb interaction	7 (1.7)

[a]n=415

[b]More than 1 suspected reason might be found in 1 patient

The prevalence of warfarin toxicity was 18.6% (267/1,434). The causes of warfarin toxicity were identified and addressed in 96.3% (257/267) of patients. Only in 3.7% (10/267) of patients presented with warfarin toxicity, the cause was not identified or not documented (see Table 2). Where the causes were identified, 57.1% (237/415) were due to drug-disease interaction and unstable underlying disease and 36.6% (152/415) were due to drug-drug interaction. The most common drug-

disease interaction and unstable underlying disease were congestive heart failure and unstable AF (83.3%, 269/323) (see Table 3). In case of drug-drug interaction, the most common drugs used which were found to have the interaction with warfarin were simvastatin (58.0%, 112/193), omeprazole (14.5%, 28/193), allopurinol (8.3%, 16/193), propylthiouracil (7.8%, 15/193) and non-steroidal anti-inflammatory drugs (NSAIDs) (5.7%, 11/193) (Table 4).

Table 3. Drug-disease interaction with warfarin (n=267)

Drug-disease interaction	Number of patients (%)
No drug-disease interaction	30 (11.2)
Drug-disease interaction	237 (88.8)
Drug-disease interaction[a,b]	
- Congestive heart failure (including unstable AF)	269 (83.3)
- Acute illness (including fever, infection, diarrhea)	33 (10.2)
- Hyperthyroidism	21 (6.5)

[a]n=323

[b]More than 1 drug-disease interaction might be found in 1 patient

Table 4. Drug-drug interaction with warfarin (n=267)

Drug-drug interaction	Number of patients (%)
No drug-drug interaction	115 (43.1)
Drug-drug interaction	152 (56.9)
Drug-drug interaction[a,b]	
- Simvastatin	112 (58.0)
- Omeprazole	28 (14.5)
- Allopurinol	16 (8.3)
- Propylthiouracil	15 (7.8)
- NSAIDs (including aspirin)	11 (5.7)
- Others (valproate, ranitidine, quinine, thyroxine)	11 (5.7)

[a]n=193

[b]More than 1 drug-drug interaction might be found in 1 patient

Clinical presentations of warfarin toxicity were shown (see Table 5) as major bleeding, minor bleeding and without bleeding. Major bleeding, such as gastrointestinal bleeding and any bleeding (including urinary tract, lung) occurred in 3.7% (10/267) of patients. Minor bleeding, such as purpura, gingival bleeding and prolonged bleeding occurred in 9.3% (25/267) of patients. Eighty seven percent (232/267) of patients had no bleeding on presentation.

Management of warfarin toxicity were dosage reduction (71.9%, 192/267), INR monitoring without giving intervention (17.2%, 46/267) and giving vitamin K_1 1 mg orally (6.4%, 17/267) (see Table 6,7). After the intervention, INR value decreased in all patients (100%, 267/267). Follow-up period depended on the dependent variables such as degree of INR elevation, severity of bleeding, patient response to intervention and patient convenience. In this study, physicians' adherence to the recommendations from several published literatures was almost 100% (266/267) of patients. Vitamin K_1 1 mg orally was given to only 1 patient (0.4%) whose INR was less than 5.0 and had no major bleeding on presentation. However, INR value decreased in all patients (100%, 267/267) after the intervention given.

Table 5. Clinical presentation of patients with elevated INR (n=267)

Clinical presentation	Number of patients (%)
Asymptomatic	232 (87.0)
Major bleeding	10 (3.7)
Minor bleeding	25 (9.3)
Major bleeding[a]	
- Gastrointestinal	7 (70.0)
- Lung	2 (20.0)
- Urinary tract	1 (10.0)
Minor bleeding[b,c]	
- Purpura	18 (64.3)
- Gingival bleeding (>10 minutes)	7 (25.0)
- Nosebleeds (>10 minutes)	2 (7.1)
- Prolonged bleeding (>10 minutes)	1 (3.6)

[a]n=10

[b]n=28

[c]More than 1 minor bleeding might be found in 1 patient

Table 6. Management of warfarin toxicity (n=267)

Management	Number of patients (%)
- Dosage reduction	192 (71.9)
- INR monitoring without giving intervention	46 (17.2)
- Vitamin K_1 1 mg orally	17 (6.4)
- Multiple management (omit next 1–2 doses and restart at lower dose)	11 (4.1)
- Omit next few warfarin doses	1 (0.4)

Table 7. Management of warfarin toxicity (subgroups) (n=267)

INR	Number of patients (%)				
	Dosage reduction	INR monitoring	Vitamin K_1 orally	Multiple management	Omit next few doses
INR 3.1-5.0	190 (71.2)	46 (17.2)	2 (0.7)	10 (3.7)	1 (0.4)
INR >5.0	2 (0.7)	0 (0)	15 (5.7)	1 (0.4)	0 (0)

Discussion

This study evaluated the causes and management of warfarin toxicity in Thai healthcare facilities. Interestingly, the suspected reasons for elevated INR were identified and addressed in 96.3% (257/267) of patients. Although, there was some inconsistency that the results from the previous studies showed the causes of warfarin toxicity were frequently not identified by clinicians and were therefore rarely addressed[1, 17]. It was possible that the causes of warfarin toxicity in this study were closely monitored and evaluated by physicians and pharmacists. The suspected reasons for elevated INR depended on the setting of healthcare facilities. In this study, the most common reasons were due to drug-disease interaction and unstable underlying disease (57.1%, 237/415) and 36.6% (152/415) were due to drug-drug interaction. While the previous study showed the causes of warfarin toxicity were due to dosing errors (56%) and drug-drug interaction (17%)[1]. Another previous study showed that the suspected reasons for elevated INR were due to poor compliance (19%), recently initiated therapy (11.9%), poor absorption (poor oral intake, vomiting, diarrhea) (11.9%) and drug-drug interaction (10.7%)[19]. The most common prescribed interacting medicines were cardiovascular medicines such as simvastatin and amiodarone[1, 19]. Moreover, a previous study revealed the causes of warfarin supratherapeutic INR values were dose adjustment (19.4%), patient's adherence (7.8%), drug-drug interaction

(4.7%) and some comorbidities such as congestive heart failure, fever and infection (2.2%)[17]. This study showed that congestive heart failure (including unstable AF), acute illness (including fever, infection, diarrhea) and hyperthyroidism were the most common causes of warfarin toxicity. These underlying diseases were associated with an increased response to warfarin by interfering warfarin metabolism[12].

In this study, only 3.7% (10/267) of patients presented with major bleeding and 9.3% (25/267) of patients presented with minor bleeding. Eighty seven percent (232/267) of patients had no bleeding on presentation. It should be noted that this study was conducted in the outpatient department. Thus, the average INR was 3.8±0.8 (range 3.01-8.7). The INR was between 3.1-5.0 in 93.3% (249/267) of patients, and greater than 5.0 only in 6.7% (18/267) of patients. While the previous studies were conducted in the emergency department and inpatient department[1, 19, 20]. The previous study showed that major bleeding occurred in 16.7% of patients, minor bleeding in 17.8%. The INR was between 6.0-10.0 in 39% of patients, and greater than 10.0 in 61% of patients[19]. Another previous study showed that 28% of patients presented with major bleeding, 18% with minor bleeding and 54% without bleeding[1].

There is no consensus on treatment and management guidelines for warfarin overdose[19]. The recommendations for the management of warfarin toxicity are from the American College of Chest Physicians (ACCP) antithrombotic therapy guideline and several published literatures[1, 11, 13-16]. The management of patients who presented with warfarin toxicity depended on the degree of INR elevation and the severity of bleeding. Patients with an elevated INR (4.5-10.0) and no evidence of bleeding can be managed by withholding warfarin and close monitoring[11, 13-16]. Moreover, the literature suggested that patients with an INR of 5.0-10.0 with minor or no bleeding should have their next 1-2 warfarin doses omitted and start a small dose of vitamin K[13-16]. The management of warfarin toxicity in this study was consistent with the previous study. It has been previously shown that the management of supratherapeutic INR values were omitting 1-2 doses of warfarin (66.7%), dosage reduction (13.9%) and giving vitamin K_1 (19.4%)[21]. In this study, physicians' adherence to the recommendations from several published literatures was almost at 100% (266/267) of patients. INR value decreased in all patients (100%, 267/267) after the intervention given.

Our finding highlighted that warfarin toxicity is quite common and is best managed by a multidisciplinary team.

Patients should be closely monitored by clinicians. Pharmacists in the anticoagulation clinic also play an important role in identifying the presumed causes and preventing warfarin toxicity. The previous study showed that 8.33% of the patients had warfarin related problems. Prescribing errors for warfarin such as improper dosage was an important problem. Interestingly, the physicians followed the suggestions from the pharmacists on dose adjustment (83.3%)[22]. A multidisciplinary team is key in order to dispense warfarin effectively and safely[10, 17, 21-23].

Study limitations

This study had a number of limitations. The retrospective review had to rely on the availability and quality of clinical records. The timing for the INR levels to normalize should be recorded. The power of the study was limited due to the short time period. This study was also conducted at a single center. These factors might affect the generalizability of the results. Further study using a longer time period should be performed. In addition, a prospective and multicenter study might increase the power of future work.

Conclusion

Anticoagulation therapy, especially warfarin, poses challenges for both patients and health care professionals. Our findings highlight that warfarin toxicity is quite common and is best managed by a multidisciplinary team. Suspected reasons for elevated INR, clinical presentation and management of warfarin toxicity depend upon the setting of healthcare facilities and individual variations. Patients should be closely monitored by clinicians. Pharmacists in the anticoagulation clinic also play an important role in identifying presumed causes and preventing warfarin toxicity. A multidisciplinary team is key in order to dispense warfarin effectively and safely.

Ethics Approval and Consent to Participate

Ethical approval for this study was obtained from Human Experimentation Committee, Lamphun Provincial Public Health Office, Ministry of Public Health, Lamphun 51120, Thailand (REC 2562-13).

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

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Conflicts of Interest

The authors declare that they have no conflicts of interest, financial or otherwise.

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