



Unveiling the impact of water-boiled cannabis on warfarin: A case report of atrial fibrillation patients after cannabis legalization in Thailand

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ARTICLE INFO

Keywords:

Cannabis
Warfarin
Atrial Fibrillation
Drug interaction

ABSTRACT

Warfarin, a commonly prescribed anticoagulant, is utilized to prevent thrombotic issues and requires careful dose adjustment due to its narrow therapeutic range. As warfarin is metabolized by essential drug-metabolizing enzymes (DMEs), it is prone to interactions with a wide range of therapeutic agents, including herbal medicines. In June 2022, Thailand became the first country in Asia to remove cannabis plants from its narcotics control list, allowing individuals to cultivate them for personal use. Consequently, this report aimed to examine the interaction between cannabis and warfarin in Thai patients following the legalization of cannabis from 2021 to 2023. These three case reports elucidated the potential for drug interactions arising from the concurrent use of warfarin and water-boiled cannabis. This process involved placing cannabis flowers into a boiling kettle and subsequently consuming the resulting cannabis-infused water instead of regular drinking water. Our findings revealed that each atrial fibrillation patient had supratherapeutic international normalized ratio (INR) levels ranging from 3.49 to 4.92, with no bleeding complications. Following the cessation of cannabis use, the INR levels decreased and returned to the therapeutic range for warfarin therapy. In summary, the current report indicates that water-boiled cannabis may influence the outcomes of warfarin therapy, as evidenced by the changes in INR levels.

1. Introduction

Warfarin is a frequently prescribed anticoagulant indicated to prevent thrombotic problems associated with atrial fibrillation and venous thromboembolism [1,2]. Moreover, warfarin is a group of drugs that require careful optimization of the dosing regimen and frequent monitoring due to its narrow therapeutic window. Hence, it is imperative that healthcare professionals maintain vigilant awareness of any medications that may potentially interact with warfarin [3]. Recently, a concern has been raised in Thailand regarding the decriminalization of cannabis. Generally, cannabis is the most extensively consumed illegal psychoactive chemical in the world [4]. Cannabis is known for a variety of therapeutic benefits and can be used to treat conditions such as anxiety, depression, sleep disorders, pain, and cancer [5,6]. Several countries have legalized the use of cannabis and its specific compositions for medical purposes in accordance with standard protocols established by

legislation [7].

In Thailand, cannabis had been classified as a Class-5 narcotic under Thailand's Narcotic Act since 1979, which prohibited the cultivation, possession, sale, and use of marijuana. However, following a legal amendment for medical use in February 2019, the Thai Food and Drug Administration officially removed all parts of the cannabis plant from the Class-5 narcotic list in June 2022. This landmark change made Thailand the first country in Asia to legalize the sale, cultivation, and possession of cannabis plants in 2022 [8,9].

Delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are two of the primary chemicals found in cannabis. THC and CBD can interact with the cannabinoid receptors (CB1 and CB2) differently. THC acts as a partial agonist at CB1 receptors and appears to mediate its psychoactive effects, including mood, consciousness, and motor control. In contrast, CBD does not target CB1 and CB2 receptors directly; however, it can interact with other receptors and displays various therapeutic effects,

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<https://doi.org/10.1016/j.toxrep.2024.101838>

Received 24 September 2024; Received in revised form 19 November 2024; Accepted 25 November 2024

Available online 28 November 2024

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such as neuroprotection, antiepileptic, analgesic, and anticancer benefits. [10,11]. According to a previous study, the cytochrome P450 (CYP450) enzymes play an essential role for the metabolism of cannabis in humans. For example, THC is primarily metabolized by CYP3A4 and CYP2C9, and CBD is metabolized by CYP3A4 and CYP2C19 [12]. Furthermore, THC and CBD have been demonstrated to act as a potent competitive inhibitor of the CYP2C9, CYP2C19, CYP1A2 and CYP3A4 [13]. Therefore, theoretically, cannabis can interact with other substances when used concomitantly. Importantly, among all the anticoagulants, warfarin is the most frequently prescribed, and it is also one of the medications that result in the highest number of adverse drug reactions requiring visits to the emergency department [14]. Consequently, it is important for healthcare providers to closely monitor patients who are receiving warfarin.

The present report illustrates the experience of warfarin users who initiated the use of cannabis to manage their health by infusing it in boiling water after cannabis legalization in Thailand. All patients utilized cannabis flowers, which they boiled in a kettle. Each patient reported consuming cannabis-infused boiling water as a substitute for regular drinking water, averaging approximately 5–8 glasses per day, equivalent to around 1–2 liters daily. All patients reported using cannabis-infused boiling water approximately one month prior to their warfarin clinic appointment. The patient's regular daily consumption of cannabis was observed to necessitate an alteration in their warfarin dosage.

2. Case presentation

2.1. Patient case 1

The first patient in this case series was a 60-year-old Thai man involved in agriculture, who was an active user of warfarin. At one point, he decided to incorporate cannabis as an alternative treatment for controlling his blood sugar. He was enrolled in the anticoagulation consultation unit at the local hospital, seeking advice on warfarin use before starting the medication. His medical history included essential hypertension, type 2 DM (with the most recent HbA1C at 6.6 %), hyperlipidemia, and atrial fibrillation with a CHA2DS2-VASc score of 2. Consequently, the patient's medication regimen included daily doses of enalapril 20 mg, carvedilol 6.25 mg, lercanidipine 20 mg, simvastatin 20 mg, metformin 1000 mg, and aspirin 81 mg. The timeline outlining his warfarin treatment, along with the monthly prescribed dosage, was elucidated (Fig. 1). Furthermore, Fig. 1 provided insights into his concurrent use of cannabis during the warfarin therapy. The patient informed the pharmacists that he began using cannabis in May–June 2022 to manage his elevated blood sugar levels. This period coincided with the Thai government's announcement of cannabis legalization, set

to commence on June 9, 2022. The demographic characteristics of the patient at the date of detection were as follows: body mass index (BMI) was recorded at 22.5 kg/m²; blood pressure was measured 132/71 mmHg; heart rate was documented at 99 beats per minute; respiratory rate was noted to be 22 breaths per minute; and body temperature was 36.6 degrees Celsius. All hematological parameters, blood urea nitrogen (BUN), creatinine, and electrolyte data were within normal limits. The lipid profile including cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) was assessed to be within normal limits.

During the consultation, he shared his personal view that cannabis had the potential to lower blood sugar levels. As a result, he began a daily cannabis regimen, which he continued for a month during the follow-up period for warfarin until his next hospital visit. His method of consumption was described as a water-boiling technique, in which he placed cannabis flowers into a boiling kettle, and then consumed the cannabis-boiling water rather than regular water. During the hospital visit, his prothrombin time (PT) test and INR were conducted. The INR of this patient, prior to consuming cannabis-infused water, was reported to be 2.61, falling within the optimal range as the safe therapeutic window for warfarin usage is between 2 and 3. However, subsequent to cannabis usage, his INR level the following month escalated to 4.92, marking a significant increase from his previous level. Additionally, this patient used cannabis-infused water again after the pharmacist adjusted his warfarin dose. As a result, his INR rose to 4.59. Despite the absence of adverse events, the clinical pharmacist advised him about the potential drug interactions associated with using cannabis and warfarin together. Acting upon the pharmacist's recommendation, the patient discontinued cannabis consumption, leading to his INR values ranging from 1.42 to 3.56 in subsequent visits.

2.2. Patient case 2

A 63-year-old Thai woman, predominantly a housewife by occupation, was enrolled in the warfarin clinic at the local hospital. Her medical history encompassed essential hypertension, type 2 DM (with the most recent HbA1C at 12 %), and atrial fibrillation with a CHA2DS2-VASc score of 3. Her medication regimen comprised daily doses of losartan 50 mg, simvastatin 40 mg, metformin 2500 mg, and glipizide 20 mg. Fig. 2 contained details regarding her concurrent cannabis usage while undergoing warfarin therapy. The patient informed the clinical pharmacist during the consultation that she had started using cannabis in September 2021 to manage her elevated blood sugar levels, as cannabis has been amended for medical use in February 2019. The demographic characteristics of the patient at the date of detection were as follows: BMI was recorded at 31.16 kg/m²; blood pressure was measured 124/

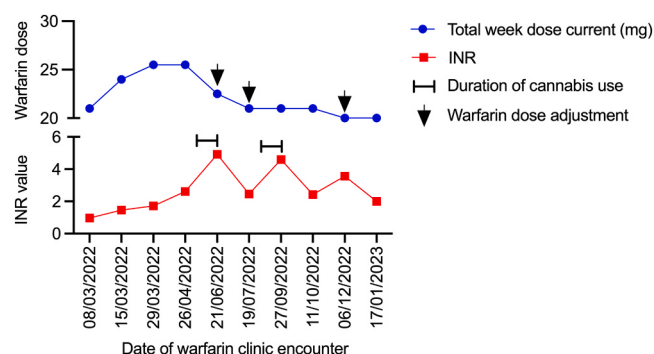


Fig. 1. Warfarin dosing, INR, and medical cannabis history of case 1. This patient consumed cannabis-infused boiling water, specifically during May–June and August–September. The dosage of warfarin was adjusted in response to an increase in the INR to ensure that it remained within clinically safe anti-coagulation parameters.

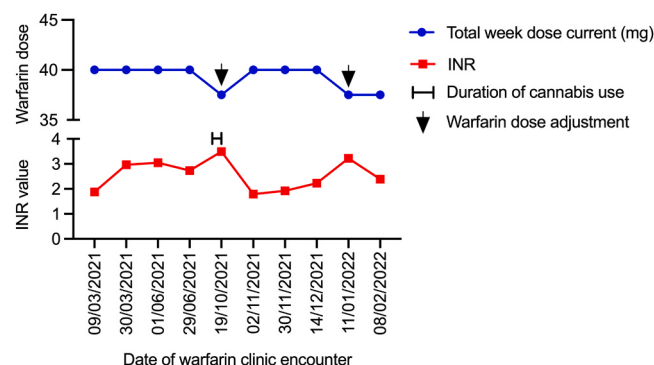


Fig. 2. Warfarin dosing, INR, and medical cannabis history of case 2. This patient consumed cannabis-infused boiling water, specifically during September–October. The dosage of warfarin was adjusted in response to an increase in the INR to ensure that it remained within clinically safe anti-coagulation parameters.

63 mmHg; heart rate was documented at 84 beats per minute; respiratory rate was noted to be 20 breaths per minute; and body temperature was 36.5 degrees Celsius. All hematological parameters, BUN, creatinine, and electrolyte data were within normal limits. The lipid profile including cholesterol, HDL, and LDL was assessed to be within normal limits.

During the consultation, she shared her personal perspective that cannabis had the potential to lower blood sugar levels. Her method of consumption was described as a water-boiling method in which she placed one stalk of cannabis flowers into a boiling kettle, and then consumed the cannabis-boiling water. Her hospital visits included PT and INR tests, revealing an increase in INR from 2.73 to 3.49 after cannabis use. Following the advice provided by the pharmacist due to potential interactions with warfarin, she ceased cannabis consumption, stabilizing her INR between 1.79 and 3.22 in subsequent visits. Additionally, she started tamoxifen treatment for breast cancer in November 2021. The pharmacist advised her to avoid using cannabis simultaneously, as it could potentially inhibit CYP2D6 and lead to possible pharmacokinetic interactions.

2.3. Patient case 3

A 65-year-old Thai man with his past medical history included essential hypertension, congestive heart failure (heart failure reduced ejection fraction), and atrial fibrillation with a CHA2DS2-VASc score 3. His medication regimen comprised daily doses of sacubitril/valsartan 200 mg, carvedilol 12.5 mg, spironolactone 12.5 mg, and empagliflozin 10 mg. Fig. 3 presented his concurrent cannabis use during the warfarin treatment. During a consultation session, the patient disclosed to the clinical pharmacist that he had started using cannabis in January 2022 to address insomnia and as a dietary supplement. He began a daily cannabis regimen until his subsequent hospital visit. The demographic characteristics of the patient at the date of detection were as follows: BMI was recorded at 24.3 kg/m²; blood pressure was measured 126/72 mmHg; heart rate was documented at 86 beats per minute; respiratory rate was noted to be 22 breaths per minute; and body temperature was 36.2 degrees Celsius. All hematological parameters, BUN, creatinine, and electrolyte data were within normal limits. The lipid profile including cholesterol, HDL, and LDL was assessed to be within normal limits.

His method of consumption was described as a water-boiling method in which he placed one stalk of cannabis flowers into a boiling kettle, and then consumed the cannabis-infused water rather than regular water. Before consuming cannabis-infused water, his INR was recorded as 2.58. However, subsequent to cannabis consumption, his INR levels the next visits were 3.59 and 4.29, which was markedly higher than his earlier record. Despite lacking adverse event, the clinical pharmacist

advised caution regarding cannabis and warfarin interactions. Eventually, the patient stopped cannabis consumption, and his INR was ranged from 1.38 to 2.61 in the following visits.

3. Discussion

Warfarin, as a standard practice, requires meticulous dosing adjustments due to its narrow therapeutic index and the risk of serious adverse events. As such, each individual receives a tailored warfarin dose based on their INR, which is used for routine therapeutic drug monitoring. The recommended INR range for most cases is 2.0–3.0. Additionally, the most serious complication of warfarin therapy is hemorrhage, which is often associated to a higher INR (INR > 3). One possible reason for the increase in INR levels is a warfarin-drug interaction involving the CYP450 enzyme, which typically affects the enzyme's catalytic activity and the overall rate of warfarin metabolism [1,3]. This report was the first to describe the effects of combining warfarin with cannabis subsequent to the legalization of medicinal cannabis in Thailand.

In this study, the use of cannabis-infused water could impact warfarin therapy and INR levels. However, none of the patients experienced bleeding or symptoms of cannabinoid hyperemesis syndrome, such as palpitations, hallucinations, nausea, or vomiting. We hypothesized that this rise in INR levels was attributed to a pharmacokinetic interaction between warfarin and cannabis. The patients began daily consumption of cannabis-infused water, averaging approximately 5–8 glasses daily, which translates to around 1–2 liters per day, coinciding with an elevation in their INR levels (Figs. 1–3). To support this finding, cannabis-based products contained an array of cannabinoids that may inhibit the cytochrome P450 enzymes CYP3A4, CYP2C19, and CYP2C9 [15]. We theorized that the patients would presumably expose to the many hundreds of molecules in the cannabis from cannabis-infused water were sufficient to interfere with metabolism of warfarin, potentially leading to increased INR levels. Prior research indicated that boiling for fifteen minutes was sufficient to achieve the highest concentrations of cannabinoids in cannabis tea solutions. A cannabis tea sample made with 500 mg of cannabis flower in 500 mL of water, boiled for 15 minutes, was analyzed using UHPLC-MS/MS and was found to contain cannabinoids such as 0.007 mg/mL of THC, 0.008 mg/mL of Δ9-tetrahydrocannabinolic acid A (THCA-A), and 0.009 mg/mL of CBD [16]. Consequently, the estimated daily cannabinoid consumption was calculated to be approximately 5–10 mg of these cannabinoids. However, the concentrations of cannabinoids might vary depending on the amount of cannabis flowers used by each patient. As a result, cannabis usage may elevate the risk of drug-drug interactions with substrates for these enzymes, including medications with a narrow therapeutic window [17]. Thus, it is crucial for healthcare practitioners to monitor the potential for interactions between medical cannabis products and medications metabolized by these enzymes, such as warfarin [18].

According to previous research, warfarin may interact with statins, simvastatin specifically augmented warfarin's anticoagulant effects [19]. However, the patient had been taking simvastatin and warfarin concurrently for approximately a year prior to cannabis use. The doctor and pharmacist observed no changes in INR levels attributable to these medications. All patients complied with the prescribed regimen, reported no modifications to their dietary habits, and did not utilize any new over-the-counter medications prior to, during, or following any episodes of INR fluctuation. Consequently, we postulated that the observed INR changes stemmed from the consumption of cannabis-infused water concurrent with warfarin therapy. This observed impact aligns with prior evidence suggesting that cannabis may interact with warfarin medication, leading to elevated INR levels [20–22].

Additionally, tamoxifen consumption was reported in patient case 2. Prior study report that tamoxifen used concomitantly with warfarin may have played a potentially role in the INR elevation [23,24]. However, in this case, the levels of INR remained within normal levels following the administration of tamoxifen alongside warfarin. Moreover, tamoxifen

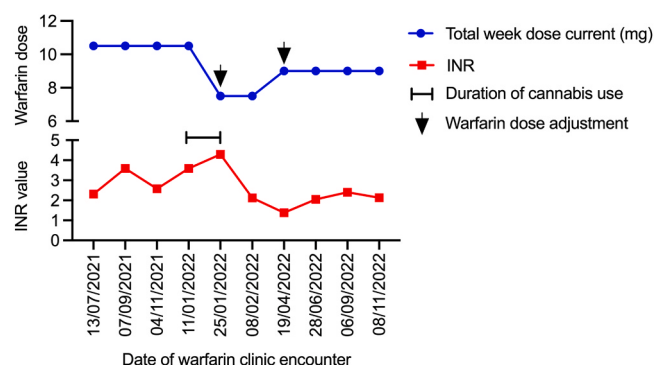


Fig. 3. Warfarin dosing, INR, and medical cannabis history of case 3. This patient consumed cannabis-infused boiling water, specifically during January. The dosage of warfarin was adjusted in response to an increase in the INR to ensure that it remained within clinically safe anticoagulation parameters.

not only interacts with warfarin but may also be associated with cannabis. Previous research indicates that tamoxifen, primarily metabolized by CYP2D6, may be affected by CBD, a known potential inhibitor of CYP2D6. CBD could potentially reduce tamoxifen's active metabolite levels compared to tamoxifen monotherapy [25]. Therefore, the clinician who prescribed warfarin to the patient should be concerned about coagulopathy resulting from the concurrent administration of warfarin, other medications, and cannabis.

In terms of limitations, the present report suggested the possibility of these drug-drug interactions, but was unable to confirm causation between cannabis use and increased INR during warfarin treatment. In addition, our clinical assessment was hindered by the absence of cannabinoids serum concentrations; however, we placed importance on the clinical history, and toxicity was verified through INR levels. Furthermore, since there was no standard dose or form for medical cannabis use, this report could not control for the dosage and form of medical cannabis, which might contribute to variability in individual side effects and responses.

4. Conclusion

In summary, all patients manifested supratherapeutic INR levels during the co-administration of cannabis and warfarin. Therefore, clinicians who manage warfarin medication should be aware of the possibility of a warfarin-cannabis interaction. As cannabis legalization for medication purpose, the number of individuals consuming cannabis products is expected to increase. Healthcare professionals should inquire extensively about cannabis usage, including the type of product (leaf, flower, or extract), the amount of cannabinoids in the product, the frequency of use, and the method of administration. All these factors will help the healthcare professional to make informed decisions about the potential for drug-drug interactions.

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the Human Research Ethics Unit (HREU), Faculty of Medicine, Prince of Songkla University (approval no. REC.66-302-19-2).

CRedit authorship contribution statement

Sucharat Tungsukruthai: Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Prasert Dolthammasiri:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Warit Ruanglertboon:** Writing – review & editing, Methodology, Conceptualization. **Supattra Limsuwanchote:** Writing – review & editing, Methodology, Conceptualization. **Suwat Wiriyapongsukit:** Supervision, Resources. **Wandee Udomuksorn:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization. **Niracha Saowaneejitak:** Resources, Methodology, Investigation, Formal analysis, Data curation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors wish to express their profound gratitude to all participants who generously devoted their time to this research project. We would also like to extend special thanks to Prof. Sawitree

Assanangkornchai, the chief of the main project, for providing us with the opportunity to contribute to this research, and to Assoc. Prof. Somsmorn Chittrakarn, who served as a consultant throughout the project. Special acknowledgment is given to the Health Systems Research Institute (HSRI) for their grant (No. HSRI 66-042) supporting this research project.

Data availability

Data will be made available on request.

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