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MINIREVIEW

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Interaction between warfarin and cannabis

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Abstract

Delta-9-tetrahydrocannabinol (THC), the main psychoactive cannabinoid in cannabis, may inhibit the cytochrome P450 enzyme CYP2C9. Consequently, cannabis use might infer a risk of drug-drug interaction with substrates for this enzyme, which includes drugs known to have a narrow therapeutic window. In this study, we describe a case report of a 27-year-old man treated with warfarin due to mechanical heart valve replacement who presented with elevated international normalized ratio (INR) value (INR = 4.6) following recreational cannabis use. We conducted a review of the available literature, using the PubMed and EMBASE databases while following PRISMA guidelines. Following screening of 85 articles, three eligible articles were identified, including one in vitro study and two case reports. The in vitro study indicated that THC inhibits the CYP2C9-mediated metabolism of warfarin. One case study reported of a man who on two occasions of increased marijuana use experienced INR values above 10 as well as bleeding. The other case study reported of a patient who initiated treatment with a liquid formulation of cannabidiol for the management of epilepsy, ultimately necessitating a 30% reduction in warfarin dose to maintain therapeutic INR values. The available, although sparse, data suggest that use of cannabinoids increases INR values in patients receiving warfarin. Until further data are available, we suggest patients receiving warfarin be warned against cannabis use.

KEYWORDS

cannabis, case report, drug-drug interaction, MiniReview, warfarin

1 | INTRODUCTION AND BACKGROUND

The use of cannabis for recreational purposes is considerable.[1] Further, medical use of cannabis is on the rise, as it has been proposed to provide some relief for pain disorders, vomiting and nausea.[2-4] Systematic assessment of the literature provides little guidance, with no or insufficient evidence for most pain conditions except for neuropathic pain. The evidence supporting the latter use remains unimpressive.[5] More positive, albeit still modest, effects have been seen in specialized use of cannabis for drug-resistant seizures in children with Dravet syndrome[6] and in the treatment of chemotherapy-induced vomiting and nausea.[7] A very recent paper described an US area-endemic incident of synthetic cannabinoids associated with many cases of bleeding. The authors suggested that these synthetic cannabinoids, manufactured specifically for abuse under uncontrolled conditions, may have been purposely contaminated with warfarin-like anticoagulants to potentiate effects of cannabinoids through inhibition of cytochrome P450.[8] However, as preparations containing cannabis are not

widely marketed as conventional pharmaceutical drugs, safety data pertaining to medical remain insufficient.

A potential safety issue of cannabis use is the risk of drug-drug interactions. In vitro studies have suggested that delta-9-tetrahydrocannabinol (THC), the main psychoactive cannabinoid in cannabis, may be a moderate inhibitor of the cytochrome P450 enzyme CYP2C9,[9] an enzyme known to play an important role in the elimination of several narrow therapeutic index drugs such as phenytoin and anticoagulants.[10] Warfarin consists of two stereoisomers: R-warfarin and S-warfarin. Both stereoisomers inhibit the vitamin K epoxide reductase complex, but S-warfarin is about five times more potent than R-warfarin. S-warfarin is metabolized via CYP2C9, and R-warfarin is predominantly metabolized via CYP3A4.[11] In vitro, the CYP2C9-mediated 7-hydroxylation of S-warfarin is inhibited by various cannabinoids with IC50 values between 2.29 and 4.81 μmol/L.[10] Consequently, the use of cannabinoids may increase the risk of bleeding during warfarin therapy.

With this study, we report a case of a patient with supratherapeutic international normalized ratio (INR) values during warfarin use potentially triggered by recreational cannabis use. Warfarin has a narrow therapeutic window, and even minor changes in the anticoagulation effect due to, for example, drug-drug interactions may increase the risk of bleeding episodes and/or thrombosis. The case report is supplemented by a review of the literature and a summation of the theoretical background for a potential drug-drug interaction between warfarin and cannabis.

2 | CASE DESCRIPTION

A 27-year-old man substance abuser was hospitalized due to aorta valve endocarditis. He was treated surgically with a mechanical valve and subsequently initiated stroke-prophylactic oral anticoagulant therapy with warfarin with a target range for INR of 2.5-3.5. During the very long admission, the patient was allowed a 24-hour leave from the hospital. On his return, the INR value had increased to 4.6. The patient had previously been abusing intravenous drugs, but stated that he had only smoked cannabis during the past months. He stated having smoked a lot more cannabis during the leave than in the weeks prior to admission. After the INR value returned to the treatment range, the patient went on a second 24-hour leave. Even though he admitted having smoked cannabis on this occasion as well, his INR did not increase above the desired range.

3 | MATERIALS AND METHODS

We conducted a literature search following the PRISMA guidelines for systematic reviews. A search string was created: ((“cannabis”[MeSH Terms] OR “cannabis”[All Fields]) OR (“cannabis”[MeSH Terms] OR “cannabis”[All Fields] OR “marihuana”[All Fields]) OR (“cannabis”[MeSH Terms] OR “cannabis”[All Fields] OR “marijuana”[All Fields]) OR weed[All Fields] OR hash[All Fields] OR (“cannabidiol”[MeSH Terms] OR “cannabidiol”[All Fields]) OR (“cannabigerol”[Supplementary Concept] OR “cannabigerol”[All Fields]) OR (“cannabidiol”[MeSH Terms] OR “cannabidiol”[All Fields]) OR (“cannabinoids”[MeSH Terms] OR “cannabinoids”[All Fields] OR “cannabinoid”[All Fields]) OR (“cannabinoids”[MeSH Terms] OR “cannabinoids”[All Fields])) AND (interactions[All Fields] OR (“Interaction”[Journal] OR “interaction”[All Fields])) AND ((“warfarin”[MeSH Terms] OR “warfarin”[All Fields]) OR (“phenprocoumon”[MeSH Terms] OR “phenprocoumon”[All Fields] OR “marcoumar”[All Fields]) OR (“coumarin”[Supplementary Concept] OR “coumarin”[All Fields])). Limit “English language” was applied. PubMed (Medline) and EMBASE (Excerpta Medica, Elsevier; Ovid) were searched from inception to the middle of March 2018. Only articles reporting on original data on the interaction between cannabis and warfarin were eligible for inclusion.

4 | RESULTS

The selection process is illustrated in Figure 1. The initial search revealed five articles on PubMed and 85 articles on EMBASE. All PubMed papers were duplicated in the EMBASE search. A screening of the initial 85 articles by titles and abstracts excluded 71 articles, because they were not relevant/off topic. Full-text screening excluded another 11 articles, as these did not have specific information on the potential interaction between warfarin and cannabis or did not contain original data. Finally, included articles were cross-referenced for additional original publications. No additional articles were found. The three included articles consist of one in vitro study and two case reports.

Yamaori et al[12] investigated the inhibitory effect of marijuana smoking (ie, delta-9-tetrahydrocannabinol, THC, cannabidiol, cannabidiol (CBD) and cannabinol, and CBN) and polycyclic aromatic hydrocarbons (PAHs)) on the catalytic activity of CYP2C9 in vitro. Their results indicated that THC, CBD and CBN but not PAHs cause a direct, concentration-dependent inhibition of the CYP2C9-mediated 7-hydroxylation of S-warfarin. The half maximal inhibitory concentration (IC50) for THC was between 2.29 and 2.84 μmol/L, for CBD 2.67-4.81 μmol/L and for CBN 2.42-2.86 μmol/L. The mechanisms of inhibition of CYP2C9 by cannabinoids were presumed to be both mixed and/or competitive.

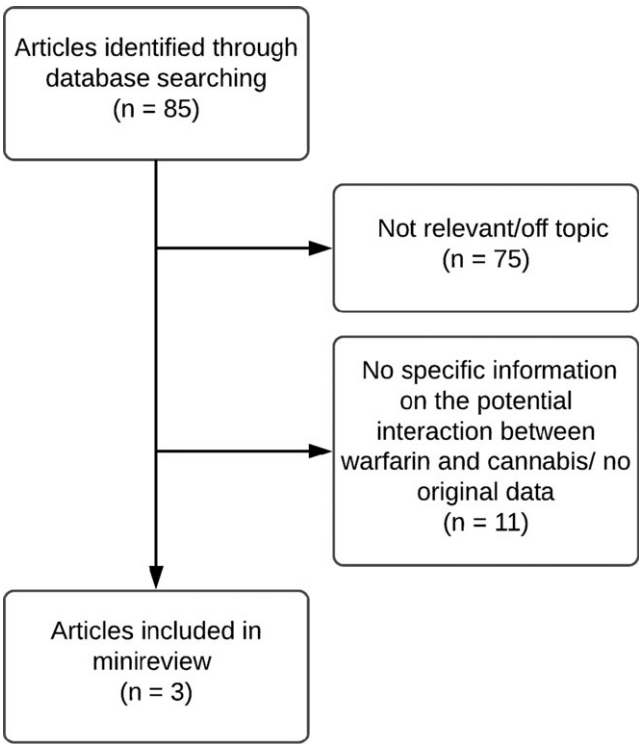

FIGURE 1 Literature search

Yamreudeewong et al reported on a 56-year-old man with multiple comorbidities (coronary artery disease with recent stent placement, mechanical valve replacement, peripheral vascular disease, seizure disorder and oesophageal reflux).[13] He had received stable warfarin therapy for 11 years and was co-treated with several other drugs (aspirin, carbamazepine, clopidogrel, furosemide, metoprolol, omeprazole, potassium chloride, sertraline, tramadol, valproic acid). On two occasions, the patient's INR increased suddenly to values above 10. Both episodes were associated with bleeding, and INR normalized in both cases following vitamin K administration. The patient was found to be adherent to his medication (all unchanged), had not had any dietary changes and did not use any new over-the-counter drugs or herbal products before, between or after any of the bleeding episodes. However, he reported having increased both his frequency and quantity of smoked marijuana from 1-2 joints per week (0.25-0.5 g/wk) to 4-5 joints (2.0-2.5 g/wk). After the patient stopped smoking marijuana, no high INR values or bleeding episodes occurred for the following 9 months of observation.

Grayson et al[11] described a 44-year-old Caucasian man with Marfan syndrome, mechanical valve replacement and post-stroke epilepsy. He was prescribed Epidiolex®, a liquid formulation of cannabidiol (CBD) 5 mg/kg/d, for the management of treatment-resistant epilepsy. The patient was also prescribed warfarin with INR values stable within treatment range for more than 6 months. During dose escalation of CBD, INR values increased in a non-linear manner. To maintain INR within the therapeutic range, warfarin dosage was reduced. At the last visit, the warfarin dose had been reduced by approximately 30% compared to baseline (from 7.5 mg to average 5.36 mg daily).

5 | DISCUSSION

The evidence of a drug-herb interaction concerning cannabis and warfarin is sparse. Indeed, we only identified one in vitro study[12] and two case reports[11,13] in our systematic search in two comprehensive bibliographic databases, PubMed and EMBASE. Collectively, these reports along with our own case study indicate that cannabinoids from smoking cannabis products increase INR values in patients receiving warfarin. In vitro studies substantiate these observations, as cannabinoids inhibit CYP2C9-mediated metabolism of S-warfarin at concentrations relevant to those obtained in abusers and recreational users of cannabis.[9,12]

The cannabis plant is most often processed to three drug products, each of which may be ingested by smoking or eating: Dry leaves and flowers (herbal cannabis), pressed, dry resin or secretion (hash) and oil (hash oil). The plant contains several cannabinoids; however, there are three major constituents: delta-9-tetrahydrocannabinol (THC; the primary psychoactive cannabinoid), cannabidiol (CBD) and cannabinol (CBN). In dry plant marijuana preparations, the THC, CBD and CBN contents are approximately 4.5%, 0.4% and 0.3%.[12] In vitro data have demonstrated that THC is metabolized by CYP3A4 and CYP2C9 and that CBD is metabolized mainly by CYP3A4.[14]

In 18 chronic cannabis users, the median plasma THC concentration measured within 24 hours of the latest recreational exposure to inhaled cannabinoids (ie, smoking a "joint") was 1.9 μg/L (~6.04 μmol/L), ranging from 0.5 to 9.0 μg/L. After 7 days of cannabis abstinence, THC was still detectable in 16 out of 18 participants, with a median plasma concentration of 1.1 μg/L (~3.5 μmol/L).[15] Thus, the plasma THC concentrations are clearly in the range of the THC IC50 values reported by Yamaori et al even after 7 days of abstinence, which supports the plausibility of a clinically relevant interaction between cannabis and warfarin.

Yamreudeewong et al suggest that cannabis, beside inhibition of warfarin metabolism, also results in a transient minor reduction in the protein binding of warfarin. This would theoretically lead to displacement of warfarin from albumin causing a higher concentration of "unbound" warfarin subsequently potentiating the anticoagulant effect.[13] This is a faulty deduction. Drug interactions based on protein binding are of no relevance to high extraction, orally administered drugs such as warfarin. Additionally, the

consequences of theoretical transient changes in unbound drug, as suggested, are irrelevant in the presence of significant pharmacokinetic-pharmacodynamic equilibrium time.[16]

The recently introduced direct oral anticoagulants (dabigatran etexilate, rivaroxaban, apixaban and edoxaban) serve as treatment alternatives to warfarin in patients with nonvalvular atrial fibrillation and venous thromboembolism. While none of the direct oral anticoagulants are metabolized via CYP2C9, they are all substrates of P-glycoprotein,[17] which have been proposed to be induced by CBD.[18] Although the potential clinical significance thereof is undocumented, a pharmacokinetic interaction may, thus, also exist between cannabis and direct oral anticoagulants.

In contrast to the past, cannabis is now, in several countries, available for patients and consumers by prescription and/or as over-the-counter drug. Hence, it is now both feasible and legal to investigate the in vivo consequence of co-administration of warfarin and standardized cannabis products. We suggest a classic interaction study, using a randomized or cross over design, where warfarin is the victim and cannabis the perpetrator drug. This will quantify the pharmacodynamics and kinetics and determine the magnitude of the interaction and thus shed light on the clinical relevance and impact thereof.

Cannabis use may inhibit CYP2C9 to an extent clinically relevant for patients receiving warfarin. We suggest such be strongly discouraged, and we suggest a clinical drug-drug interaction study to quantify the effect of cannabinoids on CYP2C9 activity.

CONFLICT OF INTEREST

Dr. Lassen received a sponsorship to participate at ASCO 2018, from Bristol-Myers Squibb Denmark; the sponsorship was of no relevance to the present submission. The remaining authors declare no conflict of interests.

REFERENCES

1. Carliner H, Brown QL, Sarvet AL, Hasin DS. Cannabis use, attitudes, and legal status in the U.S.: a review. *Prev Med*. 2017;104:13-23.
2. Häuser W, Petzke F, Fitzcharles MA. Efficacy, tolerability and safety of cannabis-based medicines for chronic pain management - an overview of systematic reviews. *Eur J Pain Lond Engl*. 2018;22(3):455-470.
3. Claflin SB, van der Mei IAF, Taylor BV. Complementary and alternative treatments of multiple sclerosis: a review of the evidence from 2001 to 2016. *J Neurol Neurosurg Psychiatry*. 2018;89(1):34-41.
4. Lim K, See YM, Lee J. A systematic review of the effectiveness of medical cannabis for psychiatric, movement and neurodegenerative disorders. *Clin Psychopharmacol Neurosci Off Sci J Korean Coll Neuropsychopharmacol*. 2017;15(4):301-312.
5. Nugent SM, Morasco BJ, O'Neil ME, et al. The effects of cannabis among adults with chronic pain and an overview of general harms: a systematic review. *Ann Intern Med*. 2017;167(5):319-331.
6. Devinsky O, Cross JH, Laux L, et al. Trial of cannabidiol for drug-resistant seizures in the dravet syndrome. *N Engl J Med*. 2017;376(21):2011-2020.
7. Allan GM, Finley CR, Ton J, et al. Systematic review of systematic reviews for medical cannabinoids: pain, nausea and vomiting, spasticity, and harms. *Can Fam Physician Med Fam Can*. 2018;64(2):e78-e94.
8. Kelkar AH, Smith NA, Martial A, Moole H, Tarantino MD, Roberts JC. An outbreak of synthetic cannabinoid-associated coagulopathy in Illinois. *N Engl J Med*. 2018;379(13):1216-1223.
9. Stout SM, Cimino NM. Exogenous cannabinoids as substrates, inhibitors, and inducers of human drug metabolizing enzymes: a systematic review. *Drug Metab Rev*. 2014;46(1):86-95.
10. Hirota T, Eguchi S, Ieiri I. Impact of genetic polymorphisms in CYP2C9 and CYP2C19 on the pharmacokinetics of clinically used drugs. *Drug Metab Pharmacokinet*. 2013;28(1):28-37.
11. Grayson L, Vines B, Nichol K, Szaflarski JP, UAB CBD Program. An interaction between warfarin and cannabidiol, a case report. *Epilepsy Behav Case Rep*. 2018;9:10-11.
12. Yamaori S, Koeda K, Kushihara M, Hada Y, Yamamoto I, Watanabe K. Comparison in the in vitro inhibitory effects of major phytocannabinoids and polycyclic aromatic hydrocarbons contained in marijuana smoke on cytochrome P450 2C9 activity. *Drug Metab Pharmacokinet*. 2012;27(3):294-300.
13. Yamreudeewong W, Wong HK, Brausch LM, Pulley KR. Probable interaction between warfarin and marijuana smoking. *Ann Pharmacother*. 2009;43(7):1347-1353.
14. Zendulka O, Dovrtělová G, Nosková K, et al. Cannabinoids and Cytochrome P450 Interactions. *Curr Drug Metab*. 2016;17(3):206-226.
15. Karschner EL, Schwilke EW, Lowe RH, et al. Implications of plasma Delta9-tetrahydrocannabinol, 11-hydroxy-THC, and 11-nor-9-carboxy-THC concentrations in chronic cannabis smokers. *J Anal Toxicol*. 2009;33(8):469-477.
16. Benet LZ, Hoener B. Changes in plasma protein binding have little clinical relevance. *Clin Pharmacol Ther*. 2002;71(3):115-121.
17. Mega JL, Simon T. Pharmacology of antithrombotic drugs: an assessment of oral antiplatelet and anticoagulant treatments. *Lancet Lond Engl*. 2015;386(9990):281-291.
18. Zhu H-J, Wang J-S, Markowitz JS, et al. Characterization of P-glycoprotein inhibition by major cannabinoids from marijuana. *J Pharmacol Exp Ther*. 2006;317(2):850-857.

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