

Potential Drug Interactions Between Cannabinoids and Its Derivatives and Oral Anticoagulants

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Abstract

The increase use of cannabidiol containing products poses potential risks with high-alert medications such as oral anticoagulants. To review the use of cannabidiol and its' derivatives with oral anticoagulants, searches (2005-May 2020) were performed by PubMed, Google Scholar, and ClinicalTrials.gov. Articles were limited to English-language only. The results yielded 4 case reports evaluating the potential drug interactions between cannabinoids and its' derivatives and oral anticoagulants. These case reports show the potential for drug interactions when using warfarin and cannabidiol containing products. At time of publication, there were no published articles on drug interactions between cannabidiol and the direct oral anticoagulants. Further research is needed to conclude drug interactions are associated with an increased risk of bleeding or thromboembolic events in these patients.

Keywords

anticoagulants, alternative medicines, herbals, drug interactions

Introduction

The Hemp Farming Act of 2018 removed hemp, which is also known as *Cannabis sativa*, from the schedule I controlled substances category, allowing the sale and consumption of these products in the United States as long as the cannabis product contains less than 0.3% of delta-9-tetrahydrocannabinol (THC).¹ The THC component of cannabis is responsible for the psychoactive properties, whereas the cannabidiol (CBD) portion has shown anti-epileptic, anxiolytic, and antiemetic properties.² CBD is one of the most prevalent active ingredients found in marijuana.² As of May 2020, 12 states have legalized marijuana for recreational use and 34 have legalized marijuana for medicinal use.³ The increasing use of CBD, medicinally and recreationally, could potentially cause pharmacokinetic drug interactions, and these interactions need to be closely monitored in high risk populations such as those on oral anticoagulation therapies.

Oral anticoagulation therapies include warfarin and direct oral anticoagulants (DOAC) (apixaban, rivaroxaban, betrixaban, dabigatran, and edoxaban) which are approved for various indications such as stroke risk reduction, systemic embolism prevention in patients with nonvalvular atrial fibrillation, prophylaxis for venous thromboembolism, or treatment of deep vein thrombosis and pulmonary embolism.⁴⁻⁹ The Institute of Safe Medication Practices classifies anticoagulants as high alert medications due to their

likelihood to cause hospital admissions and extend hospital stays related to adverse events and drug interactions.¹⁰ Unlike the newer anticoagulants, warfarin requires International Normalized Ratio (INR) monitoring to achieve its narrow therapeutic index where a minor change in serum concentration could lead to serious adverse events.⁴

Oral anticoagulants require metabolism via the hepatic system for elimination with cytochrome (CYP) P450 enzymes playing a major role in the metabolism of most oral anticoagulants. Warfarin is predominantly metabolized by CYP3A4, CYP1A2, and CYP2C9.¹¹ Apixaban and rivaroxaban, are metabolized by CYP3A4.^{5,6} For example, apixaban recommends a 50% dosage reduction when administered with strong inhibitors of CYP3A4 due to an 1.5 to 2.0 fold increase in area under the curve (AUC).⁵ On the other hand, edoxaban, dabigatran, and betrixaban are not affected by CYP P450 enzymes.⁷⁻⁹ A summary of the oral anticoagulants' pharmacokinetic properties are located in Table 1.

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Table 1. Summary of Focused Characteristics of Oral Anticoagulants Related to Drug Interactions.^{4-9,12-14}

Drug	Warfarin	Rivaroxaban	Apixaban	Edoxaban	Betrixaban	Dabigatran
Target	Vitamin K epoxide reductase	Factor Xa	Factor Xa	Factor Xa	Factor Xa	Thrombin
Bioavailability %	100	>80	50	62	34	3-7
Protein binding %	99	92-95	87	55	60	35
Half-life	20-60 h	5-9 h	12 h	10-14 h	19-27 h	12-17 h
Major CYP enzymes*	CYP2C9, CYP1A2, and CYP3A4	CYP3A4	CYP3A4	Unlikely	Unlikely	Unlikely
Drug interactions	CYP2C9, CYP1A2, CYP3A4 inhibitors	CYP3A4 inhibitors, P-gp** inhibitors	CYP3A4 inhibitors, P-gp** inhibitors	P-gp** inhibitors	P-gp** inhibitors	P-gp** inhibitors/inducers
Renal elimination %	92 (but inactive)	66	27	50	11	80
Hepatic dosing adjustments	Not reported	Avoid in Child-Pugh class B and C	Child-Pugh class C: Not recommended	Child-Pugh class B and C: Not recommended	Not Reported: Not recommended in hepatic impairment	Child-Pugh Class C/Severe Impairment: Not recommended
Recommended dosage adjustments due to drug interactions	Patient specific	Avoid use with strong inducers and inhibitors of CYP3A4 and P-gp**	50% dosage reduction when administered with strong inhibitors of CYP3A4 due to an 1.5-2.0 fold increase in AUC.***	50% dose reduction when administered with P-gp** inhibitors that increase edoxaban exposure by ≥ 1.5 fold increase	50% dose reduction when administered with P-gp** inhibitors.	50% dose reduction when administered with P-gp** inhibitors and moderate renal impairment

*CYP = cytochrome P450 enzymes; **P-gp = P-glycoprotein; ***AUC = area under the curve.

As CBD and other containing cannabinoid products become more accessible for patients, increased concern about drug interactions become apparent; however little is known about their pharmacokinetics. Jiang et al¹⁵ conducted an in vitro study to identify the cytochrome P450 enzymes responsible for cannabidiol metabolism in humans. The researchers found that the formation of the major metabolites of cannabidiol, 6a-OH-, 6b-OH-, 7-OH-, and 4-OH-CBDs, are predominantly due to the hydroxylation by CYP3A4 and CYP2C19.¹⁵ Due to the concomitant metabolism through CYP3A4 with CBD and oral anticoagulants, increased bleeding or thromboembolism risk is of concern. This manuscript reviewed the recent literature related events associated with the potential drug interaction between oral anticoagulants and CBD or its derivatives.

Methods

A literature search was conducted between March and May 2020 utilizing PubMed, Google Scholar, and Clinical Trials databases. Search terms consisted of cannabidiol, cannabis, cannabinoids, marijuana, oral anticoagulants, DOACs,

rivaroxaban, apixaban, dabigatran, edoxaban, betrixaban, warfarin, and Factor Xa inhibitors. Search results were limited to 2005-May 2020 and human studies. Case reports, case series, retrospective cohorts, or clinical trials were evaluated for the interaction of oral anticoagulants and cannabinoids and its derivatives. The results outline 4 case reports that demonstrate clinically significant drug-drug interactions in patients on anticoagulation therapy and concurrently using cannabidiol products (Table 2).

Clinical Evidence

Case Report

Grayson et al¹⁶ reported a 44-year-old caucasian male whose epileptic events were initially controlled on mono-therapy, but have since returned. Finding the source of the seizure by invasive means was limited due to the concurrent use of warfarin; therefore, the patient was enrolled in an open-label program for use of cannabidiol in treatment-resistant epilepsy. Before entering the study, the patient's INR had been stable on warfarin 7.5 mg for the past 6 months with

Table 2. Summary of Case Reports with Warfarin.

Case report	Age (years)	Initial INR	How long patient was controlled on warfarin therapy	Amount of Cannabis consumed	Outcome (increase in inr, bleed, etc)
Grayson et al ¹⁶	44	2.0-2.6	6 mo	5 mg/kg/day and doubled every 2 wk	INR varied, but ultimately required a 30% dose reduction
Yamreudeewong et al ¹⁷	56	2.5-3.5	11 y	2-2.5 g/week of marijuana	INR increase: 10.4 and 11.55 and bleeding episodes
Damkier et al ¹⁸	27	2.5-3.5	Two separate 24-h leave	Unspecified; patient reported more than usual	INR 4.6 after the first 24-h leave and normal after the second 24-h leave
Hsu and Painter ¹⁹	35	1.8-2.6	8 y	Unspecified	INR 7.2

levels between 2.0 and 2.6 (goal INR: 2-3). The patient was then started on CBD 5 mg/kg/day divided twice daily, and doses were up-titrated in 5 mg/kg/day increments every 2 weeks. During the up-titration of CBD, the patient's INR increased in a non-linear manner (max INR 6.86). To maintain the INR level the warfarin dose was reduced to eventually a 30% lower dose from baseline. The patient did not experience any bleeding episodes, and adverse events such as seizure activity were not reported.

Case Report

Yamreudeewong et al¹⁷ reported a 56-year-old male with various comorbidities such as esophageal reflux, coronary artery disease, peripheral vascular disease, and seizure disorder. The patient was stable on warfarin therapy (goal INR 2.5-3.5) for 11 years for mechanical heart valve replacement while on several other medications. On 2 occasions the patient's INR elevated to above 10 and resulted in bleeding. Four weeks before the first incident, the patient's warfarin dose was increased from 4 mg/day to 5 mg/day due to a subtherapeutic INR (2.28). The patient's INR was in goal at his 2-week check up, but 5 days later he was admitted to the hospital with an INR of 10.41 and a diagnosis of an upper gastrointestinal bleed. The patient's INR was normalized by fresh frozen plasma and oral vitamin K administration. The patient was discharged on a warfarin dose of 3 mg/day and later increased to 3.25 mg/day based on an INR of 1.94. Six days after this dose increase, the patient was readmitted with a persistent nosebleed and increased bruising, and his INR was 11.55. The patient was given oral vitamin K at this hospital admission and INR value was 1.14 at discharge. To follow up with these bleeding episodes, the patient reported to be adherent to all medications and denied any changes in diet, alcohol consumption, medications, or herbal products. The patient did however report an increase in smoking habits from smoking marijuana 1 to 2 joints/week (0.25-0.5 g/week) to smoking marijuana 4 to 5 joints/week (2.0-2.5 g/week). After the patient stopped smoking marijuana, the patient's INR ranged from 1.08 to 4.40 on a warfarin dosage range of 2 to 4 mg daily during the time period without marijuana.

The patient did not experience INRs greater than 4.40 or significant bleeding episodes during the 9 months of weekly follow-up.

Case Report

Damkier et al¹⁸ reported a 27-year-old male who was hospitalized due to aortic valve endocarditis resulting from drug abuse. The patient was treated by a mechanical valve replacement and subsequently prescribed warfarin with a goal INR of 2.5 to 3.5. The patient was allowed a 24 hour leave from the hospital, and when the patient returned for a check-up, his INR increased to 4.6. The patient denied abusing drugs intravenously over the past months, but did admit to smoking cannabis more in past 24 hours than in the previous weeks. After the INR normalized, the patient was allowed another 24 hour leave. When the patient returned for a check-up, the patient's INR stayed within goal even though he admitted to smoking cannabis during this leave as well. The patient did not suffer any bleeding or adverse events.

Case Report

Hsu and Painter¹⁹ reported a 35 year-old male with a deep vein thrombosis, ST-segment elevation myocardial infarction, and attention-deficit/hyperactivity disorder (ADHD). The patient was stable on warfarin therapy for 8 years at a goal INR of 2 to 3 while taking many other medications. After 8 years of stable therapy, the patient was instructed to increase his warfarin dose due to subtherapeutic INR (1.6) as the patient reports an increase in vegetable intake. The patient was stable on this dose increase for 6 months until he presented with an INR of 7.2 without signs of bleeding. After interviewing the patient, he denied any diet, medication, or any other modifications, but he did report smoking and consuming cannabis for the past month per advice from his psychiatrist. The patient was instructed to hold 2 warfarin doses and start at his original warfarin dose before the dose increase and discontinue cannabis use. Four days after this change, the patients INR dropped to 1.2 and has remained between 3 and 4.

At the time of publication there were no published case reports on drug interactions between apixaban, rivaroxaban, edoxaban, dabigatran, betrixaban and cannabinoids and its derivatives.

Clinical Considerations

There is a possible drug interaction between warfarin and cannabidiol containing products which could be attributed to cytochrome P450 interactions, but further studies are needed to confirm a possible drug interaction between warfarin and cannabidiol. The reports by Grayson et al¹⁶ and Yamreudeewong et al¹⁷ describe 2 instances where the patients were stable on warfarin therapy but became unstable due to cannabidiol use. Although varying results between the 2 cases, the INR of both patients increased which did lead to a bleeding event in the Yamreudeewong et al¹⁷ case report. The report from Damkier et al¹⁸ showed an increase in INR but not consistently. Based on these 3 case reports, CBD containing products probably interfere with pharmacokinetics of warfarin resulting in an increased INR and possible increased bleeding risk.

The mechanism of inhibition of warfarin metabolism leading to an increase in bleeding risk is still unknown. One proposed mechanism of this drug interaction could be due to inhibition of the CYP3A4 and CYP2C9 enzyme that is responsible for the metabolism of warfarin.⁴ Warfarin is a racemic mixture of R-warfarin which is metabolized predominantly by CYP3A4 and CYP1A2, and S-warfarin (more active) is metabolized predominantly by CYP2C9.¹¹ Inhibition of the metabolism of the S- and R-isoform of warfarin via cytochrome P450 enzymes leads to a decrease in clearance of warfarin and increased levels in the body which increases bleeding risk. Yamaori et al²⁰ performed an in-vitro study investigating the in-vitro effect of THC, CBD, and cannabidiol on CYP2C9 inhibition. The researchers found that these compounds found in marijuana smoke does inhibit the CYP2C9 metabolism of R- and S-warfarin.²⁰ Mentioned previously, Jiang et al¹⁵ found that major metabolites of CBD undergo hydroxylation by CYP3A4 and CYP2C19, which would potentially change R-warfarin metabolism and lead to an increased bleeding risk. The proposed theory of interaction of cannabis-based compounds on CYP enzymes maybe concentration dependent with acute cannabis intake,²¹ whereas chronic cannabis-based product use maybe more of a biphasic interaction.²² Another theory behind this drug interaction is protein binding displacement by THC. THC and its metabolite, THC-COOH, are 95% to 99% protein bound.² Warfarin is also extensively protein bound (99%)¹²; therefore, when THC is introduced, warfarin can be displaced from the proteins which leads to an increase in free warfarin in the plasma.

Case reports regarding drug interactions between CBD and DOACs have not been published at this time, but there could be a potential drug interaction due to

the pharmacokinetics of CBD and its derivatives. One mechanism that has potential for a drug interaction involves the P-glycoprotein (P-gp) efflux system. Holland et al²³ conducted an in vitro study looked at the effect of cannabinoids on P-gp inhibition. P-gp is an efflux system that pumps medications out of cells for subsequent elimination.²³ The researchers found that prolonged 72 hours of cannabinoid exposure can decrease P-gp expression.^{23,24} All of the DOACs are substrates of the P-glycoprotein efflux system; therefore, if used concomitantly with prolonged cannabinoid exposure, there will be decreased elimination of the DOACs and increased plasma concentrations leading to a potential increase bleeding risk. Another proposed mechanism leading to a drug interaction would be by interference of the CYP450 enzyme. In addition to being P-gp substrates, apixaban and rivaroxaban are metabolized by CYP3A4 which is also responsible for CBD metabolism found in the Jiang et al¹⁵ study; therefore, CBD could potentially alter the metabolism of apixaban and rivaroxaban to a greater extent than the other DOACs leading to increased bleeding risk. As mentioned previously, THC and its metabolites are 95% to 99% protein-bound which could additionally cause a drug interaction between CBD and its derivatives and DOACs.² Rivaroxaban and apixaban are the highest protein-bound, followed by betrixaban, edoxaban, and dabigatran; therefore, it can be hypothesized that rivaroxaban levels would increase more than the other DOACs when given with THC-containing products due to displacement of protein binding and subsequent increase in free drug.

Conclusion

Further research is needed to conclude the drug interactions are associated with an increased risk of bleeding or thromboembolic events in these patients. Based on the potential risk and limited research, patients should use caution, and possible avoid, using cannabidiol and its derivatives with oral anticoagulants. These case reports outline a potential pharmacokinetic interaction between cannabidiol and its derivatives with oral anticoagulants. Education about the potential risk becomes paramount for patients and health care providers in preventing avoidable risk with cannabidiol products and oral anticoagulants.

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