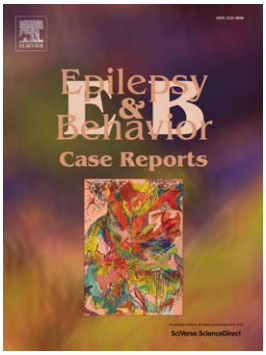

An Interaction between warfarin and cannabidiol, a case report

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Grayson, Leslie; Vines, Brannon; Nichol, Kate; Szaflarski, Jerzy P for the UAB CBD Program

1. Introduction

The use of cannabis products for the treatment of epilepsy and other chronic diseases is growing rapidly [1, 2]. Cannabis products include any pharmaceutical or artisanal derivatives of the cannabis plant [2]. One such agent is cannabidiol (CBD), one of the phytocannabinoids frequently used by patients with seizures. Current data regarding interactions between CBD and other pharmaceuticals are primarily limited to anti-seizure drugs [3,4]. This case report observes a clinically significant interaction between pharmaceutical grade cannabidiol (Epidiolex®; Greenwich Biosciences, Inc.) and warfarin, one of the most widely used oral anticoagulants.

2. Case Report

A 44-year-old Caucasian male with Marfan Syndrome, mechanical mitral valve replacement, warfarin therapy, and post-stroke epilepsy was enrolled in the University of Alabama at Birmingham open-label program for compassionate use of cannabidiol for the management of treatment-resistant epilepsy (NCT02700412). His seizures began at age 27 concurrent with diagnosis of stroke during the post-operative period from cardiac surgery. Despite initial control of seizures on monotherapy, events returned in 2011 prompting adjustment of anti-seizure medications and eventual consideration of epilepsy surgery. Following video EEG monitoring, he was determined to be a poor surgical candidate due to non-localized seizure onset. Additionally, the need for anticoagulation due to mechanical valve limited more invasive testing for localization of seizure focus as well as posed a challenge for completion of any surgical resection. He was subsequently referred to the UAB CBD program.

At the time of study enrolment, the patient was taking lamotrigine 400mg and levetiracetam 1500 mg, both twice daily. He was also taking warfarin 7.5 mg daily with a goal International Normalized Ratio (INR) of 2-3. Prior to study entry, his INR had been stable for at least 6 months with levels ranging from 2.0 to 2.6 (Figure 1). At the initial study visit, his baseline INR was obtained and he was placed on the starting dose of CBD at 5mg/kg/day divided twice daily. Per study protocol (www.uab.edu/cbd) CBD dose was increased in 5mg/kg/day increments every two weeks.

With up-titration of CBD oil, a non-linear increase in the INR was noted (Table 1, Figure 1). Warfarin dosage adjustments were made by primary care physician in effort to maintain an INR within his therapeutic range. At the most recent study visit his warfarin dose had been reduced by approximately 30%. The patient was followed clinically without bleeding complications.

3. Discussion

Despite the emergence of novel oral anticoagulants, warfarin continues to be the most commonly used oral anticoagulant worldwide [5]. A potent inhibitor of vitamin K epoxide reductase complex, warfarin functions by disrupting the production of vitamin-K-dependent clotting factors [6]. The drug is comprised of R and S stereoisomers with S-warfarin being the