United States Patent	12383567
Kind Code	B2
Date of Patent	August 12, 2025
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Use of cannabinoids in the treatment of epilepsy

Abstract

The present invention relates to the use of cannabidiol (CBD) in the treatment of patients with childhood-onset epilepsy who are concurrently taking immunosuppressant drugs. In particular the immunosuppressant drug is a calcineurin inhibitor. More particularly the immunosuppressant drug is tacrolimus. Where the CBD is used in combination with an immunosuppressant drug, caution should be taken. For example, the dose of either the CBD and/or the immunosuppressant drug may be required to be reduced. Moreover, the patient may need to be monitored for side effects of said drug-drug interaction. Preferably the CBD used is in the form of a highly purified extract of cannabis such that the CBD is present at greater than 98% of the total extract (w/w) and the other components of the extract are characterised. In particular the cannabinoid tetrahydrocannabinol (THC) has been substantially removed, to a level of not more than 0.15% (w/w) and the propyl analogue of CBD, cannabidivarin, (CBDV) is present in amounts of up to 1%. Alternatively, the CBD may be a synthetically produced CBD.

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Family ID: **1000008748692**

Appl. No.: **16/768241**

Filed (or PCT Filed): **November 30, 2018**

PCT No.: **PCT/GB2018/053483**

PCT Pub. No.: **WO2019/106386**

PCT Pub. Date: June 06, 2019

Prior Publication Data

Document Identifier	Publication Date
US 20210177773 A1	Jun. 17, 2021

Foreign Application Priority Data

GB	1720020	Dec. 01, 2017

Publication Classification

Int. Cl.: **A61K31/05** (20060101); **A61K31/00** (20060101); **A61K36/185** (20060101); **A61P25/10** (20060101); **A61P25/12** (20060101); A61K31/436 (20060101)

U.S. Cl.:

CPC **A61K31/658** (20230501); **A61K36/185** (20130101); **A61P25/10** (20180101); **A61P25/12** (20180101); A61K31/436 (20130101)

Field of Classification Search

CPC: A61K (31/05); A61K (31/436); A61K (31/02); A61K (2300/00)

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Background/Summary

CROSS-REFERENCE TO RELATED APPLICATIONS

(1) This application claims the benefit of International PCT Application No. PCT/GB2018/053483, filed Nov. 30, 2018; and Great Britain Application No. 1720020.5, filed Dec. 1, 2017; all of which are incorporated herein by reference to their entirety.

FIELD OF THE INVENTION

(2) The present invention relates to the use of cannabidiol (CBD) in the treatment of patients with childhood-onset epilepsy who are concurrently taking immunosuppressant drugs.

(3) In particular the immunosuppressant drug is a calcineurin inhibitor. More particularly the immunosuppressant drug is tacrolimus.

(4) Where the CBD is used in combination with an immunosuppressant drug, caution should be taken. For example, the dose of either the CBD and/or the immunosuppressant drug may be required to be reduced. Moreover, the patient may need to be monitored for side effects of said drug-drug interaction.

(5) Preferably the CBD used is in the form of a highly purified extract of cannabis such that the CBD is present at greater than 98% of the total extract (w/w) and the other components of the extract are characterised. In particular the cannabinoid tetrahydrocannabinol (THC) has been substantially removed, to a level of not more than 0.15% (w/w) and the propyl analogue of CBD, cannabidivarin, (CBDV) is present in amounts of up to 1%. Alternatively, the CBD may be a synthetically produced CBD.

BACKGROUND TO THE INVENTION

(6) Epilepsy occurs in approximately 1% of the population worldwide, (Thurman et al., 2011) of which 70% are able to adequately control their symptoms with the available existing anti-epileptic drugs (AEDs). However, 30% of this patient group, (Eadie et al., 2012), are unable to obtain seizure freedom from the AED that are available and as such are termed as suffering from intractable or "treatment-resistant epilepsy" (TRE).

(7) Intractable or treatment-resistant epilepsy was defined in 2009 by the International League Against Epilepsy (ILAE) as "failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom" (Kwan et al., 2009).

(8) Individuals who develop epilepsy during the first few years of life are often difficult to treat and as such are often termed treatment-resistant. Children who undergo frequent seizures in childhood are often left with neurological damage which can cause cognitive, behavioral and motor delays.

(9) Childhood-onset epilepsy is a relatively common neurological disorder in children and young adults with a prevalence of approximately 700 per 100,000. This is twice the number of epileptic adults per population.

(10) When a child or young adult presents with a seizure, investigations are normally undertaken in order to investigate the cause. Childhood epilepsy can be caused by many different syndromes and genetic mutations and as such diagnosis for these children may take some time.

(11) The main symptom of epilepsy is repeated seizures. In order to determine the type of epilepsy or the epileptic syndrome that a patient is suffering from, an investigation into the type of seizures that the patient is experiencing is undertaken. Clinical observations and electroencephalography (EEG) tests are conducted and the type(s) of seizures are classified according to the ILAE classification described below.

(12) The International classification of seizure types proposed by the ILAE was adopted in 1981 and a revised proposal was published by the ILAE

in 2010 and has not yet superseded the 1981 classification. The 2010 proposal for revised terminology includes the proposed changes to replace the terminology of partial with focal. In addition, the term “simple partial seizure” has been replaced by the term “focal seizure where awareness/responsiveness is not impaired” and the term “complex partial seizure” has been replaced by the term “focal seizure where awareness/consciousness is impaired”.
(13) Generalised seizures, where the seizure arises within and rapidly engages bilaterally distributed networks, can be split into six subtypes: Tonic-Clonic (grand mal) seizures; Absence (petit mal) Seizures; Clonic Seizures; Tonic Seizures; Atonic Seizures and Myoclonic Seizures.
(14) Focal (partial) seizures where the seizure originates within networks limited to only one hemisphere, are also split into sub-categories. Here the seizure is characterized according to one or more features of the seizure, including aura, motor, autonomic and awareness/responsiveness. Where a seizure begins as a localized seizure and rapidly evolves to be distributed within bilateral networks this seizure is known as a Bilateral convulsive seizure, which is the proposed terminology to replace Secondary Generalised Seizures (generalized seizures that have evolved from focal seizures and are no longer remain localized).
(15) Epileptic syndromes often present with many different types of seizure and identifying the types of seizure that a patient is suffering from is important as many of the standard AEDs are targeted to treat or are only effective against a given seizure type/sub-type.
(16) One such childhood epilepsy syndrome is Lennox-Gastaut syndrome (LGS). LGS is a severe form of epilepsy, where seizures usually begin before the age of 4. Seizure types, which vary among patients, include tonic (stiffening of the body, upward deviation of the eyes, dilation of the pupils, and altered respiratory patterns), atonic (brief loss of muscle tone and consciousness, causing abrupt falls), atypical absence (staring spells), and myoclonic (sudden muscle jerks). There may be periods of frequent seizures mixed with brief, relatively seizure-free periods.
(17) Seizures in LGS are often described as “drop seizures”. Such drop seizures are defined as an attack or spell (atonic, tonic or tonic-clonic) involving the entire body, trunk or head that led or could have led to a fall, injury, slumping in a chair or hitting the patient's head on a surface.
(18) Most patients with LGS experience some degree of impaired intellectual functioning or information processing, along with developmental delays, and behavioural disturbances.
(19) LGS can be caused by brain malformations, perinatal asphyxia, severe head injury, central nervous system infection and inherited degenerative or metabolic conditions. In 30-35% of cases, no cause can be found.
(20) The first line treatment for drop seizures, including the treatment of drop seizures in patients with LGS, usually comprises a broad-spectrum AED, such as sodium valproate often in combination with rufinamide or lamotrigine. Other AEDs that may be considered include felbamate, clobazam and topiramate.
(21) AEDs such as carbamezapine, gabapentin, oxcarbazepine, pregabalin, tiagabineor and vigabatrin are contra-indicated in drop seizures.
(22) Common AEDs defined by their mechanisms of action are described in the following tables:
(23) TABLE-US-00001 TABLE 1 Examples of narrow spectrum AEDs Narrow-spectrum AED Mechanism Indication Phenytoin Sodium channel Complex partial Tonic-clonic Phenobarbital GABA/Calcium Partial seizures channel Tonic-clonic Carbamazepine Sodium channel Partial seizures Tonic-clonic Mixed seizures Oxcarbazepine Sodium channel Partial seizures Tonic-clonic Mixed seizures Gabapentin Calcium channel Partial seizures Mixed seizures Pregabalin Calcium channel Adjunct therapy for partial seizures with or without secondary generalisation Lacosamide Sodium channel Adjunct therapy for partial seizures Vigabatrin GABA Secondarily generalized tonic-clonic seizures Partial seizures Infantile spasms due to Wes tsyndrome
(24) TABLE-US-00002 TABLE 2 Examples of broad spectrum AEDs Broad- spectrum AED Mechanism Indication Valproic acid GABA/ First-line treatment for tonic- Sodium channel clonic seizures, absence seizures and myoclonic seizures Second-line treatment for partial seizures and infantile spasms. Intravenous use in status epilepticus Lamotrigine Sodium channel Partial seizures Tonic-clonic Seizures associated with Lennox-Gastaut syndrome Ethosuximide Calcium channel Absence seizures Topiramate GABA/ Seizures associated with Sodium channel Lennox-Gastaut syndrome Zonisamide GABA/Calcium/ Adjunctive therapy in adults Sodium channel with partial-onset seizures Infantile spasm Mixed seizure Lennox-Gastaut syndrome Myoclonic Generalised tonic-clonic seizure Levetiracetam Calcium channel Partial seizures Adjunctive therapy for partial, myoclonic and tonic-clonic seizures Clonazepam GABA Typical and atypical absences Infantile myoclonic Myoclonic seizures Akinetic seizures Rufinamide Sodium channel Adjunctive treatment of partial seizures associated with Lennox-Gastaut syndrome
(25) TABLE-US-00003 TABLE 3 Examples of AEDs used specifically in childhood epilepsy AED Mechanism Indication Clobazam GABA Adjunctive therapy in complex partial seizures Status epilepticus Myoclonic Myoclonic-absent Simple partial Complex partial Absence seizures Lennox-Gastaut syndrome Stiripentol GABA Severe myoclonic epilepsy in infancy (Dravet syndrome)
(26) The present invention describes surprising data from a patient that was taking an immunosuppressant drug, tacrolimus during the open label extension part of a clinical trial into childhood-onset epilepsy.
(27) It was noted that there was a significant increase in the subjects blood urea nitrogen (BUN) and serum creatine levels during the time the subject was taking CBD. Such an interaction is unexpected and as such the use of these drugs in combination should be done with close monitoring of the patient.

BRIEF SUMMARY OF THE DISCLOSURE

(28) In accordance with a first aspect of the present invention there is provided cannabidiol (CBD) for use in the treatment of childhood-onset epilepsy in patients who are concurrently taking an immunosuppressant drug characterised in that the blood levels of the immunosuppressant drug and associated markers are monitored to ensure the levels do not become toxic.
(29) Preferably the dose of CBD is lowered. Alternatively the dose of the immunosuppressant drug is lowered.
(30) Preferably the immunosuppressant drug is tacrolimus.
(31) Preferably the CBD is in the form of a highly purified extract of cannabis which comprises at least 98% (w/w) CBD which comprises less than 0.15% THC and up to 1% CBDV. Alternatively, the CBD is present as a synthetic compound.
(32) Preferably the dose of CBD is below 50 mg/kg/day. More preferably the dose of CBD is greater than 20 mg/kg/day.
(33) Preferably the childhood-onset epilepsy is: Lennox-Gastaut Syndrome; Myoclonic Absence Epilepsy; Tuberous Sclerosis Complex; Dravet Syndrome; Doose Syndrome; Jeavons Syndrome; CDKL5; Dup15q; Neuronal ceroid lipofuscinoses (NCL) and brain abnormalities.
(34) In accordance with a second aspect of the present invention there is provided a method of treating childhood-onset epilepsy in an individual in need thereof, comprising administering to the patient a therapeutically effective amount of cannabidiol with caution, wherein the individual is taking an immunosuppressant drug concurrently.
(35) Preferably the said caution comprises lowering the dose of cannabidiol. Alternatively the said caution comprises lowering the dose of the immunosuppressant drug.
(36) Preferably the immunosuppressant drug is tacrolimus.
(37) Preferably the said caution comprises monitoring said individual for side effects.
(38) More preferably the said caution further comprises discontinuing cannabidiol if said side effects are observed.
(39) More preferably still the said caution comprises advising said individual of side effects from said concurrent therapy.
(40) Preferably the individual is a human.

Definitions

(41) Definitions of some of the terms used to describe the invention are detailed below:
(42) The cannabinoids described in the present application are listed below along with their standard abbreviations.
(43) TABLE-US-00004 TABLE 4 Cannabinoids and their abbreviations CBD Cannabidiol embedded image CBDA Cannabidiolic acid

embedded image CBDV Cannabidivarin embedded image CBDVA Cannabidivarinic acid embedded image THC Tetrahydrocannabinol
embedded image
(44) The table above is not exhaustive and merely details the cannabinoids which are identified in the present application for reference. So far over 60 different cannabinoids have been identified and these cannabinoids can be split into different groups as follows: Phytocannabinoids; Endocannabinoids and Synthetic cannabinoids (which may be novel cannabinoids or synthetically produced phytocannabinoids or endocannabinoids).
(45) “Phytocannabinoids” are cannabinoids that originate from nature and can be found in the cannabis plant. The phytocannabinoids can be isolated from plants to produce a highly purified extract or can be reproduced synthetically.
(46) “Highly purified cannabinoid extracts” are defined as cannabinoids that have been extracted from the cannabis plant and purified to the extent that other cannabinoids and non-cannabinoid components that are co-extracted with the cannabinoids have been substantially removed, such that the highly purified cannabinoid is greater than or equal to 98% (w/w) pure.
(47) “Synthetic cannabinoids” are compounds that have a cannabinoid or cannabinoid-like structure and are manufactured using chemical means rather than by the plant.
(48) Phytocannabinoids can be obtained as either the neutral (decarboxylated form) or the carboxylic acid form depending on the method used to extract the cannabinoids. For example, it is known that heating the carboxylic acid form will cause most of the carboxylic acid form to decarboxylate into the neutral form.
(49) “Treatment-resistant epilepsy” (TRE) or “intractable epilepsy” is defined as per the ILAE guidance of 2009 as epilepsy that is not adequately controlled by trials of one or more AED.
(50) “Childhood epilepsy” refers to the many different syndromes and genetic mutations that can occur to cause epilepsy in childhood. Examples of some of these are as follows: Dravet Syndrome; Myoclonic-Absence Epilepsy; Lennox-Gastaut syndrome; Generalized Epilepsy of unknown origin; CDKL5 mutation; Aicardi syndrome; tuberous sclerosis complex; bilateral polymicrogyria; Dup15q; SNAP25; and febrile infection related epilepsy syndrome (FIRES); benign rolandic epilepsy; juvenile myoclonic epilepsy; infantile spasm (West syndrome); and Landau-Kleffner syndrome. The list above is non-exhaustive as many different childhood epilepsies exist.

Description

BRIEF DESCRIPTION OF THE DRAWINGS
(1) Embodiments of the invention are further described hereinafter with reference to the accompanying drawings, in which
(2) FIG. **1** shows the Daily doses of Tacrolimus (Tac) and Cannabidiol (CBD) during study period; and
(3) FIG. **2** shows the Tacrolimus dose normalised trough concentration.
DETAILED DESCRIPTION
(4) Preparation of Highly Purified CBD Extract
(5) The following describes the production of the highly-purified (>98% w/w) cannabidiol extract which has a known and constant composition was used in the Examples below.
(6) In summary the drug substance used is a liquid carbon dioxide extract of high-CBD containing chemotypes of *Cannabis sativa* L. which had been further purified by a solvent crystallization method to yield CBD. The crystallisation process specifically removes other cannabinoids and plant components to yield greater than 98% CBD. Although the CBD is highly purified because it is produced from a cannabis plant rather than synthetically there is a small number of other cannabinoids which are co-produced and co-extracted with the CBD. Details of these cannabinoids and the quantities in which they are present in the medication are as described in Table 5 below.
(7) TABLE-US-00005 TABLE 5 Composition of highly purified CBD extract Cannabinoid Concentration CBD >98% w/w CBDA NMT 0.15% w/w CBDV NMT 1.0% w/w Δ.sup.9 THC NMT 0.15% w/w CBD-04 NMT 0.5% w/w >—greater than NMT—not more than
Example 1: Drug-Drug Interaction Between Cannabidiol (CBD) and Immunosuppressants
(8) The patient was a 33 year old female with refractory epilepsy receiving the immunosuppressant drug tacrolimus for interstitial nephritis.
(9) The patient had been stable on tacrolimus at a dose of 5 mg twice per day for a year prior to entry into a clinical trial on the use of CBD to treat childhood-onset epilepsy. At the time of entry into the study her blood level of tacrolimus was between 3.9 and 8.4 ng/mL. She also had a baseline Serum Creatine level of 1.16 mg/dL.
(10) The patient was initially randomized to the sesame oil placebo arm of the trial, during this phase there was no change in the levels of tacrolimus or serum creatine.
(11) However, when the patient entered into the open label phase of the study and began receiving CBD she showed signs of tacrolimus toxicity with a serum creatine level of 2.4 mg/dL.
(12) The dose of tacrolimus was reduced repeatedly while receiving CBD as described in FIG. **1**. A dose of 0.5 mg twice per day (a 10-fold reduction) was finally reached. At this dose the tacrolimus concentrations were normalised as shown in FIG. **2**.
(13) Such a finding delineates an important concern for the transplant community with the increasing legalization of marijuana. This drug-drug interaction may have implications in solid organ transplant recipients which are not correctly monitored over the course of their treatment.
CONCLUSIONS
(14) Patients that are taking immunosuppressant drugs such as tacrolimus should be carefully monitored over the course of their treatment with CBD to ensure toxicity does not occur.

Claims

1. A method of treating childhood-onset epilepsy in a patient who is concurrently taking tacrolimus, comprising: administering to the patient a drug substance comprising at least 98% (w/w) cannabidiol (CBD) and less than 0.15% (w/w) THC; detecting toxic blood levels of tacrolimus or one or more associated markers; and reducing the dose of tacrolimus to no more than 5 mg per day.
2. The method according to claim 1, wherein the dose of CBD is lowered.
3. The method according to claim 1, wherein the drug substance is in the form of a highly purified extract of cannabis which comprises at least 98% (w/w) CBD.
4. The method according to claim 1, wherein the CBD is present as a synthetic compound.
5. The method according to claim 3, wherein the extract further comprises up to 1% (w/w) CBDV.
6. The method according to claim 1, wherein the dose of CBD is below 50 mg/kg/day.
7. The method according to claim 1, wherein the dose of CBD is greater than 20 mg/kg/day.
8. The method according to claim 1, wherein the childhood-onset epilepsy is: Lennox-Gastaut Syndrome; Myoclonic Absence Epilepsy; Tuberous Sclerosis Complex; Dravet Syndrome; Doose Syndrome; Jeavons Syndrome; CDKL5; Dup15q; Neuronal ceroid lipofuscinoses (NCL) or brain abnormalities.
9. The method of claim 1, wherein the associated markers comprise serum creatine.

10. The method of claim 9, wherein the serum creatine become toxic when the blood levels are 2.4 mg/dL or more.
11. The method of claim 1, wherein the dose of tacrolimus is reduced by up to 10-fold.
12. The method of claim 1, wherein the dose of tacrolimus is reduced to 0.5 mg twice per day.