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(54) Titre : COMPOSITIONS ET PROCEDES DE TRAITEMENT DE TROUBLES EPILEPTIQUES
(54) Title: COMPOSITION AND METHOD FOR TREATING SEIZURE DISORDERS

(57) Abrégé/Abstract:
The invention provides compositions and methods for treating seizure disorders such as epilepsy in humans and animals using, in a first embodiment, the combination of (i) an effective amount of a barbiturate drug, such as phenobarbital or primidone, which solely enhances GABAergic inhibition in a patient suffering a seizure disorder; and (ii) phytocannabinoid cannabidiol (CBD) in a dosage amount sufficient to overcome the hepatic metabolic effect stimulated by the barbiturate drug and provide bioavailable CBD to the patient in clinically efficacious amounts.

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(54) **Title**: COMPOSITION AND METHOD FOR TREATING SEIZURE DISORDERS

(57) **Abstract**: The invention provides compositions and methods for treating seizure disorders such as epilepsy in humans and animals using, in a first embodiment, the combination of (i) an effective amount of a barbiturate drug, such as phenobarbital or primidone, which solely enhances GABAergic inhibition in a patient suffering a seizure disorder; and (ii) phytocannabinoid cannabidiol (CBD) in a dosage amount sufficient to overcome the hepatic metabolic effect stimulated by the barbiturate drug and provide bioavailable CBD to the patient in clinically efficacious amounts.

COMPOSITION AND METHOD FOR TREATING SEIZURE DISORDERS

Ramachandra MUKUNDA
Ranga Chelva KRISHNA

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims priority on prior U.S. Provisional Application S.N. 62/107,432, filed January 25, 2015, which is hereby incorporated herein in its entirety by reference.

FIELD OF THE INVENTION

[0002] This invention relates to compositions and methods for treating seizure disorders such as epilepsy in humans and animals (mammals) using phytocannabinoid cannabidiol (CBD) and a barbiturate drug which solely enhances GABAergic inhibition such as phenobarbital or primidone.

BACKGROUND OF THE INVENTION

[0003] Published Patent App. US 2013/0296398 reports that the combination of phytocannabinoid cannabidiol (CBD) with an anti-epileptic

barbiturate drug, which solely enhances GABAergic inhibition, such as phenobarbital, appears not to provide any benefits in treating epilepsy when tested in a pilocarpine model.

[0004] Charalambous et al in BMC Veterinary Research 2014, 10:257 report on studies done to treat canine epilepsy using phenobarbital and other drugs, but baseline variations, study designs, and sources of bias preclude definitive recommendations.

SUMMARY OF THE INVENTION

[0005] The invention provides compositions and methods for treating seizure disorders such as epilepsy in humans and animals using, in a first embodiment, the combination of (i) an effective amount of a barbiturate drug, such as phenobarbital or primidone, which solely enhances GABAergic inhibition in a patient suffering a seizure disorder; and (ii) phytocannabinoid cannabidiol (CBD) in a dosage amount sufficient to overcome the hepatic metabolic effect stimulated by the barbiturate drug and provide bioavailable CBD to the patient in clinically efficacious amounts.

[0006] In a preferred embodiment, the drug combination includes a blocking compound, such as vitamin A, vitamin E, vitamin K, or the like

compounds, in an amount effective to inhibit the hepatic metabolic effect of the barbiturate drug, thereby increasing the amount of bioavailable CBD to the patient.

[0007] Patients who are subject to seizure disorders such as epilepsy are treated to control and reduce the frequency of seizures by administering the drug combinations described above in accordance with further details of the invention that are disclosed herein.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT(S) OF THE INVENTION

[0008] In treating epilepsy, drugs such as phenobarbital or primidone, act by enhancing the GABAnergeric central nervous system inhibition. GABA is an acronym for gamma-aminobutyric acid and a GABAeric drug is a chemical which directly modulates the GABA system in the human body or brain. However, such compounds induce the cytochrome P450 hepatic system and the hepatic CYP2C19 enzyme chain that can metabolize phytocannabinoid cannabidiol (CBD). Thus any anti-seizure benefit expected from CBD is neutralized when combined with a barbiturate such as phenobarbital or primidone.

[0009] It has been found that these drawbacks can be overcome in two ways. First, by using a higher dose of CBD sufficient to inhibit and overcome the hepatic metabolic enhancement effect of a barbiturate and thus provide bioavailable CBD to a patient. And, secondly, by using a blocking compound in an amount effective to inhibit the hepatic metabolic effect of a barbiturate drug which in turn increases the amount of bioavailable CBD to the patient. It is believed that blocking compounds such as vitamins A, E or K degrade or metabolize enzymes produced or whose actions are enhanced by barbiturate drugs and thus at least partially prevent the degradation of CBD by such enzymes. The use of a blocking compound has the unexpected benefit of being able to use a lower dose of the barbiturate drug with CBD yet obtain the desired anti-convulsant effect expected from the use of barbiturate drug alone.

[0010] Chemically, phenobarbital is 5-ethyl-5-phenylpyrimidine-2,4,6(1H,3H,5H)-trione. It is a known, long-lasting barbiturate for treating epilepsy. Another barbiturate that can be used with the invention is primidone, chemically 5-ethyl-5-phenyl-hexahydropyrimidine-4,6-dione. Primidone is available under the brandname Mysoline.

[0011] CBD can be used in its pure form or as a mixture of compounds that result from extracting cannabis plants. Such mixtures

contain CBD, THC or tetrahydrocannabinol (which in turn is a mixture comprising 9-tetrahydrocannabinol (delta-9 THC), 8-tetrahydrocannabinol (delta-8 THC) and 9-THC Acid), Cannabinol (CBN), Cannabichromene (CBC), Cannabigerol (CBG), terpenoids and flavonoids.

[0012] The preferred CBD mixture is extracted from a Cannabis Indica, the composition of which is known. The use of CBD from Cannabis Indica, which can contain up to 50% THC (based on the amount of CBD), is preferred. See, for example, Qureshi et al, World Applied Sciences Journal 19 (7): 918-923, 2012 ISSN 1818-4952, IDOSI Publications, 2012, disclosing an Indicia extraction containing 54% CBD and 24% THC. Preferred mixtures for use in the invention contain at least 50% by weight CBD wherein the weight ratio of CBD to THC is at least 2:1, preferably at least 3:1.

[0013] The preferred CBD mixture is extracted from a Cannabis Indica dominant strain using high pressure and carbon dioxide as a solvent in a 1500-20L subcritical/supercritical CO_2 system made by Apeks Super Critical Systems, 14381 Blamer Rd., Johnstown, Ohio, 43031. See http://www.apekssupercritical.com/botanical-extraction-systems/

[0014] Apeks Systems use valveless expansion technology with no constrictions or regulating valves to cause clogging in the system between the extraction vessel and the CO_2 expansion separator. Flow of liquid CO_2 and dissolved oil travels from the extraction vessel into the separator, and the oil is separated from the CO_2 in the separator/collection vessel. CO_2 is recycled during the extraction process and recovered and regenerative heat capture methods are used to increase efficiency.

[0015] A further process using solvents can be used to remove THC from the mixture leaving either pure CBD or so-called "Organic CBD" containing CBD, CBN, CBC, CBG CBN, terpenoids and flavonoids. The use of essentially THC-free Organic CBD from Cannabis Indica is more preferred.

[0016] Another source of CBD essentially free of THC is the CBD mixture obtained by extracting hempseed oil. See Leizer et al, J. Nutraceuticals, Functional and Medical Foods, Vol. 2(4) 2000, The Haworth Press, Inc. Elixinol (D&G Health LLC) is a predominantly CBD product extracted from hempseed oil that contains trace amounts of THC.

[0017] The preferred blocking compound is vitamin A which is a group of unsaturated compounds that includes retinol, retinal, retinoid acid, beta-carotene and other provitamin A carotenoids.

[0018] Other useful blocking compounds that inhibit the hepatic metabolic effect of barbiturates include vitamins E and K. Vitamin A is preferred because it is less likely to interact with other medications.

[0019] Vitamin E is commonly gamma-tocopherol from corn or soybean oil, or alpha-tocopherol from wheat germ oil or sunflower and safflower oils. Vitamin K is synthesized by plants and is a family 2-methyl-1,4-naphthoquinone (3-) derivatives.

[0020] Patients being treated for seizure disorders will receive a barbiturate drug, phenobarbital or primidone, in an amount to provide from about 15 to about 40 micrograms of the drug per milliliter of blood serum in a patient. To obtain these levels, the dosage amount of the barbiturate drug will be not greater that about 2 mg/kg of patient weight.

[0021] The dosage amount of CBD to be used with phenobarbital or primidone is from about 0.5 to about 1.0 mg/kg of patient weight. When used with phenobarbital or primidone and CBD, the dosage amount of a

blocking compound such as vitamin A will be not less than about 0.5 mg/kg of patient weight.

[0022] Candidates to be treated according to the invention will generally present with symptoms or signs associated with seizure disorders such as recurrent loss of consciousness, recurrent seizures and/or a prior diagnoses of medically refractory epilepsy. The invention is especially useful in treating patients who have had recurrent and/or poorly controlled seizures or epilepsy in spite of being treated with one or more know anticonvulsant drugs.

[0023] The expected response in patients treated according to the invention is a reduction in seizure intensity and/or frequency once a steady state of the active pharmaceutical components is achieved. Up to 14 or more days of treatment may be required before benefits can be achieved.

[0024] Patients with allergies, cardiac rhythm disturbances, metabolic syndrome or a history of Cannabis abuse are not candidates to be treated according to the invention.

[0025] Animals, especially dogs and cats, can be treated according to the invention. Seizures in dogs and cats are caused by abnormal brain

activity; they can to subtle or cause violent convulsions. Some seizures only occur once but repeated seizures require treatment to prevent larger areas of the brain from becoming affected. Dosage amounts and serum levels of drug are the same as disclosed above for human patients.

[0026] While this invention has been described as having preferred sequences, ranges, ratios, steps, order of steps, materials, structures, symbols, indicia, graphics, color scheme(s), shapes, configurations, features, components, or designs, it is understood that it is capable of further modifications, uses and/or adaptations of the invention following in general the principle of the invention, and including such departures from the present disclosure as those come within the known or customary practice in the art to which the invention pertains, and as may be applied to the central features hereinbefore set forth, and fall within the scope of the invention and of the limits of the claims appended hereto or presented later. The invention, therefore, is not limited to the preferred embodiment(s) shown/described herein.

AMENDED CLAIMS

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1. Composition for treating seizure disorders such as epilepsy comprising: (i) an effective amount of a barbiturate drug which solely enhances GABAergic inhibition in a patient suffering a seizure disorder; and (ii) phytocannabinoid cannabidiol (CBD) in a dosage amount sufficient to inhibit the hepatic metabolic effect of said barbiturate drug and provide bioavailable CBD to said patient.

2. Composition of claim 1 which includes a blocking compound in an amount effective to inhibit the hepatic metabolic effect of said barbiturate drug thereby increasing the amount of bioavailable CBD to said patient.

3. Composition of claim 2 wherein said compound is vitamin A.

4. Composition of claim 1 wherein the barbiturate drug is selected from the group consisting of phenobarbital and primidone.

5. Composition of claim 1 wherein CBD is extracted from Cannabis Indica.

6. Composition of claim 5 wherein CBD is essentially free of tetrahydrocannabinol (THC).

7. Composition of claim 4 wherein said barbiturate drug is used in an amount to provide from about 15 to about 40 micrograms of said drug per milliliter of blood serum in said patient.

8. Composition of claim 1 wherein the dosage amount of said barbiturate drug is not greater that about 2 mg/kg of patient weight.

9. Composition of claim 1 wherein the dosage amount of CBD is from about 0.5 to about 1.0 mg/kg of patient weight.

10. Composition of claim 3 wherein the dosage amount of vitamin A is not less than about 0.5 mg/kg of patient weight.

11. Composition for treating seizure disorders such as epilepsy comprising: (i) an effective amount of a barbiturate drug which solely enhances GABAergic inhibition in a patient suffering a seizure disorder; (ii) a blocking compound in an amount effective to inhibit the hepatic metabolic effect of said barbiturate drug; and (iii) phytocannabinoid cannabidiol (CBD) in a dosage amount sufficient to provide bioavailable CBD to said patient.

12. Composition of claim 11 wherein said blocking compound is vitamin A.

13. Composition of claim 11 wherein the barbiturate drug is selected from the group consisting of phenobarbital and primidone.

14. Composition of claim 11 wherein CBD is extracted from cannabis Indica or from cannabis Sativa.

15. Composition of claim 14 wherein CBD is free of tetrahydrocannabinol (THC).

16. Composition of claim 13 wherein said barbiturate drug is used in an amount to provide from about 15 to about 40 micrograms of said drug per milliliter of blood serum in said patient.

17. Composition of claim 16 wherein the dosage amount of said barbiturate drug is not greater that about 2 mg/kg of patient weight.

18. Composition of claim 11 wherein the dosage amount of CBD is from about 0.5 to about 1.0 mg/kg of patient weight.

19. Composition of claim 12 wherein the dosage amount of vitamin A is not less than about 0.5 mg/kg of patient weight.

20. Method for treating seizure disorders in mammals such as epilepsy comprising administering to a subject in need thereof a composition comprising: (i) an effective amount of a barbiturate drug which solely enhances GABAergic inhibition in said patient; and (ii) phytocannabinoid cannabidiol (CBD) in a dosage amount sufficient to overcome the inhibition effect of the hepatic metabolic effect of said barbiturate drug and provide bioavailable CBD to said patient.

21. Method for treating seizure disorders in mammals such as epilepsy comprising administering to a subject in need thereof a composition comprising: (i) an effective amount of a barbiturate drug which solely enhances GABAergic inhibition in a patient suffering a seizure disorder; (ii) a blocking compound in an amount effective to inhibit the hepatic metabolic enhancement effect of said barbiturate drug; and (iii) phytocannabinoid cannabidiol (CBD) in a dosage amount sufficient to provide bioavailable CBD to said patient.

22. Composition for treating seizure disorders such as epilepsy comprising: (i) an effective amount of a barbiturate drug which solely enhances GABAergic inhibition in a patient suffering a seizure disorder; (ii) phytocannabinoid cannabidiol (CBD) in a dosage amount sufficient to inhibit the hepatic metabolic effect of said barbiturate drug and provide bioavailable

CBD to said patient: and (iii) a blocking compound in an amount effective to inhibit the hepatic metabolic effect of said barbiturate drug thereby increasing the amount of bioavailable CBD to said patient.

23. Composition of claim 22 wherein said blocking compound is vitamin A.

24. Composition for treating seizure disorders such as epilepsy comprising: (i) an effective amount of a barbiturate drug which solely enhances GABAergic inhibition in a patient suffering a seizure disorder; (ii) phytocannabinoid cannabidiol (CBD) in a dosage amount sufficient to inhibit the hepatic metabolic effect of said barbiturate drug and provide bioavailable CBD to said patient: and (iii) vitamin A in an amount effective to inhibit the hepatic metabolic effect of said barbiturate drug thereby increasing the amount of bioavailable CBD to said patient.

25. Composition for treating seizure disorders such as epilepsy comprising: (i) an effective amount of a barbiturate drug which solely enhances GABAergic inhibition in a patient suffering a seizure disorder; (ii) vitamin A in an amount effective to inhibit the hepatic metabolic effect of said barbiturate drug; and (iii) phytocannabinoid cannabidiol (CBD) in a dosage amount sufficient to provide bioavailable CBD to said patient.

26. Composition of claim 25 wherein the dosage amount of vitamin A is not less than about 0.5 mg/kg of patient weight.

27. Method for treating seizure disorders in mammals such as epilepsy comprising administering to a subject in need thereof a composition comprising: (i) an effective amount of a barbiturate drug which solely enhances GABAergic inhibition in a patient suffering a seizure disorder; (ii) vitamin A in an amount effective to inhibit the hepatic metabolic effect of said barbiturate drug; and (iii) phytocannabinoid cannabidiol (CBD) in a dosage amount sufficient to provide bioavailable CBD to said patient.