METHODS OF TREATING EPILEPSY OR STATUS EPILEPTICUS

Claims of Priority

This application claims priority to U.S.S.N. 61/691,545, filed August 21, 2012 and U.S.S.N. 61/789,491, filed March 15, 2013, the entire contents of which are incorporated herein by reference.

Field of the Invention

The present invention generally relates to methods of treating epilepsy or status epilepticus by administering a neuroactive steroid.

Summary

In one aspect, the present invention refers to a method of preparing a formulation comprising allopregnanolone, said method comprising the step of high shear mixing an aqueous 5 mg/mL solution of allopregnanolone with 25% sulfo butyl ether beta-cyclodextrin solution.

Described herein are methods of treating epilepsy or status epilepticus.*e.g.,* convulsive status epilepticus, *e.g.,* early status epilepticus, established status epilepticus, refractory status epilepticus, super-refractory status epilepticus; non-convulsive status epilepticus, *e.g.,* generalized status epilepticus, complex partial status epilepticus; generalized periodic epileptiform discharges; periodic lateralized epileptiform discharges; a seizure, *e.g.,* acute repetitive seizures, cluster seizures, the method comprising administering to the subject a neuroactive steroid. In one embodiment, the present disclosure features a method of treating a subject having epilepsy or status epilepticus by administering in combination to the subject a neuroative steroid and a benzodiazepine. In some embodiments, the method further comprises administering at least one of the neuroative steroid or benzodiazepine parenterally (*e.g.,* intranasally, buccally, intravenously or intramuscularly, for example, intravenously or intramuscularly). In some embodiments, both the neuroative steroid and benzodiazepine are administered parenterally.

In some embodiments, the neuroative steroid and benzodiazepine are co-administered (*e.g.,* administered simultaneously). In some embodiments, the neuroative steroid and benzodiazepine are administered sequentially. In some embodiments, neuroative steroid and benzodiazepine are administered in a single dosage form.

When the agents described herein (*e.g.,* the neuroactive steroid and a benzodiazepine) are administered in combination, both of the agents should be present at dosage levels of between about 1 to 100%, and more preferably between about 5 to 95% of the dosage normally administered in a in the absence of the combination regimen. The agents may be administered separately, as part of a multiple dose regimen. Alternatively, the agents may be part of a single dosage form, mixed together with the compounds of this disclosure in a single composition.

In some embodiments, the neuroactive steroid is a progestin derivative, *e.g.,* allopregnanolone. In an embodiment, the neuroactive steroid is allopregnanolone.

In some embodiments, the neruroactive steroid, *e.g.,* alloprenanolone, is formulated for parenteral administration (*e.g.,* intranasally, buccally, intravenously or intramuscularly, for example, intravenously or intramuscularly).

In some embodiments, the neneuroactive steroid, *e.g.,* allopregnanolone, is administered in a composition comprising a cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex. a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®.

In some embodiments, the cyclodextrin is a β-cyclodextrin. In an embodiment, the cyclodextrin is a sulfo butyl ether β-cyclodextrin. In an embodiment, the cyclodextrin is CAPTISOL®. In some embodiments, the cyclodextrin is a β-cyclodextrin disclosed in U.S. Patent Nos. 5,874,418; 6,046,177; or 7,635,733, which are herein incorporated by reference.

In some embodiments, the neuroactive steroid is a progestin derivative, *e.g.,* allopregnanolone, and the cyclodextrin is a β-cyclodextrin. In an embodiment, the neuroactive steroid is allopregnanolone and the cyclodextrin is CAPTISOL®.

In some embodiments, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated for parenteral administration. In an embodiment, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition. In some embodiments, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising the neuroactive steroid at a concentration between 0.25-30mg/mL, 0.5-30mg/mL; 1-30mg/mL; 5-

30mg/mL, 10-30mg/mL; 15-30mg/mL, 0.25-20mg/mL; 0.5-20mg/mL; 1-20mg/mL, 0.5-20mg/mL; 1-20mg/mL, 5-20mg/mL, 10-20mg/mL, 0.25-15mg/mL, 0.5-15mg/mL; 0.5-10mg/mL; 1-15mg/mL, 1-10mg/mL; 1-5mg/mL; 5-15mg/mL; 5-10mg/mL; 10-15mg/mL; 1-10mg/mL; 2-8mg/mL; 2-7mg/mL; 3-5mg/mL; 5-15mg/mL; 7-12mg/mL; 7-10mg/mL; 8-9mg/mL; 3-5mg/mL; or 3-4mg/mL.

In some embodiments, the benzodiazepine is clonazepam, lorazepam, midazolam, or diazepam.

In some embodiments, the benzodiazepine is formulated for oral delivery. In some embodiments, the benzodiazepine is formulated for parenteral delivery (*e.g.,* intranasally, buccally, intravenously or intramuscularly, for example, intravenously or intramuscularly).

In some embodiments, both the neuroactive steroid and the benzodiazepine are formulated for parenteral delivery (*e.g.,* intranasally, buccally, intravenously or intramuscularly, for example, intravenously or intramuscularly).

In some embodiments, the neuroactive steroid such as allopregnanolone and benzodiazepine, when administered in combination, are administered in an amount sufficient to achieve burst suppression (*e.g.,* a predetermined burst suppression pattern, *e.g.,* inter-burst intervals of between 2-30 seconds; as measured by a method of neurophysiological monitoring, *e.g.,* EEG, CFM). In some embodiments, the neuroactive steroid such as allopregnanolone and benzodiazepine, when administered in combination is administered at a dose sufficient to achieve a predetermined burst suppression pattern, *e.g.,* inter-burst intervals of between 2-30 seconds, 5-30 seconds, 10-30 seconds, 15-30 seconds, 1-30 seconds, 0-30 seconds, 2-20 seconds, 2-10 seconds, 5-20 seconds, 10-20 seconds, 15-25 seconds, 5-15 seconds or 5-10 seconds; as measured by a method of neurophysiological monitoring, *e.g.,* EEG, CFM.

In one embodiment, the present disclosure features a method of treating a subject (*e.g.,* human subject) having a seizure-related disorder, *e.g.,* status epilepticus (SE), *e.g.,* refractory status epilepticus (RSE) or super-refractory status epilepticus (SRSE), comprising: administering to said subject (*e.g.,* human subject), an effective amount of allopregnanolone, wherein, concurrent with said administering, said subject (*e.g.,* human subject) is under general anesthesia, thereby treating said subject (*e.g.,* human subject).

In one embodiment, the present disclosure features a method of treating a subject (*e.g.,* human subject) having a seizure-related disorder, *e.g.,* status epilepticus (SE), *e.g.,* refractory status epilepticus (RSE) or super-refractory status epilepticus (SRSE), comprising administering a first dose, *e.g.,* a load dose, of allopregnanolone, *e.g.,* to a patient under general anesthesia; administering a second dose, *e.g.,* maintenance dose, of allopregnanolone, which is lower than said first dose; and

some embodiments, the cyclodextrin is present in the composition at 1, 2.5, 5, 10, 12, 13, 15, 30% by weight of cyclodextrin per volume of composition and the allopregnanolone is provided at a concentration of 0.1, 0.5, 1, 1.25, 2.5, 3.75, 5, 6.25, 7.5, 8, 9, or 10 mg/mL allopregnanolone.

In some embodiments, the cyclodextrin is present in the composition at 12% by weight of cyclodextrin per volume of composition and the allopregnanolone is provided at a concentration of 5 mg/mL allopregnanolone. In some embodiments, the cyclodextrin is present in the composition at 12% by weight of cyclodextrin per volume of composition and the allopregnanolone is provided at a concentration of 3.75 mg/mL allopregnanolone. In some embodiments, the cyclodextrin is present in the composition at 12% by weight of cyclodextrin per volume of composition and the allopregnanolone is provided at a concentration of 2.5 mg/mL allopregnanolone. In some embodiments, the cyclodextrin is present in the composition at 12% by weight of cyclodextrin per volume of composition and the allopregnanolone is provided at a concentration of 1.25 mg/mL allopregnanolone.

In some embodiments, the method further comprises, evaluating the subject (*e.g.,* human subject), wherein the evaluating comprises performing c-ECG. In some embodiments, the method comprises, evaluating the subject (*e.g.,* human subject), wherein the evaluating comprises performing EEG. In some embodiments, the method further comprises evaluating the subject (*e.g.,* human subject) for serum chemistry (*e.g.,* one or more of albumin, AST, ALT, bicarbonate, bilirubin, BUN, calcium, chloride, creatine kinase, lipase, creatinine, magnesium, potassium, sodium, total protein, or glucose). In some embodiments, the method further comprises, evaluating the subject (*e.g.,* human subject) for CBC (*e.g.,* one or more of RBC, hemoglobin, hematocrit, MCV, MCH, MCHC, platelet count, WBC with differential including neutrophils, eosinophils, basophils, lymphocytes, or monocytes. In some embodiments, the method further comprises evaluating the subject (*e.g.,* human subject) for serum allopregnanolone, progesterone, and 5α-dihydrotestosterone. In some embodiments, the method comprises comparing an observed value with a reference value.

In some embodiments, said subject (*e.g.,* human subject) is evaluated for a parameter described herein during said weaning period.

In one embodiment, the present disclosure features a method of treating a subject (*e.g.,* human subject) having, SE, RSE, or SRSE comprising: administering a first/load, *e.g.,* bolus, dose concurrent with general anesthesia, wherein administration of said first dose: begins 2-120 hours after induction of general anesthesia; lasts for 30-90 minutes; and results in a plasma level of allopregnanolone of 100-

said second/maintenance dose; and the amount of allopregnanolone delivered/unit time in said third step dose is 20 to 30% of the amount of allopregnanolone delivered/unit time in said second/maintenance dose.

In some embodiments, administering a first/load, *e.g.,* bolus, dose concurrent with general anesthesia, wherein administration of said first dose lasts for 60 +/-5 minutes; administering a second/maintenance dose, wherein, the administration of said second dose begins not longer than 30 minutes after the end of the second dose; lasts for 96+/-4 hours; administering a third downward taper dose, wherein, the administration of said third downward taper dose begins not longer than 1-60 minutes after the end of the third dose; lasts for 24+/-2 hours and: the amount of allopregnanolone delivered/unit time in said first step dose is 75% of the amount of allopregnanolone delivered/unit time in said second/maintenance dose; the amount of allopregnanolone delivered/unit time in said second step dose is 50% of the amount of allopregnanolone delivered/unit time in said second/maintenance dose; and the amount of allopregnanolone delivered/unit time in said third step dose is 25% of the amount of allopregnanolone delivered/unit time in said second/maintenance dose.

In some embodiments, the method further comprises administering an amount of a composition selected from benzodiazepines (*e.g.,* midazolam), propofol, barbiturates, and ketamine sufficient to place said subject (*e.g.,* human subject) under general anesthesia;

In one embodiment, the present disclosure features a kit comprising one or more of: a preparation of allopregnanolone, *e.g.,* a plurality of preparations of allopregnanolone at a concentrations suitable for use at the first, second, and third doses; and instructions for use for treating a subject (*e.g.,* human subject) having a seizure-related disorder, *e.g.,* status epilepticus (SE), *e.g.,* super-refractory status epilepticus (SRSE).

In some embodiments, the kit further comprises a suitable diluent (*e.g.,* water, saline, cyclodextrin, *e.g.,* β-cyclodextrin, *e.g.,* sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL).

In some embodiments, the allopregnanolone is provided at a concentration of 0.1-10 mg/mL allopregnanolone. In some embodiments, the allopregnanolone is provided at a concentration of 0.5-7.5 mg/mL allopregnanolone. In some embodiments, the allopregnanolone is provided at a concentration of 1-6 mg/mL allopregnanolone. In some embodiments, the allopregnanolone is provided at a concentration of 5 mg/mL allopregnanolone. In some embodiments, the allopregnanolone is provided at a concentration of 3.75 mg/mL allopregnanolone. In some

embodiments, the allopregnanolone is provided at a concentration of 2.5 allopregnanolone. In some embodiments, the allopregnanolone is provided at a concentration of 1.25 mg/mL allopregnanolone.

In one embodiment, the present disclosure features a method of making a series of dosages, the method comprising combining a diluent and allopregnanolone in proportions to form dosage forms suitable for use as the first, second and one or more step doses for said third dose.

In one embodiment, the present disclosure features a method of adjusting the amount of diluents and / or allopregnanolone flowing into or out of a delivery device, *e.g.,* a catheter, reservoir, the method comprising altering, *e.g.,* decreasing, the flow rate of allopregnanolone flowing into the delivery device, so as to release in succession, two or more of a first dosage, a second dosage and one or more step doses of the third dose.

In one embodiment, the present disclosure features a method of treating a subject having seizure, epilepsy or status epilepticus by administering in combination to the subject a neuroactive steroid and a benzodiazepine or anesthetic/sedative. In some embodiments, the method further comprises administering at least one of the neuroactive steroid and benzodiazepine or anesthetic/sedative parenterally (*e.g.,* intranasally, buccally, intravenously or intramuscularly, for example, intravenously or intramuscularly). In some embodiments, both the neuroactive steroid and benzodiazepine or anesthetic/sedative are administered parenterally.

In some embodiments, the neuroactive steroid and benzodiazepine or anesthetic/sedative co-administered (*e.g.,* administered simultaneously, administered concurrently). In some embodiments, the neuroactive steroid and benzodiazepine or anesthetic/sedative are administered sequentially. In some embodiments, neuroactive steroid and benzodiazepine or anesthetic/sedative are administered in a single dosage form.

When the agents described herein (*e.g.,* the neuroactive steroid and a benzodiazepine or anesthetic/sedative) are administered in combination, both of the agents should be present at dosage levels of between about 1 to 100%, and more preferably between about 5 to 95% of the dosage normally administered in the absence of the combination regimen. The agents may be administered separately, as part of a multiple dose regimen. Alternatively, the agents may be part of a single dosage form, mixed together with the compounds of this disclosure in a single composition.

We claim:

1. A method of preparing a formulation comprising allopregnanolone, said method comprising the step of high shear mixing an aqueous 5 mg/mL solution of allopregnanolone with 25% sulfo butyl ether beta-cyclodextrin solution.

2. The method of claim 1, wherein the step of high shear mixing is performed for a period of time, characterized by a clear aqueous solution comprising 5 mg/mL allopregnanolone and 25% sulfo butyl ether beta-cyclodextrin.

3. The method of claim 2, where the period of time is at least about 30 minutes.