SULCARDINE ADMINISTRATION FOR TREATMENT OF ACUTE ATRIAL FIBRILLATION

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Application No. 63/038,664, filed June 12, 2020, which is hereby incorporated by reference in its entirety.

FIELD

[0002] The present teachings relate to compositions and methods for administration of sulcardine to a subject in need thereof.

BACKGROUND

[0003] U.S. Patent Nos. 8,541,464 and 8,637,566 (each of which is incorporated herein by reference in its entirety) describe the activity of *N*-[4-hydroxy-3,5-bis(1-pyrrolidinylmethyl)benzyl]-4-methoxybenzenesulfonamide (hereinafter "sulcardine") and its pharmaceutically acceptable salts, in addition to various uses and methods of administering sulcardine in therapeutically effective amounts to subjects in need thereof.

[0004] Chen *et al.* reports the pharmacokinetics profiles of sulcardine in humans when administered orally. *See* Chen *et al.*, "Pharmacokinetics, safety, and tolerability of sulcardine sulfate: an open-label, single-dose, randomized study in healthy Chinese subjects", *Fundamental & Clinical Pharmacology*. 31 (2017) 120-125.

[0005] There remains a need for developing formulations and methodology for alternative administration of sulcardine in humans to achieve different but desirable pharmacokinetic and efficacy profiles.

SUMMARY

[0006] In one example, provided herein are compositions for administering sulcardine in therapeutically effective amounts for the treatment of atrial fibrillation or atrial flutter. In one example, provided herein are compositions for enhanced and safer administration of sulcardine in therapeutically effective amounts.

[0006a] In one aspect, provided herein is a use of a pharmaceutical composition comprising sulcardine or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of atrial fibrillation (AF) or atrial flutter in a patient, wherein the

pharmaceutical composition is to be administered to the patient, wherein the use is characterized by ECG parameters increase by no more than about 25%, wherein the ECG parameters comprise QRS, PDur, PR, or QTcF, or any combination thereof.

[0006b] In another aspect, provided herein is a pharmaceutical composition comprising a compound, wherein the compound is sulcardine, or a pharmaceutically acceptable salt thereof, wherein the composition produces one or more ECG parameter changes comprising increases of less than 25% in heart rate, QRS, PDur, PR, or QTcF.

[0006c] In another aspect, provided herein is the pharmaceutical composition disclosed herein for use in therapy.

[0007] In one example, presented herein is a pharmaceutical composition comprising sulcardine or a pharmaceutically acceptable salt thereof, wherein the composition produces ECG parameter changes in QRS, PDur, PR, or OTcF, or any combination thereof, of no more than about 25%. In some examples, the pharmaceutical composition is an inhibitor of Na_L , INa; and LCa; characterized by ECG parameter changes in:: (i) a reduction or no change in JTpc of NMT of

about 15-25 msec; and (ii) no effect or increase in TpTe. In some examples, the pharmaceutical composition results in inhibition of early after depoloarizations (EADs). In some examples, the ECG parameters further comprise heart rate. In some example, pharmaceutical composition produces a bimodal effect on QTc including prolongation in QTc at lower drug exposure levels (doses) in association with predominantly INa cardiac ion channel inhibition followed by a potential plateauing or decrease in QTc interval at higher drug exposure levels (doses) associated with increasing inhibitory effect on Na_L and ICa cardiac ion channels.. In some examples, the ECG changes occur prior to, in proximity to or at about Tmax with magnitude of changes reflecting plasma concentrations following Tmax in association with drug distribution into periphery. In some examples, the pharmaceutical composition has no material (clinically meaningful) effect on heart rate or increase or decreases diastolic and/or systolic blood pressure by no more than about 25% prior to, or at Tmax. In some examples, the pharmaceutical composition does not induce 2^{nd} or 3^{rd} degree heart block.

[0008] In some examples, the pharmaceutically acceptable salt is ethane-1,2-disulfonic acid, naphthalene-1,5-disulfonic acid, 1-hydroxy-2-naphthoic acid, naphthalene-2-sulfonic acid, dihydro sulfonic acid, hydrochloric acid, or hydrobromic acid. In some examples, the composition comprises 200 mg, 350 mg, 500 mg, or 600 mg of sulcardine, or a pharmaceutically acceptable salt thereof. In some examples, the mg dosages are calculated form the free base of sulcardine. In some examples, the composition is administered to a subject in need thereof. In some examples the administration is parenteral administration or oral consumption.

[0009] In some examples, a pharmaceutical composition is provided comprising sulcardine or a pharmaceutically acceptable salt thereof, wherein the composition produces a mean average plasma profile characterized by a Cmax for the composition in a subject, after administering 200 mg of the compound, of at least about 1,500 ng/mL at about the Tmax, and at most 25% of Cmax at about 1.0 hours after administration.

[0010] In some examples, a pharmaceutical composition is provided comprising sulcardine or a pharmaceutically acceptable salt thereof, wherein the composition produces a mean average plasma profile characterized by a Cmax for the compound in a subject, after administering 350 mg of the compound, of at least about 3,000 ng/mL at about the Tmax, and at most 25% of Cmax at about 1.0 hours after administration.

[0011] In some examples, a pharmaceutical composition is provided comprising sulcardine or a pharmaceutically acceptable salt thereof, wherein the composition produces a mean average plasma profile characterized by a Cmax for the compound in a subject, after administering 500

mg of the compound, of at least about 4,000 ng/mL at about Tmax, and at most 25% of Cmax at about 1.0 hours after administration.

[0012] In some examples, a pharmaceutical composition is provided comprising sulcardine or a pharmaceutically acceptable salt thereof, wherein the composition produces a mean average plasma profile characterized by a Cmax for the compound in a subject, after administering 600 mg of the compound, of at least about 5,500 ng/mL at about Tmax, and at most 25% of Cmax at about 1.0 hours after administration.

[0013] In another example, provided herein is a method of treating atrial fibrillation (AF) or atrial flutter, comprising administering to a human subject in need thereof sulcardine, or a pharmaceutically acceptable salt thereof, resulting in robust, albeit temporary, increase of QRS, PDur, PR, changes in QTc attendant with a reduction or no change in JTpc and no effect or increase in TpTe. In one example, without being limited by a particular theory, these changes in ECG parameters are associated with rapid accumulation of the drug in the bloodstream through intravenous infusion or other parenteral routes of administration combined with rapid inherent redistribution of the drug from the bloodstream and highly vascularized organs such as the heart to secondary compartments. Such a profile leads to rapid and significant changes in relevant ECG parameters associated with temporally linked cardioversion from atrial fibrillation to sinus rhythm followed by rapid reversal of ECG parameter changes upon drug redistribution, lessening risk of proarrhythmic events associated with QT, PR and QRS prolongation.

[0014] In another example, provided herein is a method of treating atrial fibrillation (AF) or atrial flutter, comprising administering to a human subject in need thereof, sulcardine or a pharmaceutically acceptable salt thereof, resulting in: (i) an increases of less than about 25% in QRS, PDur, PR, and QTcF; (ii) a reduction of less than 25 msec or no change in JTpc; and/or (iii) no effect or increase in TpTe. In some examples, the composition produces a change in QTcF interval that does not increase by more than about 20% after administering of the pharmaceutical composition. In some examples, the composition produces an increased in QTcF interval from about 5% to about 20% after the administration. In some examples, the plasma concentration is decreases by at least about 75% within about 1 hour after administration.

[0015] In another example, provided herein is a method of treating atrial fibrillation (AF) or atrial flutter, comprising administering to a human subject in need thereof sulcardine, or a pharmaceutically acceptable salt thereof, wherein an amount of sulcardine, or a pharmaceutically acceptable salt thereof is sufficient to achieve a Tmax of plasma concentration of sulcardine, or a pharmaceutically acceptable salt thereof of about less than 2.0 hours.

[0016] In some examples, sulcardine or a pharmaceutically acceptable salt thereof, is administered over a period of less than about 1 hour. In some examples, sulcardine or a pharmaceutically acceptable salt thereof, is administered over a period of about 30 minutes. In some examples, sulcardine or a pharmaceutically acceptable salt thereof, is administered at a rate that does not produce an arrhythmia or a clinically significant change in heart rate or blood pressure.

[0017] In some examples, the AF is acute AF. In some examples, the AF is paroxysmal AF. In some examples, the AF is recurring AF. In some examples, the treatment is for atrial flutter.

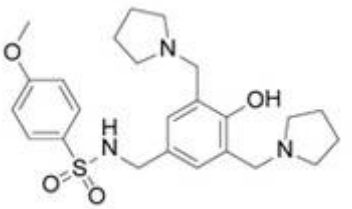
[0018] These and other features, examples and advantages of the present teachings will become better understood with reference to the following description, examples and appended claims.

DETAILED DESCRIPTION

Definitions

[0019] Unless indicated otherwise, the terms and phrases used in this description have the following meanings:

[0020] As used herein and unless otherwise specified, sulcardine (free base form) has a chemical name of *N*-[4-hydroxy-3,5-bis(1-pyrrolidinylmethyl)benzyl]-4-methoxybenzenesulfonamide, and has the following structure:



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[0021] In some embodiments, the pharmaceutically acceptable salt is ethane-1,2-disulfonic acid, naphthalene-1,5-disulfonic acid, 1-hydroxy-2-naphthoic acid, naphthalene-2-sulfonic acid, dihydro sulfonic acid, hydrochloric acid, or hydrobromic acid. In some embodiments, the pharmaceutically acceptable salt is ethane-1,2-disulfonic acid. In some embodiments, the pharmaceutically acceptable salt is naphthalene-1,5-disulfonic acid. In some embodiments, the pharmaceutically acceptable salt is 1-hydroxy-2-naphthoic acid. In some embodiments, the pharmaceutically acceptable salt is naphthalene-2-sulfonic acid. In some embodiments, the pharmaceutically acceptable salt is hydrochloric acid or hydrobromic acid.

[0022] In some embodiments, the pharmaceutically acceptable salt is sulcardine sulfate.

CLAIMS

What is claimed:

1. Use of a pharmaceutical composition comprising sulcardine or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of atrial fibrillation (AF) or atrial flutter in a patient, wherein the pharmaceutical composition is to be administered to the patient, wherein the use is characterized by ECG parameters increase by no more than about 25%, wherein the ECG parameters comprise QRS, PDur, PR, or QTcF, or any combination thereof.

2. The use of claim 1, wherein the ECG parameters further comprise a decrease in JTpc by no more than about 25 msec; and no change in TpTe.

3. The use of claim 1 or 2, wherein the ECG parameters further comprise an increases in heart rate (HR) of no more than about 25%; or wherein the ECG parameters further comprise an increase in HR that is not clinically significant.

4. The use of any one of claims 1 to 3, wherein the maximum ECG parameter change occurs prior to or at about Tmax.

5. The use of any one of claims 1 to 4, wherein the pharmaceutical composition inhibits early after depolarization.

6. The use of any one of claims 1 to 5, wherein the pharmaceutical composition increases or decreases diastolic and/or systolic blood pressure by no more than about 25%.

7. The use of any one of claims 1 to 6, wherein the pharmaceutical composition does not induce a 2^{nd} or 3^{rd} degree heart block.

8. The use of any one of claims 1 to 7, wherein sulcardine, or a pharmaceutically acceptable salt thereof, is to be administered at a dose of 200 mg, 350 mg, 500 mg, or 600 mg.

9. The use of any one of claims 1 to 8, wherein the pharmaceutically acceptable salt is ethane-1,2-disulfonic acid, naphthalene-1,5-disulfonic acid, 1-hydroxy-2-naphthoic acid, naphthalene-2-sulfonic acid, dihydro sulfonic acid, hydrochloric acid, or hydrobromic acid.

10. The use of any one of claims 1 to 9, wherein the QT and/or QRS intervals increases by about 5% to about 20% after the administration of the composition.

11. The use of any one of claims 1 to 10, wherein a mean average plasma profile characterized by a Cmax after the administration of 200 mg of the compound, of at least about 1,500 ng/mL at about Tmax, and at most 25% of Cmax at about 1.0 hours after administration.

12. The use of any one of claims 1 to 10, wherein the composition produces a mean average plasma profile characterized by a Cmax after the administration of 350 mg of the compound, of at least about 3,000 ng/mL at about Tmax, and at most 25% of Cmax at about 1.0 hours after administration.

13. The use of any one of claims 1 to 10, wherein the composition produces a mean average plasma profile characterized by a Cmax after the administration of 500 mg of the compound, of at least about 4,000 ng/mL at about Tmax, and at most 25% of Cmax at about 1.0 hours after administration.

14. The use of any one of claims 1 to 10, wherein the composition produces a mean plasma profile characterized by an average Cmax after the administration of 600 mg of the compound, of at least about 5,500 ng/mL at about Tmax, and at most 25% of Cmax at about 1.0 hours after administration.

15. The use of any one of claims 1 to 14, wherein the plasma concentration decreases by at least about 75% within about 1 hour after administration.

16. The use of any one of claims 1 to 15, wherein the administration comprises intravenous injection, intramuscular injection, intraperitoneal injections, subcutaneous injection, or oral consumption.

17. The use of any one of claims 1 to 16, wherein sulcardine, or a pharmaceutically acceptable salt thereof, is to be administered over a period less than about 1 hour.

18. The use of claim 17, wherein sulcardine, or a pharmaceutically acceptable salt thereof, is to be administered over a period of about 30 minutes.

19. The use of claim 17, wherein sulcardine, or a pharmaceutically acceptable salt thereof, is to be administered over a period of about 15 minutes.

20. The use of any one of claims 1 to 19, wherein sulcardine, or a pharmaceutically acceptable salt thereof, is to be administered at a rate that does not produce an arrhythmia or a clinically significant change in heart rate or blood pressure.

21. The use of any one of claims 1 to 20, wherein the AF is acute AF, paroxysmal AF, recurring AF or atrial flutter.

22. The use of any one of claims 1 to 21, wherein the pharmaceutical composition inhibits late sodium channels, fast sodium channels, L-type calcium channels in the heart, or a combination thereof, in the patient.

23. The use of any one of claims 1 to 22, wherein a bimodal effect on QTc can occur including prolongation in QTc at lower drug exposure levels (doses) in association with INa cardiac ion channel inhibition followed by a potential plateauing or decrease in QTc interval at higher drug exposure levels (doses) associated with increasing inhibitory effect on Na_L and ICa cardiac ion channels.

24. A pharmaceutical composition comprising a compound, wherein the compound is sulcardine, or a pharmaceutically acceptable salt thereof, wherein the composition produces one or more ECG parameter changes comprising increases of less than 25% in heart rate, QRS, PDur, PR, or QTcF.

25. The pharmaceutical composition of claim 24, wherein the composition comprises an inhibitor of Na_L in addition to INa and LCa and induces:
(i) a reduction or no change in JTpc of NMT of about 15 to 25 msec; and
(ii) no effect or increase in TpTe.

26. The pharmaceutical composition of claim 24 or 25, wherein the composition results in inhibition of early after depolarizations (EADs).

27. The pharmaceutical composition of any one of claims 24 to 26, wherein the ECG parameters further comprise heart rate.

28. The pharmaceutical composition of any one of claims 24 to 27, wherein an attenuation in prolongation or a shortening in QTc follows an increase in QTc interval.

29. The pharmaceutical composition of any one of claims 24 to 28, wherein the ECG parameter changes occur prior to, or at Tmax.

30. The pharmaceutical composition of any one of claims 24 to 29, wherein the composition has no material effect on heart rate or increases or decreases diastolic and/or systolic blood pressure by no more than about 25%. prior to, or at Tmax.

31. The pharmaceutical composition of any one of claims 24 to 30, wherein the composition does not induce 2nd or 3rd degree heart block.

32. The pharmaceutical composition of any one of claims 24 to 31, wherein the pharmaceutically acceptable salt is ethane-1,2-disulfonic acid, naphthalene-1,5-disulfonic acid, 1-hydroxy-2-naphthoic acid, naphthalene-2-sulfonic acid, dihydro sulfonic acid, hydrochloric acid, or hydrobromic acid.

33. The pharmaceutical composition of any one of claims 24 to 32, wherein the composition comprises 200 mg, 350 mg, 500 mg, or 600 mg of sulcardine, or a pharmaceutically acceptable salt thereof.

34. The pharmaceutical composition of any one of claims 24 to 33, wherein the composition is to be administered to a subject in need by parenteral administration, intravenous infusion or oral consumption.

35. The pharmaceutical composition of any one of claims 24 to 34, wherein the composition produces a mean average plasma profile characterized by a Cmax after administration of 200 mg of the compound, of at least about 1,500 ng/mL at about 0.5 hours after administration, and at most 25% of Cmax at about 1.0 hours after administration.

36. The pharmaceutical composition of any one of claims 24 to 35, wherein the composition produces a mean average plasma profile characterized by a Cmax after administration of 350 mg of the compound, of at least about 3,000 ng/mL at about 0.5 hours after administration, and at most 25% of Cmax at about 1.0 hours after administration.

37. The pharmaceutical composition of any one of claims 24 to 36, wherein the composition produces a mean average plasma profile characterized by a Cmax after administration of 500 mg of the compound, of at least about 4,000 ng/mL at about 0.5 hours after administration, and at most 25% of Cmax at about 1.0 hours after administration.

38. The pharmaceutical composition of any one of claims 24 to 37, wherein the composition produces a mean average plasma profile characterized by a Cmax after administration of 600 mg of the compound, of at least about 5,500 ng/mL at about 0.5 hours after administration, and at most 25% of Cmax at about 1.0 hours after administration.

39. The pharmaceutical composition of any one of claims 24 to 38, wherein the composition produces a mean average plasma profile characterized by an AUC after administration of 200 mg of the compound, of at least about 1,200 ng.h/mL at about 0.5 hours after administration.

40. The pharmaceutical composition of any one of claims 24 to 39, wherein the composition produces a mean average plasma profile characterized by an AUC after administration of 350 mg of the compound, of at least about 2,800 ng.h/mL at about 0.5 hours after administration.

41. The pharmaceutical composition of any one of claims 24 to 40, wherein the composition produces a mean average plasma profile characterized by an AUC after administration of 500 mg of the compound, of at least about 4,000 ng.h/mL at about 0.5 hours after administration.

42. The pharmaceutical composition of any one of claims 24 to 41, wherein the composition produces a mean average plasma profile characterized by an AUC after administration of 200 mg of the compound, of at least about 5,200 ng.h/mL at about 0.5 hours after administration.

43. The pharmaceutical composition of any one of claims 24 to 42 for use in therapy.