tissues is inhibited by loop diuretics, including furosemide, bumetanide, and benzmetanide. Espinosa et al. and Ahmad et al. have previously suggested that furosemide might be useful in the treatment of certain types of epilepsy *(Medicina Espanola* 61:280-281, 1969; and *Brit. J. Clin. Pharmacol.* 3:621-625, 1976). Bumetanide is potentially a more potent drug for treating epilepsy, but it also has a more pronounced diuretic effect. There is therefore a continuing need for methods and compositions for treating neuronal disorders that are not diuretic and that disrupt hypersynchronized neuronal activity without diminishing the neuronal excitability and spontaneous synchronization required for normal functioning of the peripheral and central nervous systems.

SUMMARY

[0006a] In an aspect, there is provided the use of a pharmaceutical composition comprising bumetanide dibenzylamide, bumetanide diethylamide or bumetanide morpholinoamide, in the manufacture of a medicament that has a therapeutic effect on seizure blockade in a patient.

[0006b] In another aspect, there is provided the use of a pharmaceutical composition comprising bumetanide dibenzylamide, bumetanide diethylamide or bumetanide morpholinoamide, in the manufacture of a medicament for treating seizures in a patient, wherein the pharmaceutical composition has a therapeutic effect on seizure blockade in the patient and wherein seizure activity in the patient is to be reduced without increasing urine output of the patient.

[0007] In one example of the present disclosure Bumetanide Dibenzylamide demonstrated antiseizure activity in a nonhuman primate model, and NKCC inhibition measure by a similar response to bumetanide in a rat anxiolytic bioassay. By contrast, although bumetanide demonstrated a potent diuretic effect, in the primate model, treatment with Bumetanide Dibenzylamide did not increase urine output. Comparing the pharmacologic activity of bumetanide and Bumetanide Dibenzylamide highlights the novel properties of Bumetanide Dibenzylamide as a potential antiseizure therapeutic agent that is not limited by diuretic effects. Taken together, the data of the present disclosure along with the published studies describing the antiseizure effects of bumetanide and furosemide, support the novel and unexpected properties of Bumetanide Dibenzylamide as an adjunct antiseizure therapy. It is believed that the observed

antiseizure effects of bumetanide and furosemide are mediated through their antagonism of NKCC1 on neurons and/or glial cells whereas their diuretic effects are mediated through antagonism of renal NKCC2.

[0008] One example of the present disclosure includes bumetanide derivatives, and compositions containing such compounds, that demonstrate therapeutically effective seizure blockade with substantially no diuretic effect.

[0009] One example of the present disclosure includes bumetanide derivatives, and compositions containing such compounds, that demonstrate therapeutically effective seizure blockade with substantially no diuretic effect, wherein the ratio of seizure-controlling effect to diuretic effect provides a therapeutic effect or therapeutic coefficient. The therapeutic effect is a ratio of a measure of seizure suppression (e.g., frequency of seizure, intensity of

seizure etc.) to a measure of diuretic effect of the therapeutic compound (e.g., urine volume, urine ion concentration etc.).

[0010] One example of the present disclosure includes a therapeutic effect based on seizure frequency and changes in blood plasma osmolarity (as a measure of dehydration). One example of the present disclosure includes a therapeutic effect based on increase in interspike interval and changes in blood plasma osmolarity (as a measure of dehydration). One example of the present disclosure includes a therapeutic effect based on seizure frequency and change in urine production in a given time period. One example of the present disclosure includes a therapeutic effect based on increase in interspike interval and changes in urine production in a given time period.

[0011] One example of the present disclosure includes a therapeutic effect based on reduction in seizure spike height or amplitude and changes in blood plasma osmolarity (as a measure of dehydration). One example of the present disclosure includes a therapeutic effect based on reduction in seizure spike height or amplitude and changes in urine production in a given time period. One example of the present disclosure includes a therapeutic effect based on seizure frequency and changes in blood ions over time, where the ions are selected from sodium, chloride, or magnesium. One example of the present disclosure includes a therapeutic effect based on increase in interspike interval and changes in blood ions over time, where the ions are selected from sodium, chloride magnesium, or pH. One example of the present disclosure includes a therapeutic effect based on reduction in seizure spike height or amplitude and changes in blood ions over time, where the ions are selected from sodium, chloride, or magnesium.

[0012] Changes in seizure activity may be changes in the amplitude and/or frequency of pharmacologically- or electrically-evoked seizure (epileptiform) activity as measured with EEG or other electrophysiological types of recordings. Changes in seizure activity may be changes in the number of unprovoked seizures over a period of time (such as seizures per day, per week, or per month).

[0013] In one example, the therapeutic effect is defined as a proportional change in seizure frequency or amplitude to urine output compared to a baseline. In one example, the therapeutic effect is proporational change in seizure frequency or amplitude in any

objective determination. In one example, the therapeutic effect is proporational change in seizure frequency or amplitude pre and post treatment with the therapeutic compound.

[0014] In one example, change in frequency post treatment is at least a 50% reduction in the frequency of seizure occurrence. In one example, the change in diuresis post treatment is less than about a two-fold increase in urine production over a twenty four hour period. In one example, change in frequency post treatment is more than a 50% reduction in the frequency of seizure occurrence. In one example, the change in diuresis post treatment is no increase in urine production over a twenty four hour period.

[0015] In one example, change in frequency post treatment is about a 50% to a 100% reduction in the frequency of seizure occurrence. In one example, the change in diuresis post treatment is in the range of about 0% to about 100% increase in urine production over a twenty four hour period.

[0016] In one example, the therapeutic effect for a specific dose of the therapeutic compound is defined as follows:

Therapeutic Effect =

[seizure activity post-treatment]/ [seizure activity pre-treatment]*

[diuresis post-treatment]/[diuresis pre-treatment]

[0017] The dose of the therapeutic compund may be below the dosage required to completely block seizure activity. If the dosage is above the amount required to completely block seizures, is to determine a therapeutic effect that is different from zero, and acertain the comparative effects of different therapeutic compunds.

[0018] One example of the present disclosure includes bumetanide derivatives, and compositions containing such compounds, that provide an unexpectedly improved increase in seizure control when compared to other bumetanide derivatives. In other words, not all derivatives of bumetanide provide this effect. Rather, the amide derivatives appear to provide a unique effect.

[0019] One example of the present disclosure includes bumetanide derivatives, and compositions containing such compounds, that provide an unexpectedly improved decrease in diuresis when compared to other bumetanide derivatives.

[0020] One example of the present disclosure includes bumetanide derivatives, and compositions containing such compounds, that demonstrate a reduction in both seizure amplitude and frequency.

[0021] One example of the present disclosure includes bumetanide derivatives, and compositions containing such compounds, in a method or use for seizure suppression.

[0022] One example of the present disclosure includes bumetanide derivatives, and compositions containing such compounds, that demonstrate a positive impact on synchronous activity without a substantial impact on excitability. One aspect includes specific bumetanide derivatives, and compositions containing such compounds, that provide a therapeutic window of effect.

[0023] One example of the present disclosure includes one or more bumetanide derivatives, and compositions containing such compounds, that provide seizure suppression, including decreasing amplitude of spikes and interval between spikes. In one aspect, the amplitude is decresed by about 50% to about 99% and the interval is decreased by about 50% to about 99%. In one aspect, the ampltide approaches zero (0) and the interval approachs infinity.

[0024] One example of the present disclosure includes bumetanide derivatives, and compositions containing such compounds, administered in a therapeutically effective dose, which is one or more doses required to observe the seizure suppression/therapeutic effect. One aspect of the disclosure includes a determination of the diuretic factor for a proposed anti-seizure treatment and then calculating the corresponsing therapeutic factor. One aspect of the present disclosure includes the unique relationship between dosage of the bumetanide amide derivatives and lack of diuretic effect. The bumetanide amide derivatives offer unexpected benefit as compared to other bumetanide derivatives. Testing demonstrates markedly different effects for different derivatives and different formulations.

[0025] One example of the present disclosure includes a method or use of treating a patient refractory to conventional anticonvulsant medication comprising administering Bumetanide Dibenzylamide. The present disclosure includes methods and uses that provide particular utility to epilepsy patients who are not well-controlled by or otherwise refractory to conventional therapies, such as one or more of phenytoin, carbamazepine, valproate, lamotrigine,

levetiracetam, ethosuximide, phenobarbital, and topiramate by administering to the patient a pharmaceutical composition comrpsing Bumetanide Dibenzylamide.

[0026] One example of the present disclosure includes a pharmaceutical composition comprising bumetanide dibenzylamide, bumetanide diethylamide or bumetanide morpholinoamide, or a salt thereof, wherein the pharmaceutical composition has a therapeutic effect on seizure blockade in a patient.

[0027] One aspect includes wherein the therapeutic effect is a ratio of a measure of seizure suppression to a measure of diuretic effect on the patient. One aspect includes wherein the measure of seizure suppression is frequency of seizure. One aspect includes wherein the measure of seizure suppression is intensity of seizure. One aspect includes wherein the measure of seizure suppression is a change in amplitude of pharmacologically- or electrically-evoked seizure (epileptiform) activity as measured with EEG or other electrophysiological types of recordings. One aspect includes wherein the amplitude is decreased by about 50% to about 99% post treatment with the composition. One aspect includes wherein the measure of seizure suppression is a change in frequency of pharmacologically- or electrically-evoked seizure (epileptiform) activity as measured with EEG or other electrophysiological types of recordings. One aspect includes wherein the measure of diuretic effect is urine volume. One aspect includes wherein the measure of diuretic effect is urine ion concentration. One aspect includes wherein the therapeutic effect is based on seizure frequency and changes in blood plasma osmolarity. One aspect includes wherein the therapeutic effect is based on increase in interspike interval. One aspect includes wherein the interspike interval is decreased by about 50% to about 99% One aspect includes wherein the therapeutic effect is based on increase in interspike interval and changes in blood plasma osmolarity. One aspect includes wherein the therapeutic effect is based on seizure frequency and change in urine production in a given time period. One aspect includes wherein the therapeutic effect is based on increase in interspike interval and changes in urine production in a given time period. One aspect includes wherein the therapeutic effect is based on reduction in seizure spike height or amplitude and changes in blood plasma osmolarity. One aspect includes wherein the therapeutic effect is effect based on reduction in seizure spike height or amplitude and changes in urine production in a given time period. One aspect includes wherein the therapeutic effect is effect based on seizure frequency and changes in blood ions over time, where the ions are selected from sodium, chloride

composition has a positive impact on neuron synchronous activity without a substantial impact on neuron excitability. One aspect includes wherein the composition provides a therapeutic window of effect. One aspect is a composition comprising Bumetanide dibenzylamide. One aspect is a composition comprising Bumetanide morpholinoamide.

[0029] One example of the present disclosure includes a method for treating seizures in a patient comprising: administering the pharmaceutical composition of the present disclosure; and reducing seizure activity in the patient without increasing urine output of the patient.

[0030] In one aspect, the pharmaceutical composition is administered orally. In one aspect, the pharmaceutical composition is administered once. In one aspect, the pharmaceutical composition is administered once a day for a fixed number of consecutive days. In one aspect, wherein the antiseizure effects of the pharmaceutical composition is mediated through its antagonism of NKCC1 on neurons and/or glial cells. In one aspect, the diuretic effects of the pharmaceutical composition is mediated through its antagonism of renal NKCC2. In one aspect, the pharmaceutical composition is administered once a day for a fixed number of consecutive days. In one aspect, the pharmaceutical composition is administered to treat epilepsy. In one aspect, the pharmaceutical composition is administered in combination with a conventional therapy to treat seizure. In one aspect, urine output is measured by blood ion concentration imbalance. In one aspect, urine output is measured by the magnitude of diuretic effect calculated as amount of bumetanide in blood (concentration) compared to bumetanide dibenzylamide. In one aspect, time to effect as measured by reduction of seizure frequency for bumetanide dibenzylamide is faster than a traditional anti-epileptic. In one aspect, the reduction in seizure frequency is measured by one or more of: a time increment selected from one or more of hours, days, weeks, and months; a seizure diary and a reduction in logged seizure activity; an increase in one or more of interictal (between) and postictal (after) spiking; and diminishing interictal activity as measured by EEG.

[0031] One or more examples or aspects may be incorporated in a different example or aspect although not specifically described. That is, all examples and aspects can be combined in any way to form another example.

BRIEF DESCRIPTION OF THE DRAWINGS

CLAIMS

What is claimed is:

1. Use of a pharmaceutical composition comprising bumetanide dibenzylamide, bumetanide diethylamide or bumetanide morpholinoamide, in the manufacture of a medicament that has a therapeutic effect on seizure blockade in a patient.
2. The use of claim 1, wherein the therapeutic effect is a ratio of a measure of seizure suppression to a measure of diuretic effect on the patient.
3. The use of any one of the claims 1-2, wherein the measure of seizure suppression is frequency of seizure.
4. The use of any one of the claims 1-3, wherein the measure of seizure suppression is intensity of seizure.
5. The use of any one of the claims 1-4, wherein the measure of seizure suppression is a change in amplitude of pharmacologically- or electrically-evoked seizure (epileptiform) activity as measured with EEG or other electrophysiological types of recordings.
6. The use of claim 5, wherein the amplitude is decreased by about 50% to about 99% post treatment with the composition.
7. The use of any one of the claims 1-6, wherein the measure of seizure suppression is a change in frequency of pharmacologically- or electrically-evoked seizure (epileptiform) activity as measured with EEG or other electrophysiological types of recordings.
8. The use of any one of the claims 1-7, wherein the measure of diuretic effect is urine volume.
9. The composition of any one of the claims 1-8, wherein the measure of diuretic effect is urine ion concentration.
10. The use of any one of the claims 1-9, wherein the therapeutic effect is based on seizure frequency and changes in blood plasma osmolarity.
11. The use of any one of the claims 1-10, wherein the therapeutic effect is based on increase in interspike interval.
12. The use of claim 11, wherein the interspike interval is decreased by about 50% to about 99%
13. The use of any one of the claims 1-12, wherein the therapeutic effect is based on increase in interspike interval and changes in blood plasma osmolarity

14. The use of any one of the claims 1-13, wherein the therapeutic effect is based on seizure frequency and change in urine production in a given time period.

15. The use of any one of the claims 1-14, wherein the therapeutic effect is based on increase in interspike interval and changes in urine production in a given time period

16. The use of any one of the claims 1-15, wherein the therapeutic effect is based on reduction in seizure spike height or amplitude and changes in blood plasma osmolarity.

17. The use of any one of the claims 1-16, wherein the therapeutic effect is effect based on reduction in seizure spike height or amplitude and changes in urine production in a given time period.

18. The use of any one of the claims 1-17, wherein the therapeutic effect is effect based on seizure frequency and changes in blood ions over time, where the ions are selected from sodium, chloride magnesium, or pH.

19. The use of any one of the claims 1-18, wherein the therapeutic effect is effect based on an increase in interspike interval and changes in blood ions over time, where the ions are selected from sodium, chloride, and magnesium.

20. The use of any one of the claims 1-19, wherein the therapeutic effect is effect based on reduction in seizure spike height or amplitude and changes in blood ions over time, where the ions are selected from sodium, chloride, and magnesium.

21. The use of any one of the claims 1-20, wherein the therapeutic effect is a proportional change in seizure frequency or amplitude to urine output compared to a baseline.

22. The use of any one of the claims 1-21, wherein the therapeutic effect is a proportional change in seizure frequency or amplitude in any objective determination.

23. The use of any one of the claims 1-22, wherein the therapeutic effect is a proportional change in seizure frequency or amplitude pre and post treatment with the composition.

24. The use of any one of the claims 1-23, wherein the therapeutic effect is a proportional change in seizure frequency and amplitude pre and post treatment with the composition.

25. The use of any one of the claims 1-24, wherein change is seizure frequency post treatment with the composition is at least a 50% reduction in frequency of seizure occurrence.

26. The use of any one of the claims 1-25, wherein change is seizure frequency post treatment with the composition is a more than a 50% to a 100% reduction in the frequency of seizure occurrence.

27. The use of any one of the claims 1-26, wherein, the measure of diuretic effect is a less than about two-fold increase in urine production over a twenty four hour period post treatment with the composition.

28. The use of any one of the claims 1-27, wherein, the measure of diuretic effect is no increase in urine production over a twenty four hour period post treatment with the composition.

29. The use of any one of the claims 1-28, wherein, the measure of diuretic effect is about a 0% to about a 100% increase in urine production over a twenty four hour period post treatment with the composition.

30. The use of any one of the claims 1-29, wherein the therapeutic effect is determined based on an effective dose of the composition.

31. The use of claim 30, wherein the therapeutic effect is determined as:

Therapeutic Effect = [seizure activity post-treatment]/ [seizure activity pre-treatment]* [diuresis post-treatment]/[diuresis pre-treatment]

32. The use of any one of the claims 30-31, wherein, the effective dose of the composition is a dosage required to completely block seizure activity.

33. The use of any one of the claims 30-32, wherein, the effective dose of the composition is above the dosage required to completely block seizures.

34. The use of any one of the claims 30-33, wherein, the effective dose of the composition is a dose that causes seizure suppression without causing the diuretic effect.

35. The use of any one of the claims 1-34, wherein the composition has a positive impact on neuron synchronous activity without a substantial impact on neuron excitability.

36. The use of any one of the claims 1-35, wherein the composition provides a therapeutic window of effect.

37. The use of any one of the claims 1-36, wherein the composition comprises Bumetanide Dibenzylamide.

38. The use of any one of the claims 1-37, wherein the composition comprises Bumetanide Morpholinoamide.

39. Use of a pharmaceutical composition comprising bumetanide dibenzylamide, bumetanide diethylamide or bumetanide morpholinoamide,

in the manufacture of a medicament for treating seizures in a patient, wherein the pharmaceutical composition has a therapeutic effect on seizure blockade in the patient and wherein seizure activity in the patient is to be reduced without increasing urine output of the patient.

40. The use of claim 39, wherein the pharmaceutical composition is to be administered orally.

41. The use of any one of the claims 39-40, wherein the pharmaceutical composition is to be administered once.

42. The use of any one of the claims 39-41, wherein the pharmaceutical composition is to be administered once a day for a fixed number of consecutive days.

43. The use of any one of the claims 39-42, wherein the antiseizure effects of the pharmaceutical composition is mediated through its antagonism of NKCC1 on neurons and/or glial cells.

44. The use of any one of the claims 39-43, wherein the diuretic effects of the pharmaceutical composition is mediated through its antagonism of renal NKCC2.

45. The use of any one of the claims 39-44, wherein the pharmaceutical composition is to be administered once a day for a fixed number of consecutive days.

46. The use of any one of the claims 39-45, wherein the pharmaceutical composition is to be administered to treat epilepsy.

47. The use of any one of the claims 39-46, wherein the pharmaceutical composition is to be administered in combination with a conventional therapy to treat seizure.

48. The use of any one of the claims 39-47, wherein urine output is measured by blood ion concentration imbalance.

49. The use of any one of the claims 39-48, wherein urine output is measured by the magnitude of diuretic effect calculated as amount of bumetanide in blood (concentration) compared to bumetanide dibenzylamide.

50. The use of any one of the claims 39-49, wherein time to effect as measured by reduction of seizure frequency for bumetanide dibenzylamide is faster than a traditional anti-epileptic.

51. The use of claim 50, wherein the reduction in seizure frequency is measured by one or more of:

a) a time increment selected from one or more of hours, days, weeks, and months;

b) a seizure diary and a reduction in logged seizure activity;
c) an increase in one or more of interictal (between) and postictal (after) spiking; and
d) diminishing interictal activity as measured by EEG.

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