2007/079670 and US Patents 8,026,2854 and 8,129,433 disclose enterically coated cysteamine products and a method of reducing dosing frequency of cysteamine.

[0008] Cysteamine is addressed in International Patent Application Nos. WO 2009/070781, and WO 2007/089670, and U.S. Patent Publication Nos. 20110070272, 20090048154, and 20050245433.

SUMMARY

[0008a] In one aspect of the present disclosure, there is provided a use of cysteamine or a derivative thereof, or cystamine or a derivative thereof, in the manufacture of a medicament for treating an inherited or acquired mitochondrial disorder in a subject suffering from an inherited or acquired mitochondrial disorder.

[0009] The present disclosure also provides a method of treating a subject suffering from an inherited or acquired mitochondrial disorder comprising administering a therapeutically effective amount of a cysteamine product, e.g., cysteamine or cystamine or derivatives thereof. It is contemplated that administration of the cysteamine product increases levels of free thiols in mitochondrial disease patients, which can improve the detrimental effects of respiratory chain dysfunction in patients. It is understood that such inherited or acquired mitochondrial disorders are due to inherited or acquired mutations in mitochondrial DNA or nuclear DNA used in mitochondria activity.

[0010] In various embodiments, the disclosure provides a method of treating a subject suffering from an inherited or acquired mitochondrial disease or disorder comprising administering a cysteamine product or composition, e.g., cysteamine or derivative thereof or cystamine or derivative thereof.

[0011] In various embodiments, the mitochondrial disease or disorder is selected from the group consisting of Friedreich's Ataxia, Leber's hereditary optic neuropathy, myoclonic epilepsy and ragged-red fibers (MERRF), Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like syndrome (MELAS), Kearn-Sayre syndrome, subacute necrotizing encephalopathy (Leigh's Syndrome), and mitochondrial cardiomyopathies and other syndromes due to multiple mitochondrial DNA deletions. Additional mitochondrial diseases include neurogenic muscle weakness, ataxia and retinitis pigmentosa (NARP), progressive external opthalmoplegia (PEO), and Complex I disease, Complex II disease, Complex III disease, Complex IV disease and Complex V disease, which relates to dysfunction of the

OXPHOS complexes, and MEGDEL syndrome (3-methylglutaconic aciduria type IV with sensorineural deafness, encephalopathy and Leigh-like syndrome. Inherited or acquired mitochondrial diseases contemplated herein exclude diseases caused by CAG repeat expansion in protein-coding portions of non-mitochondrial genes (e.g., Huntington's disease)

mimetics, levo-carnitine, acetyl-L-carnitine, dichloroacetate, dimethylglycine, and lipoic acid.

[0025] In various embodiments, the subject is a child or adolescent.

[0026] ~~In one aspect, t~~The methods of the disclosure also include use of a cysteamine product in preparation of a medicament for treatment an inherited or acquired mitochondrial disease, and use of a cysteamine product in preparation of a medicament for administration in combination with a second agent for treating an inherited or acquired mitochondrial disease. Also included is use of a second agent for treating an inherited or acquired mitochondrial disease in preparation of a medicament for administration in combination with a cysteamine product. Further provided are kits comprising a cysteamine product for treatment of an inherited or acquired mitochondrial disease, optionally with a second agent for treating an inherited or acquired mitochondrial disease, and instructions for use.

DETAILED DESCRIPTION

[0027] The present disclosure relates, in general, to methods of treating inherited or acquired mitochondrial disorders using a cysteamine product, e.g., cysteamine or cystamine or derivatives thereof. It is contemplated that administration of a cysteamine product to a subject suffering from a mitochondrial disease or disorder, especially those in which decreased levels of free thiols are detected, will increase glutathione production and decrease the levels of free radical byproducts that result from oxidative phosphorylation in the mitochondria.

Definitions

[0028] As used herein and in the appended claims, the singular forms "a," "and," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a derivative" includes a plurality of such derivatives and reference to "a patient" includes reference to one or more patients and so forth.

[0029] Also, the use of "or" means "and/or" unless stated otherwise. Similarly, "comprise," "comprises," "comprising" "include," "includes," and "including" are interchangeable and not intended to be limiting.

[0030] It is to be further understood that where descriptions of various embodiments use the term "comprising," those skilled in the art would understand that in some specific

WHAT IS CLAIMED:

1. Use of cysteamine or a derivative thereof, or cystamine or a derivative thereof, in the manufacture of a medicament for ~~A method of~~ treating an inherited or acquired mitochondrial disorder ~~comprising, administering an effective amount of cysteamine or a derivative thereof or cystamine or a derivative thereof to~~ in a subject suffering from an inherited or acquired mitochondrial disorder.

2. The ~~method~~ use of claim 1, wherein the inherited mitochondrial disorder is selected from the group consisting of Friedreich's ataxia, Leber's hereditary optic neuropathy (LHON), myoclonic epilepsy and ragged-red fibers, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like syndrome (MELAS), Kearn-Sayre syndrome and subacute necrotizing encephalopathy (Leigh's Syndrome).

3. The use ~~method~~ of ~~any one of the preceding~~ claims 1, wherein the ~~method comprises administering~~ cysteamine or a derivative thereof, or cystamine or a derivative thereof, is to be administered to said subject.

4. The use ~~method~~ of ~~any one of the preceding~~ claims 1, wherein the cysteamine or derivative thereof or cystamine or derivative thereof is to be administered orally.

5. The use ~~method~~ of ~~the preceding~~ claim 1, wherein the cysteamine or derivative thereof or cystamine or derivative thereof is a delayed or controlled release cysteamine composition.

6. The use ~~method~~ of claim 5, wherein the delayed or controlled release dosage form comprises an enteric coating that releases the cysteamine composition when the composition reaches the small intestine or a region of the gastrointestinal tract of a subject in which the pH is greater than about pH 4.5.

7. The use ~~method~~ of ~~any one of the preceding~~ claims 1, wherein the cysteamine or derivative thereof or cystamine or derivative thereof is to be administered less than four times per day.

8. The use ~~method~~ of ~~any one of the preceding~~ claims 1, wherein the cysteamine or derivative thereof or cystamine or derivative thereof is to be administered twice a day.

9. The ~~method~~ use of ~~any one of the preceding~~ claims 1, wherein the subject has decreased thiol levels compared to a non-affected subject.

10. The use ~~method~~ of ~~any one of the preceding~~ claims 3, wherein the administering results in improvement in mitochondrial activity markers compared to levels before administration of the cysteamine or derivative thereof or cystamine or derivative thereof.

11. The use ~~method~~ of claim 10, wherein the mitochondrial activity marker is selected from the group consisting free thiol levels, glutathione (GSH), reduced glutathione (GSSH), total glutathione, advanced oxidation protein products (AOPP), ferric reducing antioxidant power (FRAP), lactic acid, pyruvic acid, lactate/pyruvate ratios, phosphocreatine, NADH(NADH+H^+) or NADPH(NADPH+H^+), NAD or NADP levels, ATP, anaerobic threshold, reduced coenzyme Q, oxidized coenzyme Q; total coenzyme Q, oxidized cytochrome C, reduced cytochrome C, oxidized cytochrome C/reduced cytochrome C ratio, acetoacetate, β-hydroxy butyrate, acetoacetate/β-hydroxy butyrate ratio, 8-hydroxy-2'-deoxyguanosine (8-OHdG), levels of reactive oxygen species, levels of oxygen consumption (VO2), levels of carbon dioxide output (VCO2), and respiratory quotient (VCO2/VO2).

12. The use ~~method~~ of ~~any one of the preceding~~ claims 3, wherein the administering results in increased thiol levels compared to levels before administration of the cysteamine or derivative thereof or cystamine or derivative thereof.

13. The use ~~method~~ of ~~any one of the preceding~~ claims 1, wherein the cysteamine or cystamine or derivative thereof is formulated in a tablet or capsule which is enterically coated.

14. The ~~method~~ use of ~~any one of the preceding~~ claims 1, wherein the cysteamine or derivative thereof or cystamine or derivative thereof is to be administered parenterally.

15. The ~~method~~ use of ~~any one of the preceding~~ claims 1, wherein the cysteamine or derivative thereof or cystamine or derivative thereof is to be administered orally.

16. The ~~method~~ use of ~~any one of the preceding~~ claims 1, wherein the medicament~~cysteamine or derivative thereof or cystamine or derivative thereof~~ further comprises a pharmaceutically acceptable carrier.

17. The ~~method~~ use of any ~~one of the preceding~~ claims 1, wherein the cysteamine or derivative thereof or cystamine or derivative thereof is formulated as a sterile pharmaceutical composition.

18. The ~~method~~ use of ~~any one of the preceding~~ claims 1, wherein the inherited mitochondrial disorder is Friedreich's ataxia.

19. The use ~~method~~ of ~~any one of the preceding~~ claims 1, wherein the inherited mitochondrial disorder is Leber's hereditary optic neuropathy.

20. The use ~~method~~ of claim 19, wherein the cysteamine or derivative thereof or cystamine or derivative thereof is to be administered topically in the eye.

21. The use ~~method~~ of ~~any one of the preceding~~ claims 1, wherein the inherited mitochondrial disorder is Leigh's syndrome.

22. The use ~~method~~ of ~~any of the preceding~~ claims 1, wherein the medicament further comprises ~~cysteamine or derivative thereof or cystamine or derivative thereof is administered with~~ a second agent useful to treat inherited or acquired mitochondrial diseases or disorders.

23. The ~~method~~ use of claim 22, wherein the second agent is selected from the group consisting of coenzyme Q10, coenzyme Q10 analogs, idebenone, decylubiquinone, Epi-743, resveratrol and analogs thereof, arginine, vitamin E, tocopherol, MitoQ, glutathione peroxidase mimetics, levo-carnitine, acetyl-L-carnitine, dichloroacetate, dimethylglycine and lipoic acid.

24. The use ~~method~~ of ~~any of the preceding~~ claims 1, wherein the subject is a child or adolescent.

25. The use ~~method~~ of ~~any of the preceding~~ claims 3, wherein the administering results in improved results in the Newcastle Paediatric Mitochondrial Disease Scale and Barry Albright Dystonia Scale compared to levels before administration of the cysteamine or derivative thereof or cystamine or derivative thereof.