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(54) Title: OMEGA-3 FATTY ACIDS FOR USE IN TREATING RESISTANT HYPERTENSION

(57) Abstract: Compositions comprising omega-3 fatty acids, where the compositions are useful for treating resistant hypertension, reducing blood pressure in a patient suffering from resistant hypertension, and/or controlling blood pressure in a patient suffering from resistant hypertension. The compositions are also useful in methods for treating resistant hypertension in a subject group of patients suffering from resitant hypertension, where the blood pressure of the subject group is reduced by a statistically significant amount as compared to a control group.

Omega-3 Fatty Acids For Use In Treating Resistant Hypertension

RELATED APPLICATION DATA

[0001] This application claims priority from U.S. Provisional Application No. 60/832,156, which was filed on July 21, 2006, the contents of which are incorporated herein by reference.

Background of the Invention

1. Field of the Invention

[0002] The present invention relates, generally, to compositions comprising omega-3 fatty acids, where the compositions are useful for treating resistant hypertension. The present invention also includes pharmaceutical formulations made from the compositions, methods of making such formulations and methods of using the formulations to treat resistant hypertension.

2. Description of the Related Art

[0003] Hypertension is a dangerous condition which increases heart activity and contributes to atherosclerosis. Hypertension increases the risk of heart disease and stroke, which are the first- and third-leading causes of death among Americans. High blood pressure also can result in other conditions, such as congestive heart failure, kidney disease, and blindness.

[0004] According to the National Institutes of Health, a blood pressure level of 140/90 mmHg (systolic/diastolic) or higher is considered "high." About two-thirds of people over 65 have hypertension. For many people, reduction of blood pressure levels may be achieved by lifestyle changes, such as weight reduction, dietary sodium reduction, exercise, moderation of alcohol consumption and smoking

cessation. However, for others, lifestyle changes are not suitable or adhered to, or more intervention is needed. For these patients, drug treatment is prescribed.

[0005] A large number of drugs are currently available for reducing blood pressure. However, more than two-thirds of hypertensive individuals cannot be controlled on one drug, and require two or more antihypertensive agents chosen from different classes. In hypertensive patients with lower blood pressure goals or with substantially elevated blood pressure, three or more antihypertensive drugs may be utilized. The use of at least a second antihypertensive drug is recommended when use of a single agent is inadequate to achieve the goal blood pressure levels, for example when blood pressure is greater than 20 mmHg above the systolic goal or 10 mmHg above the diastolic goal.

[0006] A particularly persistent form of hypertension is resistant hypertension. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (commonly known as "JNC 7"), published by the National Heart, Lung, and Blood Institute in August 2004, defines resistant hypertension as "the failure to achieve goal blood pressure in patients who are adhering to full doses of an appropriate three-drug regimen that includes a diuretic."

[0007] Omega-3 fatty acids are known to reduce serum triglycerides by inhibiting diacylglycerol acyltransferase (DGAT) and by stimulating peroxisomal and mitochondrial beta oxidation. Marine oils, also commonly referred to as fish oils, are a good source of two omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which have been found to regulate lipid metabolism. Omega-3 fatty acids have been found to have beneficial effects on the risk factors for cardiovascular diseases, especially mild hypertension, hypertriglyceridemia and on

the coagulation factor VII phospholipid complex activity. Further, omega-3 fatty acids seem to be well tolerated, without giving rise to any severe side effects.

[0008] One form of omega-3 fatty acids is a concentrate of omega-3, long chain, polyunsaturated fatty acids from fish oil containing DHA and EPA that is sold under the trademark Lovaza®. Such a form of omega-3 fatty acids is described, for example, in U.S. Patent Nos. 5,502,077, 5,656,667 and 5,698,594, each of which is incorporated herein by reference. These patents disclose the use of such a concentrated form of omega-3 fatty acids in the treatment of hypertension.

[0009] Various studies have been conducted to determine the effects of dietary supplementation with omega-3 fatty acids on hypertensive patients that are being treated with more than one hypertension medication. The results of such studies have been mixed.

[00010] Lungershausen et al., J. Hypertension 1994, 12:1041-1045, assessed the effects of omega-3 fatty acid supplementation on blood pressure in hypertensives treated with diuretics, beta-blockers, or both. Forty-three patients with uncomplicated essential hypertension controlled by either taking a beta-blocker only (n=29), a diuretic only (n=3), or a beta-blocker plus diuretic (n=11) were subjected to a cross-over trial in which either a placebo (4 g corn oil) or fish oil (4 g Lovaza®, containing 85% EPA and DHA) was administered. All participants had been taking antihypertensive medication for at least one year, which had resulted in satisfactory control in all cases. Pre-medication baseline blood pressure levels averaged 172/103 mmHg for the group taking corn oil initially, and 173/103 mmHg for the group taking Lovaza® initially. The study found that the average values of both systolic blood pressure and diastolic blood pressure were significantly lower in each group during the period of omega-3 fatty acid supplementation.

[0010] Wing et al., J. Hypertension 1990, 8:339-343, examined the effect of dietary supplementation with fish oil on blood pressure in 20 treated hypertensives with controlled blood pressure. Of the patients on three antihypertensive medications, two were on a beta-blocker, diuretic and nifedipine or prazosin, and three were on an ACE inhibitor, diuretic and beta-blocker or nifedipine. Patients were administered either a placebo (15 g olive oil) or fish oil (15 g Lipitac™, containing 30% EPA and DHA) in a cross-over trial. Patients had an average pre-entry blood pressure of 144.7/84.5 mmHg. The study failed to show any difference in blood pressure between the two phases of treatment with fish oil and olive oil.

[0011] Woodman et al., Am. J. Clin. Nutr. 2002, 76:1007-1015, examined whether treatment with either purified EPA or purified DHA had differential effects on blood pressure in treated hypertensives. Fifty-one patients were subjected to a single-arm study, in which either 4 g purified (about 96%) EPA, purified (about 92%) DHA or olive oil placebo were given once a day for six weeks. Twenty-four percent of the subjects used three or more antihypertensive agents. Average baseline blood pressure was 135.9/73.0 mmHg in the olive oil group, 137.1/75.8 mmHg in the EPA group, and 138.5/71.8 mmHg in the DHA group. There were no significant differences in systolic blood pressure or diastolic blood pressure between the groups at baseline. In comparison with changes in the olive oil group, there were no significant changes in systolic blood pressure or diastolic blood pressure in either the EPA or DHA groups.

[0012] Bao et al., Hypertension 1998, 32:710-717, examined the effects of dietary fish and weight reduction on blood pressure in overweight hypertensives. Patients were randomized into one of four groups: a control group, a fish diet group in which patients included a daily fish meal (approximately 3.65 g of omega-3 fatty acids), a

weight loss group, or a fish diet + weight loss group. Two of the 16 subjects in the control group, one of the 17 subjects in the fish diet group, one of the 16 subjects in the weight loss group, and one of the 14 subjects in the fish diet + weight loss group were taking three or more antihypertensive medications. The average baseline blood pressure for the four groups was 135.9/75.4 mmHg for the control group, 132.1/75.2 mmHg in the fish diet group, 137.6/78.3 mmHg in the weight loss group, and 132.1/74.9 mmHg in the fish diet + weight loss group. The study found that the incorporation of a daily meal of fish rich in omega-3 fatty acids into a reduced-fat, energy-restricted diet in obese treated hypertensive subjects resulted in additive effects on blood pressure reduction.

[0013] Gray et al., Pharmacother. 1996, 16(2):295-300, examined the effects of omega-3 fatty acid supplementation on blood pressure controls in 19 subjects whose blood pressure was not optimally controlled with antihypertensive agents. The subjects received either 18 g of menhaden oil (containing 25% omega-3 fatty acids) or 18 g of corn oil placebo. Subjects in the placebo group had an average baseline supine blood pressure of 151/93 mmHg in the placebo group, and 151/97 mmHg in the fish oil group. Subjects receiving fish oil had a significant reduction in blood pressure by 4 weeks of treatment, but the decrease was less pronounced after 8 weeks.

[0014] None of the above-mentioned art discloses that omega-3 fatty acids may be useful for treating resistant hypertension. There is a need in the art for treatments for resistant hypertension.

Summary of the Invention

[0015] The present invention meets the unmet needs of the art, as well as others, by providing compositions containing natural or synthetic omega-3 fatty acids, and/or

their pharmaceutically acceptable esters, derivatives, conjugates, precursors or salts, or mixtures thereof, as an effective treatment for resistant hypertension.

[0016] The present invention also provides natural or synthetic omega-3 fatty acids, and/or their pharmaceutically acceptable esters, derivatives, conjugates, precursors or salts, or mixtures thereof, to provide an effective pharmaceutical treatment for resistant hypertension, while minimizing unwanted side effects.

[0017] One embodiment of the present invention provides a method of utilizing natural or synthetic omega-3 fatty acids, and/or their pharmaceutically acceptable esters, derivatives, conjugates, precursors or salts, or mixtures thereof, in the treatment of subjects with resistant hypertension.

[0018] Another embodiment of the present invention is an oral formulation of natural or synthetic omega-3 fatty acids or pharmaceutically acceptable esters, derivatives, conjugates, precursors or salts thereof, or mixtures thereof, wherein the formulation is used in the treatment of subjects with resistant hypertension.

[0019] Another subject of the invention is a method of reducing blood pressure in a patient suffering from resistant hypertension, comprising administering natural or synthetic omega-3 fatty acids or pharmaceutically acceptable esters, derivatives, conjugates, precursors or salts thereof, or mixtures thereof.

[0020] Another subject of the invention is a method of controlling blood pressure in a patient suffering from resistant hypertension, comprising administering natural or synthetic omega-3 fatty acids or pharmaceutically acceptable esters, derivatives, conjugates, precursors or salts thereof, or mixtures thereof.

[0021] Another subject of the invention is the use of natural or synthetic omega-3 fatty acids or pharmaceutically acceptable esters, derivatives, conjugates, precursors

or salts thereof, or mixtures thereof, for the manufacture of a medicament for treating resistant hypertension.

[0022] Another subject of the invention is a method of treating resistant hypertension in a subject group, comprising administering to the subject group natural or synthetic omega-3 fatty acids or pharmaceutically acceptable esters, derivatives, conjugates, precursors or salts thereof, or mixtures thereof.

[0023] Another subject of the invention is a method of treating resistant hypertension in a subject group, comprising administering to the subject group natural or synthetic omega-3 fatty acids or pharmaceutically acceptable esters, derivatives, conjugates, precursors or salts thereof, or mixtures thereof, wherein after administration to the subject group the blood pressure of the subject group is reduced in a statistically significant amount as compared to a control group.

[0024] Other novel features and advantages of the present invention will become apparent to those skilled in the art upon examination of the following or upon learning by practice of the invention.

Detailed Description of the Invention

[0025] The present invention relates to compositions comprising omega-3 fatty acids, methods of making same, and their use in treating resistant hypertension.

[0026] In some preferred embodiments the omega-3 fatty acids comprise Lovaza® omega-3 fatty acids, as described in U.S. Patent Nos. 5,502,077, 5,656,667 and 5,698,594. In other preferred embodiments the omega-3 fatty acids are present in a concentration of at least 40% by weight as compared to the total fatty acid content of the composition. In still other preferred embodiments the omega-3 fatty acids comprise at least 50% by weight of EPA and DHA as compared to the total fatty acid content of the composition. Preferably, the EPA and DHA are in a weight ratio of

EPA:DHA of from 99:1 to 1:99, preferably from 1:4 to 4:1, more preferably from 1:3 to 3:1, and most preferably from 1:2 to 2:1. The omega-3 fatty acids may also comprise pure EPA or pure DHA.

[0027] As used herein, the term "omega-3 fatty acids" includes natural or synthetic omega-3 fatty acids, or pharmaceutically acceptable esters, derivatives, conjugates (see, e.g., Zaloga et al., U.S. Patent Application Publication No. 2004/0254357, and Horrobin et al., U.S. Patent No. 6,245,811, each hereby incorporated by reference), precursors or salts thereof and mixtures thereof. Examples of omega-3 fatty acid oils include but are not limited to omega-3 polyunsaturated, long-chain fatty acids such as a eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and α-linolenic acid; esters of omega-3 fatty acids with glycerol such as mono-, di- and triglycerides; and esters of the omega-3 fatty acids and a primary, secondary or tertiary alcohol such as fatty acid methyl esters and fatty acid ethyl esters. Preferred omega-3 fatty acid oils are long-chain fatty acids such as EPA or DHA, triglycerides thereof, ethyl esters thereof and mixtures thereof. The omega-3 fatty acids or their esters, derivatives, conjugates, precursors, salts and mixtures thereof can be used either in their pure form or as a component of an oil such as fish oil, preferably purified fish oil concentrates. Commercial examples of omega-3 fatty acids suitable for use in the invention include Incromega F2250, F2628, E2251, F2573, TG2162, TG2779, TG2928, TG3525 and E5015 (Croda International PLC, Yorkshire, England), and EPAX6000FA, EPAX5000TG, EPAX4510TG, EPAX2050TG, K85TG, K85EE, K80EE and EPAX7010EE (Pronova Biocare a.s., 1327 Lysaker, Norway).

[0028] Another preferred composition includes omega-3 fatty acids present in a concentration of at least 40% by weight, preferably at least 50% by weight, more preferably at least 60% by weight, still more preferably at least 70% by weight, most

preferably at least 80% by weight, or even at least 90% by weight. Preferably, the omega-3 fatty acids comprise at least 50% by weight of EPA and DHA, more preferably at least 60% by weight, still more preferably at least 70% by weight, most preferably at least 80%, such as about 84% by weight. Preferably the omega-3 fatty acids comprise about 5 to about 100% by weight, more preferably about 25 to about 75% by weight, still more preferably about 40 to about 55% by weight, and most preferably about 46% by weight of EPA. Preferably the omega-3 fatty acids comprise about 5 to about 100% by weight, more preferably about 25 to about 75% by weight, still more preferably about 30 to about 60% by weight, and most preferably about 38% by weight of DHA. All percentages above are by weight as compared to the total fatty acid content in the composition, unless otherwise indicated. The percentage by weight may be based on the free acid or ester forms, although it is preferably based on the ethyl ester form of the omega-3 fatty acids even if other forms are utilized in accordance with the present invention.

[0029] The omega-3 fatty acids can be present in an amount from about 350 mg to about 10 grams, more preferably about 500 mg to about 6 grams, and most preferably from about 750 mg to about 4 grams. This amount may be in one or more dosage forms, preferably one dosage form. The omega-3 fatty acid composition optionally includes chemical antioxidants, such as alpha tocopherol, oils, such as soybean oil and partially hydrogenated vegetable oil, and lubricants such as fractionated coconut oil, lecithin and a mixture of the same.

[0030] The most preferred form of omega-3 fatty acids is Lovaza® omega-3 fatty acids (K85EE, Pronova Biocare A.S., Lysaker, Norway) and preferably comprises the following characteristics (per dosage form):

Test	Minimum Value	Maximum Value
Eicosapentaenoic acid C20:5	430 mg/g	495 mg/g
Docosahexaenoic acid C22:6	347 mg/g	403 mg/g
EPA and DHA	800 mg/g	880 mg/g
Total n-3 fatty acids	90 % (w/w)	

[0031] The active ingredients of the present invention, omega-3 fatty acids, may be administered with a combination of one or more non-active pharmaceutical ingredients (also known generally herein as "excipients"). Non-active ingredients, for example, serve to solubilize, suspend, thicken, dilute, emulsify, stabilize, preserve, protect, color, flavor, and fashion the active ingredients into an applicable and efficacious preparation that is safe, convenient, and otherwise acceptable for use.

[0032] Excipients include surfactants, such as propylene glycol monocaprylate, mixtures of glycerol and polyethylene glycol esters of long fatty acids, polyethoxylated castor oils, glycerol esters, oleoyl macrogol glycerides, propylene glycol monolaurate, propylene glycol dicaprylate/dicaprate, polyethylene-polypropylene glycol copolymer, and polyoxyethylene sorbitan monooleate, cosolvents such ethanol, glycerol, polyethylene glycol, and propylene glycol, and oils such as coconut, olive or safflower oils. The use of surfactants, cosolvents, oils or combinations thereof is generally known in the pharmaceutical art, and as would be understood to one skilled in the art, any suitable surfactant may be used in conjunction with the present invention and embodiments thereof.

[0033] The compositions and methods of the present invention may further comprise co-administration of one or more additional compounds useful in the treatment of hypertension. Also included are unit dosage forms including the natural or synthetic omega-3 fatty acids or pharmaceutically acceptable esters, derivatives, conjugates, precursors or salts thereof, or mixtures thereof, and said one or more

additional compounds, and methods for administering same to a patient in need thereof.

[0034] These additional compounds may be one or more, preferably two or more, most preferably three or more different compounds each independently selected from the classes of diuretics, aldosterone receptor blockers, beta-blockers, combined alpha- and beta-blockers, ACE inhibitors, angiotensin II antagonists, calcium channel blockers, alpha-1 blockers, central alpha-2 agonists, and direct vasodilators. Preferably, at least one of the additional compounds is a diuretic. More preferably, the additional compounds include at least three different types of compounds indicated above, including a diuretic. Already-existing treatment with three different types of compounds including a diuretic is typically found in subjects having resistant hypertension.

[0035] Also envisioned in accordance with the present invention is the use of similar compounds to those set forth above, which may be discovered in the future, or already existing compounds that may be approved for treatment of hypertension in the future.

[0036] The composition comprising omega-3 fatty acids may be prepared in the form of a capsule, such as a hard gelatin capsule; a tablet; a powder that can be dispersed in a beverage; a liquid; or a soft gel capsule. The composition may also be contained in a liquid suitable for injection or infusion. However, the methods of preparing the inventive compositions for administration are not to be limited to any particular dosage form. Rather, they may be prepared as any pharmaceutically acceptable dosage form, including other solid oral dosage forms, other liquid oral dosage forms, and any other suitable dosage forms. When provided, the one or

more optional additional ingredients may also be provided in the dosage form with the omega-3 fatty acids, so as to create a convenient unit dose form.

[0037] The omega-3 fatty acids can be administered in a daily amount of from about 0.1 g to about 10 g, more preferably about 1 g to about 6 g, and most preferably from about 2 g to about 4 g, to a patient suffering from resistant hypertension. The daily dosages of omega-3 fatty acids can be administered together in from 1 to 10 dosages, with the preferred number of dosages from 1 to 4 times a day, most preferred 1 to 2 times a day. The administration is preferably oral administration, although other forms of administration that provide a unit dosage of omega-3 fatty acids may be used. The administration of the dosages is preferably effective in lowering blood pressure levels, more preferably effective in controlling blood pressure. Ideally, treatment in accordance with the present invention reduces systolic blood pressure levels to under 140 mmHg and/or reduces diastolic blood pressure levels to under 90 mmHg.

[0038] Blood pressure levels may be measured in accordance with any recognized method in the art, such as but not limited to, supine, sitting, upright, standing or 24-hr ambulatory.

[0039] Throughout this application, various patents and publications have been cited. The disclosures of these patents and publications in their entireties are hereby incorporated by reference into this application, in order to more fully describe the state of the art to which this invention pertains.

[0040] The invention is capable of considerable modification, alteration, and equivalents in form and function, as will occur to those ordinarily skilled in the pertinent arts having the benefit of this disclosure.

[0041] While the present invention has been described for what are presently considered the preferred embodiments, the invention is not so limited. To the contrary, the invention is intended to cover various modifications and equivalent arrangements included within the spirit and scope of the detailed description provided above.

WHAT IS CLAIMED:

1. A method of treating resistant hypertension in a patient suffering therefrom, comprising the steps of:

providing a composition comprising one or more omega-3 fatty acids; and

administering the composition to the patient in an amount effective to treat resistant hypertension.

2. A method of reducing blood pressure in a patient suffering from resistant hypertension, comprising the steps of:

providing a composition comprising one or more omega-3 fatty acids; and

administering the composition to the patient in an amount effective to reduce blood pressure.

3. The method of claim 2, wherein the treatment reduces systolic blood pressure levels to under 140 mmHg and/or reduces diastolic blood pressure levels to under 90 mmHg.

4. A method of controlling blood pressure in a patient suffering from resistant hypertension, comprising the steps of:

providing a composition comprising one or more omega-3 fatty acids; and

administering the composition to the patient in an amount effective to control blood pressure.

5. Use of one or more omega-3 fatty acids for manufacturing a medicament for treating resistant hypertension, in patients suffering therefrom.

6. A method of treating resistant hypertension in a subject group of patients suffering from resistant hypertension, comprising the steps of:

providing a composition comprising one or more omega-3 fatty acids; and

administering the composition to the subject group in an amount effective to treat resistant hypertension in the subject group.

7. A method of treating resistant hypertension in a subject group of patients suffering from resistant hypertension, comprising the steps of:

providing a composition comprising one or more omega-3 fatty acids; and

administering the composition to the subject group wherein after administration to the subject group the blood pressure of the subject group is reduced by a statistically significant amount as compared to a control group.

8. The method or use of any one of claims 1-7, wherein the one or more omega-3 fatty acids comprise EPA and DHA.

9. The method or use of any one of claims 1-8, wherein the one or more omega-3 fatty acids is present in a concentration of at least 40% by weight as compared to the total fatty acid content of the composition.

10. The method or use of any one of claims 1-8, wherein the one or more omega-3 fatty acids is present in a concentration of at least 80% by weight as compared to the total fatty acid content of the composition.

11. The method or use of any one of claims 1-10, wherein the one or more omega-3 fatty acids comprise at least 50% by weight of EPA and DHA as compared to the total fatty acid content of the composition.

12. The method or use of any one of claims 1-10, wherein the one or more omega-3 fatty acids comprise at least 80% by weight of EPA and DHA as compared to the total fatty acid content of the composition.

13. The method or use of any one of claims 1-12, wherein the one or more omega-3 fatty acids comprise about 40% to about 55% by weight of EPA as compared to the total fatty acid content of the composition.

14. The method or use of any one of claims 1-13, wherein the one or more omega-3 fatty acids comprise about 30% to about 60% by weight of DHA as compared to the total fatty acid content of the composition.

15. The method or use of any one of claims 1-14, wherein the one or more omega-3 fatty acids are selected from the group consisting of omega-3 polyunsaturated, long-chain fatty acids; esters of omega-3 fatty acids with glycerol; esters of omega-3 fatty acids and a primary, secondary or tertiary alcohol; and mixtures thereof.

16. The method or use of any one of claims 1-15, wherein the EPA and DHA are in a weight ratio of EPA:DHA of from 1:2 to 2:1.

17. The method or use of any one of claims 1-16, wherein the composition further comprises one or more additional compounds useful in the treatment of hypertension.

18. The method of claim 17, wherein the one or more additional compounds are each selected from the group consisting of diuretics, aldosterone receptor blockers, beta-blockers, combined alpha- and beta-blockers, ACE inhibitors, angiotensin II antagonists, calcium channel blockers, alpha-1 blockers, central alpha-2 agonists, and direct vasodilators.

19. The method of claim 17 or 18, wherein the one or more additional compounds include at least three different types of additional compounds useful in the treatment of hypertension.

20. The method of claim 19, wherein at least one of the three types of additional compounds is a diuretic.