"ESSENTIAL FATTY ACIDS IN THE PREVENTION OF CARDIOVASCULAR EVENTS"

DESCRIPTION

This invention concerns the use of a pharmaceutical composition containing essential fatty acid ethyl esters originating from fish oils, in particular as a high concentration mixture of ethyl esters of (20:5ω 3) eicosapentaenoic acid (EPA) and (22:6ω 3) docosahexaenoic acid (DHA) in the prevention of cardiovascular events, especially of mortality in patients who have survived the hospitalization phase of acute myocardial infarction (AMI).

It is well known that certain essential fatty acids contained in fish oil have a therapeutic effect in the prevention and treatment of cardiovascular disorders, such as in the treatment of thrombosis, hypercholesterolemia, arteriosclerosis, cerebral infarction and hyperlipemias.

U.S. Patents US 5,502,077, US 5,656,667 and US 5,698,594 can be quoted as examples.

From the above prior art, it is known in particular the utility of fatty acids belonging to the ω-3 family, more specifically (20:5ω 3) eicosapentaenoic acid (EPA) and (22:6ω 3) docosahexaenoic acid (DHA) in treating the above-mentioned disorders.

Indeed EPA, being a precursor of PGI3 and TxA3, exerts a preventing platelet aggregation effect and an antithrombotic effect that can be ascribed to inhibition of cyclooxygenase (similar effect to that of aspirin) and/or to competition with arachidonic acid for this enzyme, with consequent reduction in the synthesis of PGE2 and TxA2, which are well known platelet aggregating agents.

On the other hand DHA is the most important component of cerebral lipids in man and furthermore, being a structural component of the platelet cell,

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it intervenes indirectly in increasing platelet fluidity, thus playing an important role in antithrombotic activity.

International patent application W089/11521, whose description is herein incorporated by reference, describes in particular an industrial process for extracting mixtures with a high content in poly-unsaturated acids, including EPA and DHA and their ethyl esters, from animal and/or vegetable oils.

Mixtures of fatty acids, especially EPA/DHA, obtained according to W089/11521, are reported to be particularly useful in the treatment of cardiovascular diseases.

However, currently used treatments in human therapy have been shown to be insufficient in preventing cardiovascular events, and more specifically mortality, in particular due to sudden death, which happen in patients who have had a myocardial infarction, on account of recurrences after a first acute myocardial infarction episode.

Therefore, there still is the need for an effective drug, in particular for preventing these recurrences.

Object of this invention, therefore, is the use of essential fatty acids with a high content in EPA-ethyl ester or DHA-ethyl ester or a high concentration mixture thereof, in the preparation of a medicament useful for preventing mortality, due, for instance, to cardiovascular events or sudden death, in patients who have suffered from a myocardial infarction.

According to a preferred aspect this invention therefore provides the use of essential fatty acids with a high content in EPA-ethyl ester or DHA-ethyl ester or a high concentration mixture thereof, in the preparation of a medicament useful for preventing sudden death in patients who have suffered from a myocardial infarction.

For ease of description "EPA-ethyl ester" and "DHA-ethyl ester" will be also quoted here as "EPA" and "DHA".

An essential fatty acid with high content in EPA-ethyl ester or DHA-ethyl

ester, according to the present invention, preferably contains more than 25% by weight (b.w.), in particular from about 60 to about 100% of such ester.

These compounds can be obtained by known methods.

In an essential fatty acid with a high concentration mixture of EPA-ethyl ester and DHA-ethyl ester, preferably such mixture has a content in EPA + DHA greater than 25% by weight, in particular from about 30 to about 100% by weight, preferably about 85% by weight.

In the EPA/DHA mixture, EPA preferably is present in a percentage from about 40 to about 60% by weight and DHA, preferably in a percentage from about 25 to about 45-50%.

In any case the preferred EPA/DHA ratio in such EPA/DHA mixture is about 0.9/1.5.

PHARMACOLOGY

The efficacy of the treatment, according to the invention, is, for instance, proven by the fact that a surprising and highly significant reduction in post-infarction mortality was observed by such treatment in a clinical trial that lasted for 3.5 years, with protocols substantially designed as follows:

1 a "control " group received the standard therapy which is usually given to infarcted patients;

2 a "treatment" group, besides the therapy that was given to the "control" group, received 85% EPA+DHA (1 g daily);

3 a "treatment" group, besides the therapy that was given to the "control" group received vitamin E; and

4 a "treatment" group, besides the therapy that was given to the control group, received vitamin E and 85% EPA+DHA (1 g daily).

In fact the group of patient "treated" according to protocol 2 showed, in comparison to "control" group 1, a decrease of about 20% in total

mortality, with a decrease of about 40% of mortality due to sudden death and a notable reduction in mortality due to other cardiovascular events.

On the contrary, no significant results were achieved in group 3 as compared to the control group 1, whereas there was a reduction in total mortality of about 19% in group 4 as compared to the control group, with results that were similar to those obtained in treated group 2.From the above clinical results, the person skilled in the art will appreciate that, the use of a pharmaceutical composition in accordance to the present invention is certainly useful in human therapy in preventing mortality in patients who have suffered from a myocardial infarction.

Accordingly, this invention provides a method for preventing mortality in a patient who has survived a myocardial infarction, comprising administering to such patient a therapeutically effective amount of a medicament containing essential fatty acids with a high content in EPA-ethyl ester or DHA-ethyl ester or a high concentration mixture thereof.

As known, sudden death is an important contributor to the mortality rate in patients with cardiac disease, accounting for over 450,000 death per year in the USA.

About 80% of such patients, particularly those survivors of acute myocardial infarction with low ventricular ejection fractions, are at high risk of sudden death or reinfarction.

The above clinical results show that the present invention provides a new and valuable therapeutic tool for preventing sudden death in patients in particular in those who survived acute myocardial infarction.

Accordingly, as a preferred aspect, the present invention also provides a method for preventing sudden death in a patient, who is survivor of myocardial infarction, comprising administering to such patient a therapeutically effective amount of a medicament containing essential fatty acids with a high content in EPA-ethyl ester or DHA-ethyl ester or a high concentration mixture thereof.

The essential fatty acids, according to the invention, can either have a high content, for instance more than 25% b.w., in EPA-ethyl ester or DHA-ethyl ester or in a mixture thereof. However EPA-ethyl ester and DHA-ethyl ester are preferably present as a mixture thereof with a content in EPA+DHA higher than 25% b.w, in particular from about 30 to about 100% b.w., preferably about 85% b.w.

Based on the obtained clinical results, according to a preferred aspect of the invention, the dosage of an essential fatty acid containing a EPA+DHA mixture with 85% b.w. titer for oral administration to a patient may vary from about 0.7 g to about 1.5 g daily, preferably about 1 g daily.

This amount of product as EPA+DHA mixture (or amount of EPA-ethyl ester alone or DHA-ethyl ester alone) may be administered in several divided doses throughout the day or preferably in a single administration, in order to achieve the desired hematic level. Obviously it is at the discretion of the physician to adjust the quantity of product to be administered according to the age, weight and general conditions of the patient.

The medicament, e.g. in the form of a pharmaceutical composition, according to this invention can be prepared according to known methods in the art. The preferred route of administration is the oral one, however leaving alternative routes of administration, such as the parenteral route, to the discretion of the physician.

The following examples illustrate preferred formulations for oral administration, but do not intend to limit the invention in any way.

Gelatin capsules

According to known pharmaceutical techniques, capsules having the composition below and containing 1 g of active ingredient (EPA + DHA, 85% titer) per capsule are prepared.

Formulation 1

EPA-ethyl ester	525 mg/capsule;
DHA-ethyl ester	315 mg/capsule;
d-alpha tocopherol	4 IU/capsule;
gelatin	246 mg/capsule
glycerol	118 mg/capsule;
red iron oxide	2.27 mg/capsule;
yellow iron oxide	1.27 mg/capsule

Formulation 2

Ethyl esters of poly-unsaturated fatty acids with content in ethyl esters of ω-3 poly-unsaturated esters (eicosapentaenoic EPA , docosahexaenoic (DHA)	1000 mg
	850 mg
d-1-α tocopherol	0.3 mg
gelatin succinate	233 mg
glycerol	67 mg
sodium p-oxybenzoate	1.09 mg
sodium propyl p-oxobenzoate	0.54 mg

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CLAIMS

1. Use of essential fatty acids containing a mixture of eicosapentanoic acid ethyl ester (EPA) and docosahexaenoic acid ethyl ester (DHA) in the preparation of a medicament useful for preventing mortality in a patient who has suffered from a myocardial infarction where the content in EPA+DHA in such mixture is greater than 25% b.w.

2. Use according to claim 1, wherein the medicament is useful for preventing mortality due to sudden death in a patient who has suffered from a myocardial infarction.

3. Use according to claim 1 or 2, wherein the content in EPA+DHA in such mixture is from about 30 to about 100% b.w.

4. Use according to claim 1 or 2, wherein the content in EPA+DHA in such mixture is about 85% b.w.

5. Use according to anyone of claims 1 to 4, wherein the medicament is for oral administration.

6. Use according to claim 4, wherein the medicament is for oral administration, at a dosage from about 0.7 g to about 1.5 g daily.

7. Use according to claim 6, wherein the EPA/DHA ration in the EPA+DHA mixture is about 0.9/1.5.

8. Use of essential fatty acids containing eicosapentaenoic acid ethyl ester (EPA) or docosahexaenoic acid ethyl ester (DHA) in the preparation of a medicament useful for preventing mortality in a patient who has suffered from a myocardial infarction, wherein the EPA or DHA content is greater than 25% b.w.

9. Use according to claim 8, wherein the medicament is useful for preventing mortality due to sudden death in a patient who has suffered from a myocardial infarction.

10. Use according to claim 8 or 9, wherein the EPA or DHA content is from about 60 to about 100% b.w.

11. Use according to anyone of claims 8 to 10, wherein the medicament is

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for oral administration.

12. A method for preventing mortality in a patient who has survived a myocardial infarction, comprising administering to said patient a therapeutically effective amount of a medicament containing essential fatty acids containing a mixture of eicosapentaenoic acid ethyl ester (EPA) and docosahexaenoic acid ethyl ester (DHA) wherein the content in EPA+DHA in such mixture is greater than 25% b.w.

13. A method according to claim 12, wherein the content in EPA+DHA in such mixture is from about 30 to about 100% b.w.

14. A method according to claim 12, wherein the content in EPA+DHA in such mixture is about 85% b.w.

15. A method according to claim 12, 13 or 14, wherein the medicament is administered orally.

16. A method according to claim 14, wherein the medicament is administered orally at a dosage from about 0.7g to about 1.5 g daily.

17. A method according to claim 16, wherein the EPA/DHA ratio in the EPA+DHA mixture is about 0.9/1.5

18. A method for preventing sudden death in a patient, who is survivor of myocardial infarction, comprising administering to said patient a therapeutically effective amount of a medicament containing essential fatty acids containing a mixture of eicosapentaenoic acid ethyl ester (DPA) and docosahexaenoic acid ethyl ester (DHA), wherein the content in EPA+DHA in such mixture is greater than 25% b.w.

19. A method according to claim 18, wherein the content in EPA+DHA in such mixture is from about 30 to about 100% b.w.

20. A method according to claim 18, wherein the content in EPA+DHA in such mixture is about 85% b.w.

21. A method according to claim 18,19 or 20, wherein the medicament is



administered orally.

22. A method according to claim 20, wherein the medicament is administered orally at a dosage from about 0.7g to about 1.5 g daily.

23. A method according to claim 22, wherein the EPA/DHA ration in the EPA+DHA mixture is about 0.9/1.5.

24. A method for preventing morality in a patient who has survived a myocardial infarction, comprising administering to said patient a therapeutically effective amount of a medicament containing essential fatty acids with a content in eicosapentaenoic acid ethyl ester (EPA) or in docosahexaenoic acid ethyl ester (DHA) greater than 25% b.w.

25. A method according to claim 24, wherein the contention EPA or DHA is form about 60 to about 100% b.w.

26. A method according to claim 24 or 25, wherein the medicament is administered orally.

27. A method for preventing sudden death in a patient who is survivor of myocardial infarction, comprising administering to said patient a therapeutically effective amount of a medicament containing essential fatty acids with a content in eicosapentaenoic acid ethyl ester (EPA) or docosahexaenoic acid ethyl ester (DHA) greater than 25% b.w.

28. A method according to claim 27, wherein the content in EPA or DHA is from about 60 to about 100% b.w.

29. A method according to claim 27 or 28, wherein the medicament is administered orally.

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