ESSENTIAL N-3 FATTY ACIDS IN CARDIAC INSUFFICIENCY AND HEART FAILURE THERAPY



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The present invention belongs to the field of pharmaceutical chemistry and cardiovascular medicine and provides a method of prevention and management of cardiac insufficiency and heart failure: two heart diseases in which the second one is the result of the progressive evolution of the first one.

Cardiac insufficiency is a condition in which the heart pump function is inadequate to meet the bodily metabolic requirements. Depending on the different severity of the pump deficit, cardiac insufficiency may be symptom-free or clinically manifest.

Cardiac insufficiency could have various causes, e.g.:

- disorders of myocardial function, which is the most frequent cause, due to a reduced contractility, but also to a loss of contractile tissue;
- a volume load, due to disorders requiring the ventricle to expel more blood than the normal per minute;
- a pressure load, due to disorders increasing the resistance to the outflow from the ventricles.

Heart failure is the result of the progressive evolution of cardiac insufficiency.

Moreover, a broad spectrum of diseases could cause an impaired filling or emptying of heart chambers, such as: the diseases resulting from a monogenic (familial hypertrophic cardiomyopathy, mitochondral cardiomyopathies) or multigenic defect which are bound to environmental factors such as cigarette smoking, diet, physical exercise, secondary heart diseases. All these diseases take the "common end path" towards heart failure, which sees at first an impairment of the molecular mechanisms and then an impairment of the ventricular function and heart failure. Therefore, heart failure is a syndrome with a various etiology resulting from an anatomo-functional anomaly of the heart with inability in keeping a stroke adequate to the metabolic requirements of the tissues or maintaining the stroke volume by a high filling pressure.



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Heart failure is characterized by clinical signs and symptoms secondary to the inadequate response to the body metabolic requirements. This condition could occur acutely or have a chronic course.

The pathophysiological interpretations of heart failure have had a remarkable evolution in time. This syndrome was considered as a pump deficiency associated with a renal dysfunction in years '50-'60, a pump dysfunction associated with an increase in peripheral resistance in years '70-'80 and is considered at present as a failure of the pump function associated with the neuro-hormonal activation with resulting hemodynamic impairments which take to a dysfunction of many organs and apparatuses.

The present drug therapy of cardiac "pump function" includes the use of drugs acting by various modes of action on different points of the etiopathogenesis of the diseases. We mention as an example: ACE-inhibitors (Angiotensin Converting Enzymes inhibitors), diuretics, non-digitalis positive inotropic drugs such as adrenergics and inhibitors of phosphodiesterase, arteriolar and venular vasodilators, e.g. hydralazine and isosorbide dinitrate, beta-blockers e.g. metoprolol and bisoprolol and digitalis derivatives, e.g. digotoxin.

Heart failure is at present one of the most important causes of morbidity and mortality in the industrialized countries, as clearly demonstrated by the present case-series: in USA 4.7 million persons have a congestive heart failure, with an incidence equal to 400,000 new cases a year.

The prevalence of chronic cardiac insufficiency rises from 8 cases of heart failure out of 1,000 subjects of age ranging from 50 to 59 years, to 66 cases out of 1,000 subjects between 80 and 89 years.

If we consider that about 35% of patients with heart failure are hospitalised at least once a year and that 80% of men and 65% of women die within 6 years, the social-health entity of the problem emerges in its full dramatic evidence.

Moreover, the incidence of heart failure seems to increase paradoxically with the reduction of death rate for myocardial infarction and for other cardiovascular diseases. The ageing of the population seems to be a contributing factor to amplify the relevance of the phenomenon.

Therefore, there is the need of a safe and convenient method of prevention and therapeutic treatment of cardiac insufficiency and heart failure, in particular in elderly patients, in order to restore (or to control) the usual pump function of the heart.

The present invention provides a method for the prevention and therapeutic treatment of cardiac insufficiency and heart failure in a patient in need of this treatment comprising the administration to such patient of a therapeutically effective amount of an essential fatty acid containing a mixture of (20:5ω 3) eicosapentaenoic acid ethyl ester (EPA) and of (20:6ω 3) docosahexaenoic acid ethyl ester (DHA), either alone or in combination with another therapeutic agent.

It is well known in the art that some essential fatty acids, in particular ω 3 PUFA, contained for example in the fish oil, have a therapeutic effect in the prevention and therapy of cardiovascular disorders, e.g. in the prevention and treatment of atherothrombotic events and hyperlipidemia.

WO 89/11521 describes in particular an industrial process for the extraction of mixtures having a high content in poly-unsaturated acids, also including EPA and DHA and their ethyl esters, from animal and/or vegetable oils. Mixtures of fatty acids, in particular EPA/DHA, obtained according to WO 89/11521, are indicated as particularly useful in the treatment of cardiovascular pathologies.

Therefore, object of the present invention is the use of an essential fatty acid containing a mixture of eicosapentaenoic acid ethyl ester (EPA) and docosahexaenoic acid ethyl ester (DHA) in the preparation of a medicament for the prevention and treatment of a heart disease chosen from cardiac insufficiency and heart failure, both chronic and acute.

For convenience of description, eicosapentaenoic acid ethyl ester and docosahexaenoic acid ethyl ester are mentioned here below respectively as "EPA" and "DHA".

An essential fatty acid, according to the invention, is preferably a fatty acid having a high content in EPA and DHA, for example with a content in EPA and DHA higher than 25% by weight, preferably from about 30% to about 100% by weight, in particular about 85%.

EPA is present in the EPA/DHA mixture preferably in a percentage ranging from 25% to about 45% by weight and DHA is present preferably in a percentage ranging from 55% to about 75% by weight.

At any rate, the most preferred ratio between EPA and DHA is about 0.6-1.1/1.3-1.8; in particular about 0.9/1.5.

An essential fatty acid according to the present invention can be obtained by known methods, e.g. as described in US Patent No. 5,656,667 and WO 89/11521.

Object of the present invention is also the use of an essential fatty acid containing a mixture of eicosapentaenoic acid ethyl ester (EPA) and docosahexaenoic acid ethyl ester (DHA) in the preparation of a medicament for the prevention and treatment of a heart disease chosen from cardiac insufficiency and heart failure, both chronic and acute, where the medicament is for combined therapy with another therapeutic agent.

The term "another therapeutic agent" means an additional single agent or two or more additional agents, preferably from 2 to 10, in particular from 2 to 6 according to physician's instructions, which may be administered in combination, namely either along or separately (substantially simultaneously or sequentially) with the essential fatty acid containing the mixture of EPA and DHA.

Examples of therapeutic agents for such a prophylaxis or combined therapy according to the invention are ACE-inhibitors, NEP-inhibitors, ACE/NEP-inhibitors, angiotensin II converting enzyme inhibitors, diuretics, positive inotropic drugs, phosphodiesterase inhibitors, arteriolar and venular vasodilators, beta-blockers and digitalis glycosides, or a mixture thereof.

NEP means degradation peptidase of atrial natriuretic peptide (ANP).

Examples of ACE-inhibitors are: captopril, enalapril, lisinopril, fosinopril, cilazapril, benazapril, perindopril, quinapril, ramipril, trandolapril and delapril, in particular cilazapril, captopril and enalapril.

Examples of ACE/NEP-inhibitors are: omapatrilat, sampatrilat and L-phenylalanine,N-[(2S)-2-(mercaptomethyl)-1-oxo-3-phenylpropyl]-4-(2-thiazolyl) (compound Z13752A, a product of Zambon Company).

Examples of angiotensin II receptors antagonists (angiotensin II converting inhibitors) are: candesartan, valsartan and losartan.

Examples of diuretics are: hydrochlorothiazide, trichlormethiazide, chlorothiazide, chlortalidone, triamterene, clofenamide, furosemide, torasemide, ethacrynic acid, etozoline, spironolactone and amiloride, if the case in association with potassium sparing drugs, which are well known in the art, in particular furosemide and hydrochlorothiazide.

Examples of dopaminergic agents are dopamine and ibopamine.

Examples of phosphodiesterase inhibitors are: amrinone, milrinone, enoximone and bucladesine, in particular amrinone and enoximone.

Examples of arteriolar and venular vasodilators are: hydralazine and isosorbide dinitrate.

Examples of beta-blockers are: visoprolol, practotol, metoprolol, bucindol, carvedilol, atenolol, bisoprolol, celiprolol and nevibolol, in particular visoprolol, carvedilol and metoprolol.

Examples of digitalis glycoside agents are: acetyl digitoxin, acetyldigoxin, digitoxin, digoxin, lanatoside C, deslanoside, methyldigoxin and gitoformat, in particular digitoxin, digoxin, acetyldigoxin and metidigoxin.

Examples of positive inotropic agents are: pimobendan and vesnarinone, in particular pimobendan.

A further object of the invention is a method for preventing and treating a heart disease chosen from cardiac insufficiency and heart failure, both chronic and acute, comprising administering to a patient in need thereof a therapeutically effective amount of an unsaturated essential acid containing a mixture of eicosapentaenoic acid ethyl ester (EPA) and docosahexaenoic acid ethyl ester (DHA).

A further object of the invention is a method to prevent and treat a heart disease chosen from cardiac insufficiency and heart failure, both chronic and acute, comprising administering to a patient in need thereof a therapeutically effective amount of an essential fatty acid containing a mixture of eicosapentaenoic acid ethyl ester (EPA) and docosahexaenoic acid ethyl ester (DHA), in combination with another therapeutic agent.

The term "in combination" means that the essential fatty acid containing the mixture EPA+DHA and the other therapeutic agent are administered in such an amount and separated by such administration times as to produce a therapeutic effect.

The use of an essential fatty acid according to the invention is extremely useful in the prevention and treatment of cardiac insufficiency and heart failure both chronic and acute, in particular, in the elderly people, e.g. older than 60 years, in subjects with other further cardiopathic forms and, in particular, in subjects surviving a myocardial infarction, thanks to the fact that this is a well tolerated drug.

The amount of essential fatty acid to be administered to a patient, either as a single therapeutic agent or in combination with another therapeutic agent, depends on its EPA/DHA content. In particular, the amount of essential fatty acid having a EPA/DHA content of about 85%, to be administered to a patient, may vary from about 0.7 g to about 1.5 g daily. More specifically, the amount of essential fatty acid, with a EPA/DHA content of about 85% and an EPA/DHA ratio of about 0.9/1.5 is of about 1 g daily.

This amount of product may be administered in the form of several daily divided doses or preferably as a single dose, in order to reach the desired blood level. Of course, the clinician may vary the amount of product (or mixture with another therapeutic agent) to be administered, basing on the patient's conditions, age and weight.

The amount of additional therapeutic agent, when administered in combination with the essential fatty acid, is substantially the amount usually employed by the clinician in therapy. At any rate, the clinician may vary the amount of this additional drug (or mixture of additional drugs) basing on the patient's clinical picture.

The combined use of an essential fatty acid according to the invention and of another therapeutic agent produces a synergic or superadditive effect, namely an improvement of the patient's clinical picture surely greater than the one observed with the administration of the essential fatty acid or of the "other therapeutic agent" alone. Moreover, the greater therapeutic effect in the combined treatment is not accompanied by an increased toxicity.

Therefore, the present invention provides the clinician with a new method of therapeutic treatment effective for preventing and treating cardiac insufficiency and heart failure or at least improving the conditions of a patient suffering from such heart diseases or improving his/her quality of life. Indeed, on the basis of clinical markers, which are to-day useful to understand the various stages of cardiac insufficiency and

progressive evolution towards an overt heart failure, the clinician can make use of the present invention and prevent or at least delay its evolution.

The pharmaceutical preparations according to the present invention can be prepared by methods well known in the art. A preferred route of administration is the oral one, but the physician may use to adopt other routes of administration e.g. the parenteral one.

The therapeutic agent for the combined therapy, according to the present invention, can be formulated as well known in the art.

The essential fatty acid can be formulated, for example, in the form of gelatin capsules as stated below.

Gelatin capsules

According to the methods known from pharmaceutical technique, capsules are prepared with the following composition and containing 1 g of active ingredient (85% EPA-DHA) in each capsule.

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	1000 mg;
- with content in ethyl esters of ω-3 poly-unsaturated acids (eicosapentaeonic EPA, docosahexaenoic DHA)	850 mg;
- d,l-alpha-tocopherol	0.3 mg;
- gelatin succinate	233 mg
- glycerol	67 mg;
- sodium p-hydroxybenzoate	1.09 mg;
- propyl sodium p-hydroxybenzoate	0.54 mg.

CLAIMS

1. Use of an essential fatty acid containing a mixture of eicosapentaenoic acid ethyl ester (EPA) and of docosahexaenoic acid ethyl ester (DHA) in the preparation of a medicament useful for the prevention and treatment of a heart disease chosen from cardiac insufficiency and heart failure, both chronic and acute.

2. Use according to claim 1, wherein the medicament is for the combined therapy with another therapeutic agent.

3. Use according to claims 1 or 2, wherein the content in EPA+DHA in the mixture is higher than 25% by weight.

4. Use according to claim 3, wherein the content in EPA+DHA is from about 30% and about 100% by weight.

5. Use according to claim 3, wherein the content in EPA+DHA is about 85% by weight.

6. Use according to claim 3, wherein in EPA+DHA mixture, EPA is present in an amount ranging from about 25% to about 45% by weight and DHA is present in an amount ranging from about 55% to about 75% by weight.

7. Use according to claim 3, wherein the EPA/DHA ratio is about 0.6-1.1/1.3-1.8.

8. Use according to claim 5, wherein the EPA/DHA ratio is about 0.9/1.5.

9. Use according to claim 5, wherein the essential fatty acid is administered by oral route at a dose ranging from about 0.7 g and about 1.5 g daily.

10. Use according to claim 1 or 2, wherein the heart disease is cardiac insufficiency.

11. Use according to claim 1 or 2, wherein the heart disease is heart failure.

12. Use according to claim 11, wherein heart failure is chronic or acute.

13. Use according to claim 2, wherein the therapeutic agent for the combined therapy is chosen from ACE-inhibitors, NEP-inhibitors, ACE/NEP-inhibitors, angiotensin II converting enzyme inhibitors, diuretics, positive inotropic drugs, phosphodieserase inhibitors, arteriolar and venular vasodilators, beta-blockers and digitalis glycosides or a mixture thereof.

14. Use according to claim 13, wherein the therapeutic agent for the combined therapy is chosen from one or more agents chosen from cilazapril, captopril, enalapril, candesartan, valsartan, losartan, furosemide, hydrochlorothiazide, dopamine, ibopamine, amrinone, enoximone, hydralazine, isosorbide dinitrate, visopropol, carvedilol, metoprolol, digitoxin, digoxin, acetyldigoxin, metidigoxin, pimobendan, omapatrilat, sampatrilat and compound Z13752A.

15. Use according to each of the previous claims, wherein the treated patient is a person older than 60 years.

16. Use according to each of the previous claims wherein the treated patient is a person suffering from other cardiopathic disorders.

17. Use according to each of the previous claims, wherein the treated patient is a person who survived a myocardial infarction.

18. A method for preventing and treating a heart disease chosen from cardiac insufficiency and heart failure, both chronic and acute, comprising administering to a patient in need thereof a therapeutically effective amount of an unsaturated essential acid containing a mixture of eicosapentaenoic acid ethyl ester (EPA) and docosahexaenoic acid ethyl ester (DHA).

19. A method to prevent and treat a heart disease chosen from cardiac insufficiency and heart failure, both chronic and acute, comprising administering to a patient in need thereof a therapeutically effective amount of an essential fatty acid containing a mixture of eicosapentaenoic acid ethyl ester (EPA) and docosahexaenoic acid ethyl ester (DHA), in combination with another therapeutic agent.