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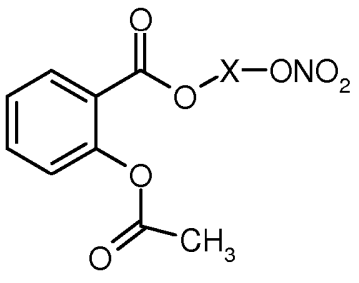
(54) Title: USE OF COMBINATIONS OF NITRIC OXIDE-RELEASING ASPIRIN AND ASPIRIN FOR THE TREATMENT OF CARDIOVASCULAR DISEASES



(I)

(57) Abstract: The present invention relates to combinations of a nitric oxide-releasing aspirins of formula (I) and aspirin and their use for treating disorders of the cardiovascular system.

USE OF COMBINATIONS OF NITRIC OXIDE-RELEASING ASPIRIN AND ASPIRIN FOR THE TREATMENT OF CARDIOVASCULAR DISEASES

The present invention relates to combinations of a nitric oxide-releasing aspirin of formula (I) and aspirin and their use for treating disorders of the cardiovascular system.

Many individuals are at an elevated risk of suffering serious to life-threatening cardiovascular events, such as myocardial infarction (heart attack), cardiac arrest, congestive heart failure, stroke, peripheral vascular disease, and/or claudication such as symptomatic peripheral arterial obstructive disease (PAOD). The risk factors are numerous and widespread throughout the world population. They include cigarette smoking, diabetes, hypercholesterolemia (high serum cholesterol), hypertension, angina, systemic lupus erythematosus, prior heart attacks or strokes, hemodialysis, hyperhomocysteine levels, obesity, sedentary lifestyle, receiving an organ transplant, and others. Many of these risk factors are mediated through vascular inflammation, endothelial dysfunction and atherosclerosis, which are major risk factors for cardiovascular events.

In current clinical practice, low dose aspirin (ASA), is well documented for efficacy in both prevention and treatment of thrombotic diseases. Moreover, in conditions such as myocardial infarction and stroke, platelet inhibition has become the standard of care.

However, the use of ASA increases the risk of bleeding, which limits the dose of the agent and duration of treatment, another limitation of aspirin is represented by its gastro-intestinal and renal toxicity.

The use of therapeutic doses of aspirin (typically 75 mg or more) is commonly associated with gastro-intestinal disturbances (e.g. nausea, dyspepsia, vomiting) and can also cause gastric mucosal damage such as ulceration. Dizziness, tinnitus, deafness and sweating are also known to occur with larger and/or repeated doses.

It is well known that nitric oxide-releasing aspirin and in particular 2-(acetyloxy)benzoic acid 3-(nitrooxymethyl) phenyl ester, known as NCX 4016 or nitro-aspirin, exerts a wider range of antiplatelet actions compared to aspirin and shows superior antithrombotic activity (Lechi et al., Tromb Haemost 1996, 76: 791-798, Momi et al., Eur J Pharmacol 397: 177-185); moreover nitroaspirin does not induce gastric damage. (Fiorucci et al., Gastroenterology 2003, 124: 600-607.

In a comparative phase II clinical study of symptomatic peripheral arterial obstructive disease (PAOD) in patients treated with either nitro-aspirin (NCX4016) (800 mg bid) or aspirin (100 mg od), nitro-aspirin, but not aspirin, reversed vascular endothelium dysfunction induced by physical exercise.

The data show the advantages of the use of nitro-aspirin but a limitation of its use is represented by the high dosage which causes poorly compliance of the patients and high costs of the treatment.

Momi et al, Tromb Haemost 2005, 93: 535-543, reports the results of a study comparing the antithrombotic effect of a combination of NCX 4016 plus clopidogrel versus combinations of aspirin and clopidogrel and of NCX 4016 plus clopidogrel and aspirin in a platelet pulmonary tromboembolism model and bleeding. This study shows that the combination NCX 4016 plus clopidogrel possesses a stronger antithrombotic activity, as shown by platelet

consumption and platelet lung emboli, it displays antiproliferative effects in mice more effectively than the aspirin plus clopidogrel combination, and it shows a lesser prolongation of the bleeding time. The data refer to the percentage of the vessel occluded by platelet emboli demonstrated that the combination comprising NCX 4016 plus clopidogrel showed a significantly stronger effect in reducing the number of occluded vessels than the combination aspirin plus clopidogrel, but the addition of aspirin to the combination NCX 4016 plus clopidogrel did not further reduce lung vessel occlusion.

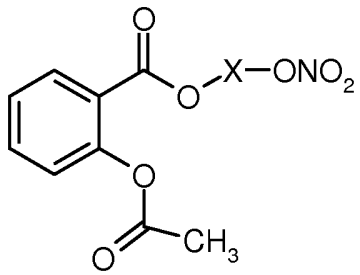
The data also show that the combination comprising NCX 4016 plus clopidogrel does not prolong the bleeding time more than the individual drugs when they are administered alone, but the addiction of aspirin to the combination comprising NCX 4016 plus clopidogrel leads to a prolongation of the bleeding time.

Moreover it is known that other combinations of anti-platelet aggregation agents, such as the combination aspirin-dipyridamole, have been the subject of clinical studies against dipyridamole alone or aspirin alone in the study of the prevention of cerebral vascular accidents or occlusion of the vascular shunt in patients. The conclusion of these studies was that the aspirin-dipyridamole combination does not possess any significant beneficial effect greater than that observed with dipyridamole alone or aspirin alone in the secondary prevention of cerebral atherothrombotic ischaemia or towards thrombosis (Acta. Neurol. Scand., 1987, 76(6), 413-421; Thrombosis, 1994, Alert No. 12; Thrombosis, 1994, Alert No. 9. Thrombosis, 1993, Alert No. 9; Thrombosis, 1993, Alert No. 2).

There is a need for a safe and convenient treatments that would effectively reduce the risk of incurring a

cardiovascular event in individuals who have these risk factors.

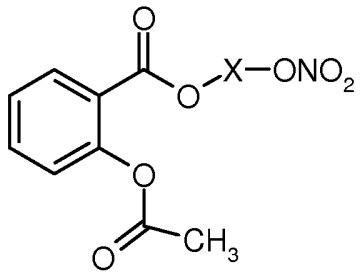
It has now surprisingly found that the combination comprising a nitric oxide-releasing aspirin of formula (I)



(I)

wherein X is as below defined, and aspirin has shown a synergic effect which makes it possible to provide effective and safe therapy for the treatment or prevention of the cardiovascular diseases using sub-pharmacological doses of the respective components. The synergic effect therefore makes it possible to use lower doses and consequently the side effects of the individual components can be reduced or eliminated. Another advantage is that the use of lower dosage forms improves the compliance of the patients.

It is an object of the invention a combination comprising aspirin and a nitric oxide-releasing aspirin of formula (I)

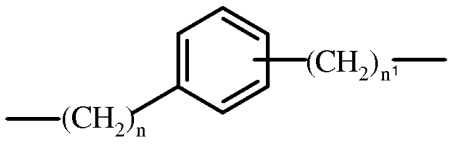


(I)

wherein X is a bivalent radical having the following meanings:

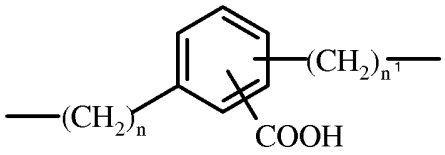
a) straight or branched C_1-C_{20} alkylene, preferably a straight or branched C_1-C_{10} alkylene; being optionally substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxy, $-ONO_2$ or T, wherein T is $-OC(O)(C_1$-C_{10} alkyl)$-ONO_2$ or $-O(C_1$-C_{10} alkyl)$-ONO_2$; preferably X is a straight C_1-C_{10} alkylene;

b)



(II)

c)

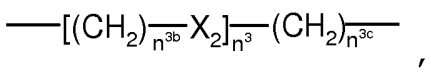


(III)

wherein n is an integer from 0 to 20, preferably n is an integer from 0 to 5; more preferably n is 0 or 1;

n^1 is an integer from 1 to 20, preferably n^1 is an integer from 1 to 5; more preferably n^1 is 1;

d)



(IV)

wherein

X_2 is -O- or -S-, preferably X_2 is -O-;

n^3 is an integer from 1 to 6, preferably from 1 to 4, and n^{3b} is an integer from 1 to 10, preferably from 1 to 6, more preferably n^{3b} is 1 or 2;

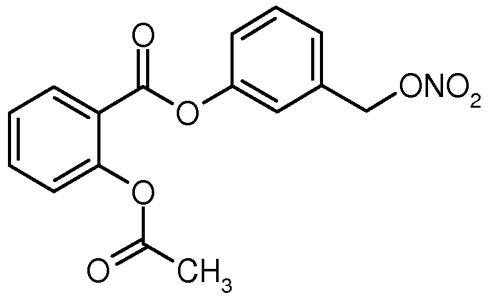
n^{3c} is an integer from 1 to 10, preferably from 1 to 6, more preferably n^{3c} is 2.

In the combinations according to the invention the amount of nitric oxide-realising aspirin of formula (I) is

in the range from 100 to 1200 mg and the amount of aspirin is in the range from 25 to 125 mg.

Preferred combinations include 200 to 600 mg of nitric oxide-realising aspirin and 40 to 100 mg of aspirin.

In a preferred embodiment, the combination according to the invention comprises the nitric oxide-realising aspirin of formula (Ia) i.e. 2-(acetyloxy)benzoic acid 3-(nitrooxymethyl)phenyl ester



(Ia)

Another embodiment of the present invention provides combination of 2-(acetyloxy)benzoic acid 3-(nitrooxymethyl) phenyl ester of formula (Ia) and aspirin wherein the amounts of 2-(acetyloxy)benzoic acid 3-(nitrooxymethyl) phenyl ester is in the range from 100 to 1200 mg and the amount of aspirin is in the range from 25 to 125 mg.

Preferred combinations include 200 to 600 mg of 2-(acetyloxy)benzoic acid 3-(nitrooxymethyl)phenyl ester and 40 to 100 mg of aspirin.

Most preferred combination comprise 400 mg of 2-(acetyloxy)benzoic acid 3-(nitrooxymethyl)phenyl ester and 40 mg aspirin.

The combination of the present invention show a clearly better pharmacological profile than that hitherto obtained with the individual drugs when they are administered alone, and fewer adverse side effects.

Further, the present invention includes the use of the combinations of the invention for the treatment of

cardiovascular disease and for preventing, inhibiting or reducing the risk of onset of a cardiovascular event.

In a preferred embodiment the combinations of the invention are used for the treatment of patients suffering from increased cardiovascular risk, vascular inflammation, endothelial dysfunction, atherosclerosis, peripheral vascular disease and in particularly for patients suffering from symptomatic peripheral arterial obstructive disease (PAOD).

In a most preferred embodiment, the combinations of the present invention are efficacy in the treatment of diabetic patients suffering from vascular inflammation or endothelial dysfunction or atherosclerosis or peripheral vascular disease and in particularly for diabetic patients suffering from symptomatic peripheral arterial obstructive disease (PAOD).

More preferred, the combination according to the invention comprising the 2-(acetyloxy)benzoic acid 3-(nitrooxymethyl) phenyl ester of formula (Ia) above reported and aspirin is used for the treatment of cardiovascular disease and for preventing, inhibiting or reducing the risk of onset of a cardiovascular event in particular peripheral vascular disease and more particular for treating symptomatic peripheral arterial obstructive disease (PAOD).

In particular the combination according to the invention comprising the 2-(acetyloxy)benzoic acid 3-(nitrooxymethyl) phenyl ester of formula (Ia) above reported and aspirin is used in the treatment of diabetic patients suffering from vascular inflammation or endothelial dysfunction or atherosclerosis or peripheral vascular disease and in particularly for diabetic patients

suffering from symptomatic peripheral arterial obstructive disease (PAOD).

The terms "cardiovascular event(s)" and "cardiovascular disease" as employed herein refer to coronary and/or cerebrovascular event(s) and disease including primary myocardial infarction, secondary myocardial infarction, myocardial ischemia, angina pectoris (including unstable angina), congestive heart failure, sudden cardiac death, cerebral infarction, cerebral thrombosis, cerebral ischemia, transient ischemic attack, peripheral vascular diseases such as peripheral arterial obstructive disease (PAOD).

The term "coronary artery disease" (CAD) as employed herein refers to diseases including atherosclerosis of the coronary arteries, previous myocardial infarction, ischemia, angina pectoris and/or heart failure.

The doses to be administered are determined depending upon, for example, age, body weight, symptom, the desired therapeutic effect, the route of administration, and the duration of the treatment.

As mentioned above, the doses to be used depend upon various conditions. Therefore, there are cases wherein doses lower than or greater than the ranges specified above may be used.

The combinations of the present invention may be formulate with pharmaceutical acceptable eccipients according to the method known in the art.

Another object of the present invention involves pharmaceutical formulations comprising the combinations of the present invention with pharmaceutical acceptable eccipients according to the method known in the art. The pharmaceutical formulation may be administered in the form, for example, of solid compositions, of liquid compositions

or other compositions for oral administration, injections, liniments or suppositories for parenteral administration.

Another object of the present invention relates to a kit comprising aspirin in a dosage formulation and a nitric oxide-releasing aspirin of formula (I) in a separate dosage formulation.

The separate dosage formulations of the aspirin and of the nitric oxide-releasing aspirin of formula (I) can be administered at essentially the same time, i.e., concurrently, or at separately staggered times, i.e, sequentially.

Preferably in the kit the **nitric oxide-releasing aspirin of formula (I) is 2-(acetyloxy)benzoic acid 3-(nitrooxymethyl)phenyl ester of formula (Ia).**

Another object of the present invention relates to the use of the kit above reported for in the treatment of cardiovascular disease and for preventing, inhibiting or reducing the risk of onset of a cardiovascular event in particular peripheral vascular disease and more particular for treating symptomatic peripheral arterial obstructive disease (PAOD).

Another object of the present invention involves the use of the kit comprising above reported for the treatment of diabetic patients suffering from vascular inflammation, or endothelial dysfunction or atherosclerosis or peripheral vascular disease and in particularly for diabetic patients suffering from symptomatic peripheral arterial obstructive disease (PAOD).

The general synthesis of the nitric oxide-releasing aspirins of formula (I) wherein X is above defined, is described in the EP 7 559 899.

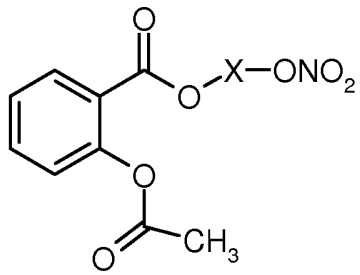
The synthesis of the nitric oxide-releasing aspirins of formula (I) wherein X has formula (II) wherein n and n'

are as above reported can be prepared as described in EP 0 871 606.

The process of synthesis of 2-(acetyloxy)benzoic acid 3-(nitrooxymethyl)phenyl ester of formula (Ia) is described in EP 1 194 397.

Claims

1. A combination comprising aspirin and a nitric oxide-releasing aspirin of formula (I)

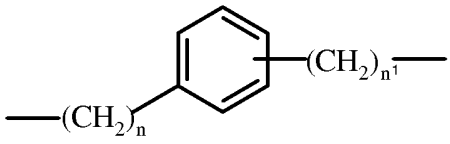


(I)

wherein X is a bivalent radical having the following meanings:

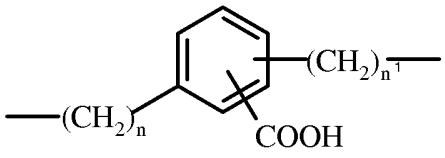
a) straight or branched C_1-C_{20} alkylene, preferably a straight or branched C_1-C_{10} alkylene; being optionally substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxy, $-ONO_2$ or T, wherein T is $-OC(O)(C_1$-C_{10} alkyl)-ONO_2 or $-O(C_1$-C_{10} alkyl)-ONO_2; preferably X is a straight C_1-C_{10} alkylene;

b)



(II)

c)

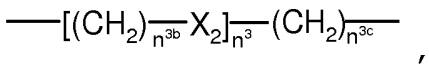


(III)

wherein n is an integer from 0 to 20, preferably n is an integer from 0 to 5; more preferably n is 0 or 1;

n^1 is an integer from 1 to 20, preferably n^1 is an integer from 1 to 5; more preferably n^1 is 1;

d)



(IV)

wherein

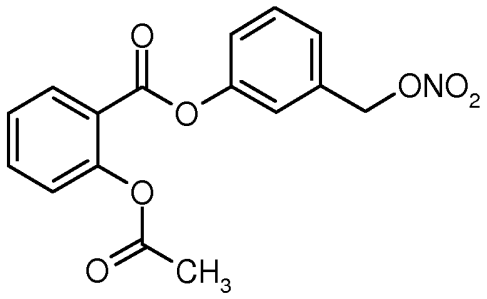
X_2 is -O- or -S-, preferably X_2 is -O-;

n^3 is an integer from 1 to 6, preferably from 1 to 4, and

n^{3b} is an integer from 1 to 10, preferably from 1 to 6, more preferably n^{3b} is 1 or 2;

n^{3c} is an integer from 1 to 10, preferably from 1 to 6, more preferably n^{3c} is 2.

2. A combination according to claim 1 wherein the nitric oxide-releasing aspirin of formula (I) is 2-(acetyloxy)benzoic acid 3-(nitrooxymethyl)phenyl ester of formula (Ia)



(Ia)

3. A combination according to claim 1 wherein the amount of nitric oxide-realising aspirin of formula (I) is in the range from 100 to 1200 mg and the amount of aspirin is in the range from 25 to 125 mg.

4. A combination according to claim 1 wherein the amount of nitric oxide-realising aspirin of formula (I) is in the

range from 200 to 600 mg and the amount of aspirin is in the range from 40 to 100 mg.

5. A combination according to claim 2 wherein the amount of 2-(acetyloxy)benzoic acid 3-(nitrooxymethyl)phenyl ester is in the range from 100 to 1200 mg and the amount of aspirin is in the range from 25 to 125 mg.

6. A combination according to claim 2 wherein the amount of 2-(acetyloxy)benzoic acid 3-(nitrooxymethyl)phenyl ester is in the range from 200 to 600 mg and the amount of aspirin is in the range from 40 to 100 mg.

7. A combination according to claim 2 wherein the amount of 2-(acetyloxy)benzoic acid 3-(nitrooxymethyl)phenyl ester is 400 mg and the amount of aspirin is 40 mg.

8. Use of a combination according to any claims of 1 to 7 for the preparation of drug for the treatment of cardiovascular diseases and for preventing, inhibiting or reducing the risk of onset of a cardiovascular event.

9. Use of a combination according to any of claims 1 to 7 for the preparation of drug for the treatment of vascular inflammation and atherosclerosis.

10. Use of a combination according to any of claims 1 to 7 for the preparation of drug for the treatment of peripheral vascular disease.

11. Use of a combination according to any of claims 1 to 7 for the preparation of drug for the treatment of peripheral arterial obstructive disease.

12. Use of a combination according to any of claims 1 to 7 for the preparation of drug for the treatment of symptomatic peripheral arterial obstructive disease in diabetic patients.

13. Pharmaceutical compositions comprising a combination according to any of claims 1 to 7 and pharmaceutical acceptable ecipients.

14. A kit comprising aspirin in a dosage formulation and a nitric oxide-releasing aspirin of formula (I) as described in claim 1 in a separate dosage formulation.

15. A kit according to claim 14 wherein the nitric oxide-releasing aspirin of formula (I) is 2-(acetyloxy)benzoic acid 3-(nitrooxymethyl)phenyl ester of formula (Ia).

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/067983

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/616 A61K31/603 A61K45/06 A61P3/10 A61P9/00
A61P9/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, EMBASE, BIOSIS, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FIORUCCI S ET AL: "Co-administration of nitric oxide-aspirin (NCX-4016) and aspirin prevents platelet and monocyte activation and protects against gastric damage induced by aspirin in humans" JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, ELSEVIER, NEW YORK, NY, US, vol. 44, no. 3, 4 August 2004 (2004-08-04), pages 635-641, XP004534931 ISSN: 0735-1097	1,2,8,9, 13-15
Y	page 636, column 1, paragraphs 2,4 page 637 - page 640; figures 1-4 page 638, column 2, last paragraph - page 639, column 1, paragraph 1 page 640, column 1, paragraph 2 page 640, column 2, paragraph 2 - page 641, column 1, paragraph 2	1-15

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[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 January 2007	31/01/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kerkmann, Miren

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LEVIN R I: "Theriac found? Nitric oxide-aspirin and the search for the universal cure" JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, ELSEVIER, NEW YORK, NY, US, vol. 44, no. 3, 4 August 2004 (2004-08-04), pages 642-643, XP004534932 ISSN: 0735-1097 page 642, column 2, paragraph 2-4	1,2,8,9, 13-15
Y	PIEPER GALEN M ET AL: "Vascular protective actions of a nitric oxide aspirin analog in both in vitro and in vivo models of diabetes mellitus." FREE RADICAL BIOLOGY & MEDICINE. 1 JUN 2002, vol. 32, no. 11, 1 June 2002 (2002-06-01), pages 1143-1156, XP002414619 ISSN: 0891-5849 page 1144, column 2, last paragraph page 1149, column 2, paragraph 1 page 1154, column 1, paragraph 2 abstract	1-15
A	DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; October 2004 (2004-10), JAYET PIERRE-YVES ET AL: "Nitro-aspirin improves insulin sensitivity in obese insulin-resistant men" XP002414630 Database accession no. PREV200510317340 abstract & CIRCULATION, vol. 110, no. 17, Suppl. S, October 2004 (2004-10), pages 820-821, 77TH SCIENTIFIC MEETING OF THE AMERICAN-HEART-ASSOCIATION; NEW ORLEANS, LA, USA; NOVEMBER 07 -10, 2004 ISSN: 0009-7322	1-15
A	DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; October 2005 (2005-10), LORIGA GIACOMINA ET AL: "Nitric-oxide releasing aspirin improves insulin activity and systemic hemodynamics in subjects with type 2 diabetes and early nephropathy" XP002414624 Database accession no. PREV200600048508 abstract	1-15

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	& CIRCULATION, vol. 112, no. 17, Suppl. S, October 2005 (2005-10), page U608, 78TH ANNUAL SCIENTIFIC SESSION OF THE AMERICAN-HEART-ASSOCIATION; DALLAS, TX, USA; NOVEMBER 13 -16, 2005 ISSN: 0009-7322	