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(54) Titre : UTILISATION DE DIPYRIDAMOLE EN ASSOCIATION AVEC DE L'ACIDE ACETYLSALICYLIQUE ET UN ANTAGONISTE DE L'ANGIOTENSINE II AUX FINS DE LA PREVENTION DES ACCIDENTS CEREBRO-VASCULAIRES

(54) Title: USE OF DIPYRIDAMOLE IN COMBINATION WITH ACETYLSALICYLIC ACID AND AN ANGIOTENSIN II ANTAGONIST FOR STROKE PREVENTION

(57) Abrégé/Abstract:
This invention relates to a method of preventing stroke or reducing the risk of stroke in a patient in need thereof, especially in a patient at risk for a stroke or a secondary stroke, using dipyridamole in combination with acetylsalicylic acid (ASA) and an angiotensin II antagonist, corresponding pharmaceutical compositions, and the use of dipyridamole for the manufacture of a corresponding pharmaceutical composition comprising a combination of dipyridamole, acetyl salicylic acid and an angiotensin II antagonist.

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(54) Title: USE OF DIPYRIDAMOLE IN COMBINATION WITH ACETYLSALICYLIC ACID AND AN ANGIOTENSIN II ANTAGONIST FOR STROKE PREVENTION

(57) Abstract: This invention relates to a method of preventing stroke or reducing the risk of stroke in a patient in need thereof, especially in a patient at risk for a stroke or a secondary stroke, using dipyridamole in combination with acetylsalicylic acid (ASA) and an angiotensin II antagonist, corresponding pharmaceutical compositions, and the use of dipyridamole for the manufacture of a corresponding pharmaceutical composition comprising a combination of dipyridamole, acetyl salicylic acid and an angiotensin II antagonist.

Use of dipyridamole in combination with acetylsalicylic acid and an angiotensin II antagonist for stroke prevention

Field of the Invention

This invention relates to a method of preventing stroke or reducing the risk of stroke in a patient in need thereof, especially in a patient at risk for a stroke or a secondary stroke, using dipyridamole in combination with acetylsalicylic acid (ASA) and an angiotensin II antagonist, a pharmaceutical composition comprising a combination of dipyridamole, acetyl salicylic acid and an angiotensin II antagonist, and the use of dipyridamole for the manufacture of a corresponding pharmaceutical composition comprising a combination of dipyridamole, acetyl salicylic acid and an angiotensin II antagonist.

Background of the Invention

Dipyridamole {2,6-bis(diethanolamino)-4,8-dipiperidino-pyrimido[5,4-d]pyrimidine}, closely related substituted pyrimido-pyrimidines and their preparation have been described in e.g. U.S.Patent 3,031,450. Dipyridamole was introduced as a *coronary vasodilator* in the early 1960s. It is also well known having *platelet aggregation inhibitor properties* due to the inhibition of adenosine uptake. Subsequently, dipyridamole was shown to reduce thrombus formation in a study of arterial circulation of the brain in a rabbit model. These investigations led to its use as an *antithrombotic agent*; it soon became the therapy of choice for such applications as stroke prevention, maintaining the patency of coronary bypass and valve-replacement, as well as for treatment prior to coronary angioplasty.

Furthermore, the European Stroke Prevention Study 2 (ESPS-2; J Neurol Sci. 1996; 143: 1-13; Neurology 1998; 51: 17-19) proved that treatment by dipyridamole alone was as effective as low-dose aspirin in the reduction of stroke risk, and combination

therapy with dipyridamole and aspirin was more than twice as effective as aspirin alone.

Dipyridamole appears to inhibit thrombosis through multiple mechanisms. Early studies showed that it inhibits the uptake of adenosine, which was found to be a potent endogenous anti-thrombotic compound. Dipyridamole was also shown to inhibit cyclic AMP phosphodiesterase, thereby increasing intracellular c-AMP.

Dipyridamole also has *antioxidant properties* (Free Radic. Biol. Med. 1995; 18: 239-247) that may contribute to its antithrombotic effect. When oxidized, low density lipoproteins become recognized by the scavenger receptor on macrophages, which is assumed to be the necessary step in the development of atherosclerosis (Ann. Rev. Med. 1992; 43: 219-25).

The inhibition of free radical formation by dipyridamole has been found to inhibit fibrinogenesis in experimental liver fibrosis (Hepatology 1996; 24: 855-864) and to suppress oxygen radicals and proteinuria in experimental animals with amino-nucleoside nephropathy (Eur. J. Clin. Invest. 1998; 28: 877-883; Renal Physiol. 1984; 7: 218-226). Inhibition of lipid peroxidation also has been observed in human nonneoplastic lung tissue (Gen. Pharmacol. 1996; 27: 855-859).

Angiotensin (ANG) II plays a major role in pathophysiology, especially as the most potent blood pressure increasing agent in humans. ANG II antagonists therefore are suitable for treating elevated blood pressure and congestive heart failure in a mammal. Examples of ANG II antagonists are described in EP-A-0 502 314, EP-A-0 253 310 , EP-A-0 323 841, EP-A-0 324 377, US-A-4,355,040 and US-A-4,880,804 . Specific ANG II antagonists are sartans such as candesartan, eprosartan, irbesartan, losartan, telmisartan or valsartan, furthermore olmesartan and tasosartan.

It is known that ANG II, besides its blood pressure increasing effect, additionally features growth promoting effects contributing to left ventricular hypertrophy, vascular thickening, atherosclerosis, renal failure and stroke. Bradykinin, on the other hand, exerts vasodilating and tissue protective actions, as disclosed for instance by W.

Wienen et al.: Antihypertensive and renoprotective effects of telmisartan after long term treatment in hypertensive diabetic (D) rats, 2nd. Int. Symposium on Angiotensin II Antagonism, February 15-18, 1999, The Queen Elizabeth II Conference Center, London, UK, Book of Abstracts, Abstract No. 50.

Losartan and irbesartan provide a renoprotective effect found within first clinical trials, as disclosed for instance by S. Andersen et al.: Renoprotective effects of angiotensin II receptor blockade in type 1 diabetic patients with diabetic nephropathy, Kidney Int 57 (2), 601-606 (2000).

ANG II antagonists selectively block the AT_1 receptor, leaving the AT_2 receptor, which plays a role in anti-growth and tissue regenerative actions, unopposed. Completed clinical trials with Ang II antagonists appear to display similar blood pressure reducing and tissue protective effects as with ACE inhibitors, as disclosed forb instance by D.H.G. Smith et al.: Once-daily telmisartan compared with enalapril in the treatment of hypertension, Adv. Ther 1998, 15: 229-240, and by B.E. Karlberg et al.: Efficacy and safety of telmisartan, a selective AT1 receptor antagonist, compared with enalapril in elderly patients with primary hypertension, J Hypertens 1999, 17: 293-302.

EP-A-1 013 273 discloses the use of AT_1 receptor antagonists or AT_2 receptor modulators for treating diseases associated with an increase of AT_1 receptors in subepithelial area or increase of AT_2 receptors in the epithelia, especially for treatment of several lung diseases.

Summary of the Invention

It has now surprisingly been found that dipyridamole when administered in combination with acetylsalicylic acid and an angiotensin II antagonist provides a stroke preventing effect superior to conventional medications or treatment regimes, for instance a combination regime of clopidogrel together with acetyl salicylic acid, especially in a patient at risk for a stroke or a secondary stroke.

ASA inhibits aggregation through direct effects on the platelet, in more detail, by irreversibly acetylating platelet cyclooxygenase, thus inhibiting the production of thromboxane, which is strongly thrombotic. In high doses, however, aspirin crosses over into endothelial cells (N. Eng. J. Med. 1984; 311: 1206-1211), where it interrupts the production of prostacyclin, a potent natural inhibitor of platelet aggregation and by-product of the "arachidonic cascade" (N. Engl. J. Med. 1979; 300: 1142-1147). These observations led to the concept of low-dose antiplatelet therapy with ASA to maximize inhibition of thromboxane while minimizing the loss of prostacyclin (Lancet 1981; 1: 969-971). In the method of prevention according to the invention a combination of low-dose ASA with dipyridamole and an angiotensin II antagonist is preferred.

Viewed from one aspect the present invention provides a method of stroke prevention or reducing the risk of stroke or secondary stroke in a patient in need thereof, especially in a patient with elevated risk for stroke, e.g. in hypertensive patients or patients suffering from cerebrovascular disorders, said method comprising administering to said patient an effective amount of a pharmaceutical composition comprising dipyridamole or a pharmaceutically acceptable salt thereof in combination with ASA and an angiotensin II antagonist. The main risk for a second stroke is a prior stroke due to degenerative processes in the wall of blood vessels supplying the brain. Patients at high risk of a second stroke with all its consequences readily seek preventive treatment. The vascular pathobiology of ischaemic stroke is multiple and antithrombotic mechanisms in the cerebro-vascular microenvironment beyond platelet inhibition seem to be potentially disease-modifying and a means of reducing ischaemic stroke.

Viewed from a second aspect the present invention provides a pharmaceutical composition comprising dipyridamole or a pharmaceutically acceptable salt thereof in combination with ASA and an angiotensin II antagonist, adapted for simultaneous, separate or sequential administration.

The pharmaceutical composition according to the invention is meant to comprise a fixed dose combination comprising the active ingredients in one formulation together as well as

a kit of parts comprising

(a) a first containment containing a pharmaceutical composition comprising a therapeutically effective of dipyridamole; and

(b) a second containment containing a pharmaceutical composition comprising acetylsalicylic acid and a pharmaceutically acceptable carrier; and

(c) a third containment containing a pharmaceutical composition comprising an angiotensin II antagonist.

Viewed from a different aspect the present invention provides the use of dipyridamole or a pharmaceutically acceptable salt thereof in combination with ASA and an angiotensin II antagonist for the manufacture of a pharmaceutical composition for stroke prevention or reducing the risk of stroke or secondary stroke in a patient in need thereof.

Detailed Description of the Invention

The invention provides a new and improved approach for stroke prevention or reducing the risk of stroke or secondary stroke in a patient in need thereof, especially in a patient with elevated risk for stroke, comprising administering to the patient an effective amount of a pharmaceutical composition containing as acive ingredients dipyridamole or a pharmaceutically acceptable salt thereof in combination with ASA and an angiotensin II antagonist.

In the method of the invention any of the oral dipyridamole retard, instant or the parenteral formulations on the market may be used, the retard formulations being preferred, for instance those available under the trademark Persantin®, or, already in combination with ASA the formulations available under the trademark Asasantin® or Aggrenox®. Suitable dipyridamole retard formulations are disclosed in EP-A-0032562, instant formulations are disclosed in EP-A-0068191 and

combinations of ASA with dipyridamole are disclosed in EP-A-0257344 which are incorporated by reference. Any Angiotensin II antagonist known in the art may be used in the method of prevention of the invention, e.g. the sartans such as candesartan, eprosartan, irbesartan, losartan, telmisartan (trademark Micardis®), valsartan, olmesartan or tasosartan, including the salts thereof or polymorphs thereof, using for instance the dosages disclosed in Rote Liste®2003, Editio Cantor Verlag Aulendorf, Germany, or in Physician's Desk Reference, 57 edition, 2003.

In the method of prevention according to the invention a plasma level of dipyridamole of about 0.2 to 5 μmol/L, preferably of about 0.5 to 2 μmol/L or particularly of about 0.8 to 1.5 μmol/L may be maintained. Dipyridamole can be administered orally in a daily dosage of 50 to 750 mg, preferably 100 to 500 mg, most preferred 200 to 450 mg, for instance 200 mg twice a day.

With respect to ASA this component of the ternary medication may be administered orally in a daily dosage of 10 to 200 mg, preferably 25 to 100 mg, most preferred 30 to 75 mg, for instance 25 mg twice a day.

With respect to the third component the angiotensin II antagonist telmisartan is preferred. This component can be administered orally in a daily dosage of 10 to 200 mg, for instance in a daily dosage of 20, 40, 80 or 160 mg, preferably in a daily dosage of 40 to 160 mg, most preferred 60 to 100 mg, for instance 20 or 40 mg once a day.

A specific method of prevention according to the invention comprises the combination of dipyridamole administered orally 200 mg twice a day, ASA administered orally 25 mg twice a day and telmisartan administered orally 20, 40 or 80 mg once a day.

With respect to all aspects of the invention the combination of dipyridamole, ASA and telmisartan is preferred, especially in the oral dosages indicated hereinbefore as most preferred.

CLAIMS

1. A method of stroke prevention or reducing the risk of stroke or secondary stroke in a patient in need thereof, comprising administering to the patient an effective amount of a pharmaceutical composition comprising dipyridamole or a pharmaceutically acceptable salt thereof in combination with acetylsalicylic acid and an angiotensin II antagonist.

2. The method of claim 1 wherein the angiotensin II antagonist is telmisartan.

3. A pharmaceutical composition comprising dipyridamole or a pharmaceutically acceptable salt thereof, acetyl salicylic acid and an angiotensin II antagonist as a combined preparation for simultaneous, separate or sequential use.

4. The pharmaceutical composition of claim 3 wherein the angiotensin II antagonist is telmisartan.

5. The use of dipyridamole or a pharmaceutically acceptable salt thereof in combination with acetylsalicylic acid and an angiotensin II antagonist for the manufacture of a pharmaceutical composition for stroke prevention or reducing the risk of stroke or secondary stroke in a patient.

6. The use of claim 5 wherein the angiotensin II antagonist is telmisartan.