NOVEL ASSOCIATION OF AN ANTITHROMBOTIC AGENT WITH ASPIRIN AND USE THEREOF FOR TREATING ATHEROTHROMBOTIC DISEASES

The new invention relates to a new association of an antithrombotic and aspirin and to pharmaceutical compositions containing them.

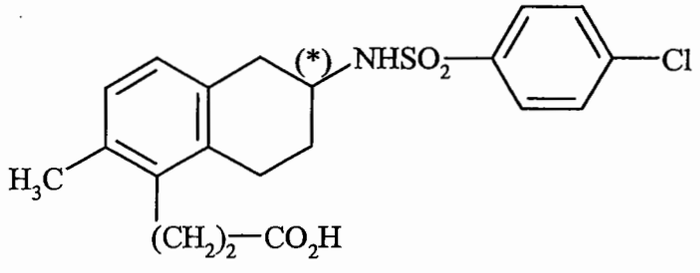
More specifically, the present invention relates to the association of a TP receptor antagonist and aspirin.

Thromboxane A_2 (TXA_2) is an unstable metabolite of arachidonic acid which is involved in the pathogenesis of numerous disorders of blood circulation. Thromboxane A_2 is a powerful platelet activator but is also a powerful vasoconstrictor which has cell proliferative and pro-adhesive properties.

TXA_2 and other metabolites of arachidonic acid such as endoperoxide (PGH_2), HETEs and isoprostanes exert their action by way of common receptors called TP receptors.

Numerous research studies have recently been carried out with the aim of preventing circulatory disorders caused by the excessive production of thromboxane A_2. Among such antagonists, those described in the Patent Specification EP 648 741 have been found to be powerful and selective antagonists of TP receptors, to be active *via* the oral route and to have a long duration of action.

More specifically, the compound (A) of formula (I) :



(I),

in racemic form or in the form of an optically pure isomer, and also pharmaceutically acceptable salts thereof, has been found to be a powerful antithrombotic.

That compound selectively inhibits blood platelet aggregation caused by activation of the TP receptors and, moreover, has anti-atherosclerotic properties after administration by the oral route.

We have now found that the association of compound A and aspirin allows, surprisingly, a synergy to be obtained in terms of antithrombotic activity.

It has been described in the literature that certain associations of anti-platelet aggregation agents such as dipyridamole and aspirin have additive effects and that such an association has been shown to be of value in the prevention of cerebral vascular accidents.

Other associations of anti-platelet aggregation agents with aspirin have been described in the literature. In view of the fact that those anti-aggregation agents act on platelet aggregation pathways (such as the purinergic pathways, ADP) which are different from those of aspirin, which acts via the pathway of arachidonic acid metabolism, it was expected that additive effects on the activity of those compounds would be observed.

The association to which the present invention relates is, for its part, completely different: compound A and aspirin both act on the arachidonic acid metabolism pathways: the former acts by irreversibly inhibiting the cyclo-oxygenases, which convert arachidonic acid into endoperoxide (PGH_2) and the latter acts by opposing the activity of certain metabolites of arachidonic acid such as thromboxane A_2, the isoprostanes and endoperoxide.

It has been found, surprisingly, that the association of compound A and aspirin allows substantial synergy to be obtained in terms of activity, which could not have been foreseen from any teaching of the literature.

That synergistic effect has been demonstrated in an arterial thrombosis test in the guinea-pig. In the course of that test it was shown that the antithrombotic activity of compound A is potentiated in the presence of aspirin and increases in extremely substantial and entirely unforeseeable manner.

In the associations according to the invention, compound (A) and aspirin can be present in the form of pharmaceutically acceptable salts.

Among the addition salts of compound (A), there may be mentioned, without implying any limitation, addition salts with a pharmaceutically acceptable base, such as sodium, potassium, *tert*-butylamine and diethylamine salts etc..

Preference will be given to use of the sodium salt.

Among the addition salts of aspirin, there may be mentioned, without implying any limitation, addition salts with a pharmaceutically acceptable acid, such as acetate, benzoate, fumarate, maleate, citrate, tartrate, the lysine salt etc..

In the associations according to the invention, compound (A) preferably has the absolute configuration (R).

The present invention relates also to pharmaceutical compositions comprising an association of compound (A) and aspirin, where appropriate in the form of pharmaceutically acceptable salts, together with one or more appropriate, inert, non-toxic excipients.

Among the pharmaceutical compositions according to the invention there may be mentioned more especially those that are suitable for oral, parenteral or nasal administration, tablets or dragées, sublingual tablets, gelatin capsules, lozenges, suppositories, creams, ointments, dermal gels etc..

The dosage can be varied according to the nature and severity of the condition, the administration route and also the age and weight of the patient.

In the compositions according to the invention, the amounts of active ingredients are in the range from 1 to 300 mg for compound (A) and from 100 to 1000 mg for aspirin.

The compositions according to the invention are accordingly useful in the treatment of atherothrombotic illnesses involving the activation of TP receptors and/or the formation of metabolites and also in the treatment of consequences of those illnesses. Those pathologies include, without implying any limitation, stable or unstable angina, endothelial or vascular dysfunction accompanying illnesses such as hypertension, diabetes, heart failure, disorders of the cardiovascular or cerebrovascular system, or thrombo-embolic disorders associated especially with atherosclerosis.

The associations according to the invention have been studied and the synergy effect has been demonstrated in an arterial thrombosis test in the guinea-pig.

This test is based on the model initially described by Roux *et al.* (Thromb Haemost 71 : 252-256, 1994). The guinea-pigs are anaesthetised using ketamine + xylazine (90 + 12) mg.kg i.m.. The trachea is cannulated and spontaneous respiration by the animals maintained. The jugular vein is cannulated, allowing the intravenous administration of the compounds being tested. The carotid artery is isolated, and a Doppler probe is installed allowing the arterial blood flow to be measured. After stabilisation, a lesion to the artery wall is produced by means of a clip applied distally to the Doppler probe. Subsequent to that lesion, the blood flow decreases. When the flow reaches zero, the artery is lightly shaken, which allows the flow to be restored. The thrombosis process continues, leading again to the flow reducing and ceasing. The thrombotic phenomena accordingly result in cyclic flow reductions (CFR), which are observed over a period of 20 minutes. After that period, the animal is treated, or not, with compound (A), and the CFR are again observed for a period of 20 minutes. The experiments are carried out in control animals or in animals treated by the intravenous route with aspirin (2 mg/kg).

This study was carried out using the sodium salt of the (R) isomer of compound (A).

The results show that 10 ± 1 CFR/20 min are observed in the untreated animals. Compound (A), administered by the intravenous route, reduces the CFR in dose-dependent manner; a significant effect is obtained from the 0.3 mg/kg dose (5 ± 2 CFR/20 min). Almost total inhibition (2 ± 2 CFR/20 min) is obtained with a dose of 1 mg/kg.

In the animals treated with aspirin, 8 ± 1 CFR/20 min are observed; that value is not different from that obtained in the control animals.

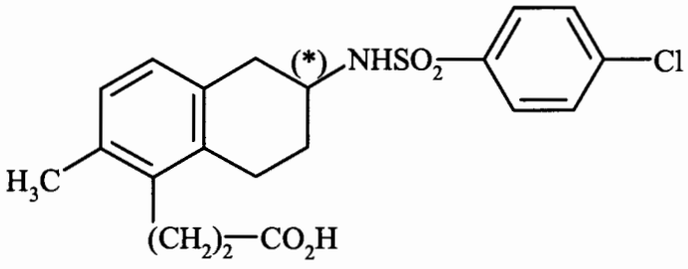
Compound (A), administered by the intravenous route to animals already treated with aspirin, reduces the CFR in dose-dependant manner; a significant effect is now obtained from the 0.01 mg/kg dose (5 ± 1 CFR/20 min), and almost complete inhibition is obtained with a dose of 0.1 mg/kg (2 ± 1 CFR/20 min).

Those results firstly show the powerful antithrombotic activity of compound (A), which is active from the 0.3 mg/kg dose.

Moreover, in the presence of a dose of aspirin which does not bring about an antithrombotic effect, the antithrombotic activity of compound (A) is potentiated and increased by at least 30 times. In fact, that effect is observed from the 0.01 mg/kg dose, which means that there exists a very substantial synergy effect when the two active ingredients are administered simultaneously.

CLAIMS

1- Association of compound (A) of formula (I), optionally in the form of an optical isomer or one of its pharmaceutically acceptable salts, and aspirin, or one of its pharmaceutically acceptable salts :



(I).

2- Association according to claim 1, characterised in that compound (A) is in (R) configuration optical isomer form.

3- Association according to either claim 1 or claim 2, characterised in that compound (A) is in the form of a sodium salt.

4- Pharmaceutical composition comprising as active ingredients an association of compound (A), optionally in the form of an optical isomer or one of its pharmaceutically acceptable salts, and aspirin, or one of its pharmaceutically acceptable salts, in combination with one or more pharmaceutically acceptable, inert excipients or carriers.

5- Pharmaceutical composition according to claim 4, characterised in that compound (A) is in (R) configuration optical isomer form.

6- Pharmaceutical composition according to either claim 4 or claim 5, characterised in that compound (A) is in sodium salt form.

7- Pharmaceutical composition according to any one of claims 4 to 6, characterised in that the amounts of active ingredients are in the respective ranges of from 1 to 300 mg for compound (A) and from 10 to 1000 mg for aspirin.

8- Pharmaceutical composition according to any one of claims 4 to 7, for use in the treatment of atherothrombotic illnesses involving the activation of TP receptors and/or the formation of metabolites and also in the treatment of consequences of those illnesses.