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(54) Title: ~~USE OF PROSTANOID ANTAGONISTS~~ FOR THE TREATMENT OF PRIMARY HEADACHE DISORDERS AND DRUG-INDUCED HEADACHES

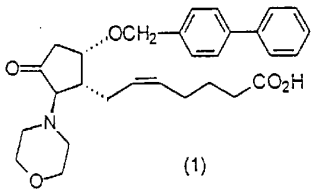
MEDICAMENTS

(57) Abstract

The present invention relates to the use of EP_4 antagonists in the treatment of primary headache disorders and drug–induced headaches and in the preparation of medicaments for the treatment of primary headache disorders and drug–induced headaches. A new use for AH22921 and AH23848 is described.

MEDICAMENTS FOR THE TREATMENT OF PRIMARY HEADACHE DISORDERS AND DRUG-INDUCED HEADACHES .

The present invention relates to a method of treatment of primary headache disorders and drug-induced headaches in humans and other mammals and to the use of compounds in the preparation of a medicament for the treatment of primary headache disorders and drug-induced headaches. In particular, this invention relates to a new medicinal use for compounds which act as antagonists at prostanoid EP_4 receptors and pharmaceutical compositions containing them. Two such EP_4 receptor antagonists are AH22921(1) and AH23848(2).



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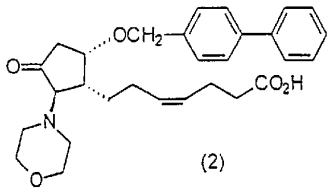

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It has unexpectedly been discovered that EP_4 antagonists can alleviate the headache symptoms of primary headache disorders such as migraine. As used herein the term "primary headache disorder" includes migraine, tension-type headaches, cluster headache, analgesic rebound headache, chronic paroxysmal hemicrania and headaches associated with vascular disorders. Accordingly, the present invention relates to methods useful in the treatment of primary headache disorders and drug induced headaches in humans and other mammals by administering an effective amount of an EP_4 antagonist or a pharmaceutically acceptable salt and/or solvate thereof.

There is thus provided the use of an EP_4 antagonist in the preparation of a medicament for use in the treatment of primary headache disorder and drug-induced headaches.

In any of the above aspects of the invention the EP_4 antagonist may be prostanoid or non-prostanoid in type. The invention is intended to encompass all known EP_4 antagonists.

In a presently preferred aspect the invention provides for the use of AH22921(1) or AH23848(2) or pharmaceutically acceptable salts and/or solvates thereof in the preparation of a medicament for the use in the treatment of primary headache disorders or drug induced headaches.

In a further aspect of the present invention EP_4 antagonists may, if desired, be used in combination with one or more other therapeutic agents such as an ergot derivative, for example dihydroergotamine, a 5-HT_2 antagonist, for example ketanserin, or a 5-HT_{1D} agonist, for example sumatriptan, naratriptan or zolmitriptan, or a β-blocker for example propranolol.

There is a widely held view that the pain of migraine headache originates from abnormally distended blood vessels in the cerebral vasculature. Dilation in cerebral blood vessels would cause local pressure resulting in the activation of local sensory pathways and pain. This is the case also for the other aforementioned primary headache disorders and drug-induced headaches.

Many drugs are used to treat primary headache disorders such as migraine including NSAIDS, ergot alkaloids, and several compounds that interact with different subtypes of 5-hydroxytryptamine (5-HR) receptors either as agonists (e.g. sumatriptan) or antagonists (e.g. ketanserin). However, of the drugs that interact with 5-HT receptors only the class of compounds described as 5-HT_{1D} agonists, of which

sumatriptan is an example, will relieve an established headache. 5-HT_{1D} agonists are well known to cause vasoconstriction in the cerebral vasculature which supports the vasodilatation theory [Humphrey, P.P.A., Feniuk, W., Motevalian, M., Parsons A.A. and Whalley, E.T., 'The vasoconstrictor action of sumatriptan on human dura mater' in 'Serotonin: Molecular Biology, Receptors and Functional effects' ed. Fozard, J. and Saxena, P.R., Birkhauser Verlag, Basel, 1991].

Exogenous administration of the potent vasodilator E-series, but not I-series, prostanoids to migraineurs is known to induce migraine-like symptoms [Carlson, L.A., Ekelund, L.G. and Oro, L. (1986) Acta Med. Scand. 183, 423; Peatfield, R. (1981) Headache 32, 98-100]. This evidence, together with the effectiveness of NSAIDS (which act by inhibiting the biosynthesis of prostanoids) in both preventing or relieving a migraine attack [Karachalios, G.N., Fotiadou, A., Chrisikos, N., Karabetsos, A. and Kehagoiglou (1992) Headache 21,190; Hansen, P. (1994) Pharmacol. Toxicol. 75, Suppl.2, 81-82] supports the involvement of prostanoids in the aetiology of the disease. The precise role of prostanoids is unclear but could involve a combination of local vasodilator, inflammatory, or hyperalgesic actions. The prostanoid most often associated with such actions is PGE_2.

We have examined the action of a number of prostanoids on human isolated cerebral blood vessels and made the unexpected discovery that PGE_2 has a complex action on these vessels whereas the other vasodilator prostanoids, PGD_2 and PGF_{2a}, produce no effects. PGE_2 causes constriction of larger vessels (>than 1mm diameter), but more significantly we believe, in the context of pain associated with migraine, it surprisingly causes a potent concentration-related relaxation of smaller cerebral vessels (<1mm diameter). By studying a variety of pharmacologically active agents this relaxant effect was found to be mediated by prostanoid EP_4 receptors.

We believe this unexpected action of PGE_2 could account for the pain in migraine and that a selective EP_4 antagonist would be a novel and effective anti-migraine agent with advantages over existing therapies, especially NSAIDS. As well as less side effect liability, an EP_4 antagonist should exhibit greater efficacy than an NSAID because an NSAID would eliminate both the detrimental vasodilator and beneficial vasoconstrictor effects on cerebral vasculature caused by endogenous prostaglandins. In contrast, an EP_4 antagonist should only inhibit the detrimental vasodilator effect.

A further embodiment of the invention is the combination of an EP_4 receptor antagonist with other therapeutic agents used in the treatment of migraine for example, with an ergot derivative (e.g. dihydroergotamine), a 5-HT_2 antagonist (e.g. ketanserin), or a 5-HT_{1D} agonist (e.g. sumatriptan, naratriptan or zolmitriptan) or a β-blocker (e.g. propranolol).

Thromboxane A_2 (TXA_2), an active metabolite of arachidonic acid in human platelets, is a potent constrictor of vascular smooth muscle and aggregator of platelets. AH22191(1), AH23848(2) and related compounds antagonise the actions of TXA_2 and therefore inhibit platelet aggregation and bronchoconstriction. Hence these compounds have been claimed for use in the treatment of asthma and as anti-thrombotic agents in cardiovascular disorders (GB Patent 2, 028, 805 and US Patent 4, 342, 756 describe AH22191 and AH23848, respectively). Additionally, both AH22191 and AH23848 have also been shown to be weak antagonists of PGE_2-induced relaxation of piglet saphenous vein (pA_2 values 5.3 and 5.4, respectively) through blockade of EP_4 receptors [Coleman, R.A., Grix, S.P., Head, S.A., Louttit, J.B., Mallett, A. and Sheldrick, R.L.G. (1994) Prostaglandins 47, 151-168; Coleman, R.A., Mallett, A. and Sheldrick, R.L.G. (1995) Advances in Prostaglandin,

Thromboxane and Leukotriene Research, 23, 241-246] but have no effect on the other EP receptor subtypes EP_1, EP_2 and EP_3. However, we have now shown that AH23848 is an antagonist of the relaxant effect of PGE_2 on human cerebral vessels. AH23848 shows similar EP_4 antagonist potency on human isolated cerebral arteries as it does on piglet saphenous vein. Thus, EP_4 receptor antagonists as a class, and AH22191 and AH23848 in particular, should be effective in the treatment of migraine.

A method of identifying and quantifying EP_4 receptor antagonists is described in the two publications by Coleman, R.A. listed above. The entire text of these publications is hereby imported by reference and forms an integral part of this disclosure and the inventive concepts described.

The characterisation of EP_4 receptors is also discussed in the review by Coleman R. A. et al [Coleman R. A. et al Eicosanoids: From Biotechnology to Therapeutic Applications, Folco, Samuelsson, Maclouf, and Velo, eds., Plenum Press, New York, 1996, p137-154], the text of which is also imported herein by reference and forms an integral part of this disclosure.

For the avoidance of doubt, in the context of this invention, an EP_4 receptor antagonist is any compound, agent or mixture showing antagonist activity at EP_4 receptors using the methodology set out above, including and especially antagonist activity against PGE_2 induced relaxation of human isolated cerebral blood vessels.

The EP_4 antagonists may be administered as the raw chemical but the active ingredients are preferably presented as a pharmaceutical formulation. Suitable pharmaceutical formulations are described in the above referenced patent specifications.

Thus, the EP_4 antagonists may be formulated for oral, buccal, parenteral, topical, depot or rectal administration or in a form suitable for administration by

inhalation or insufflation (either through the mouth or nose). Oral and parenteral formulations are preferred.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia; non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxbenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The EP_4 antagonists may be formulated for parenteral administration by bolus injection or continuous infusion. Formulations for injection may be presented in

unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The EP_4 antagonists may be formulated for topical administration in the form of ointments, creams, gels, lotions, pessaries, aerosols or drops (e.g. eye, ear or nose drops). Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents. Drops may be formulated with an aqueous or non aqueous base also comprising one or more dispersing agents, stabilising agents, solubilising agents or suspending agents. They may also contain a preservative.

The EP_4 antagonists may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The EP_4 antagonists may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion

exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For intranasal administration, the EP_4 antagonists may be formulated as solutions for administration via a suitable metered or unit dose device or alternatively as a powder mix with a suitable carrier for administration using a suitable delivery device.

Suitable dose ranges may be calculated by those skilled in the art in light of toxicological data. It will be appreciated that it may be necessary to make routine variations to the dosage, depending on the age and condition of the patient, and the precise dosage will be ultimately at the discretion of the attendant physician or veterinarian. The dosage will also depend on the route of administration and the particular compound selected. A suitable dose range is for example 0.1mg/kg to about 400mg/kg bodyweight per day.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. The use of an EP_4 antagonist in the preparation of a medicament for use in the treatment of a primary headache disorder or drug-induced headache.

2. The use according to claim 1 wherein the EP_4 antagonist is a prostanoid-type antagonist.

3. The use according to claim 1 wherein the EP_4 antagonist is a non-prostanoid-type antagonist.

4. The use according to claim 1 or claim 2 wherein the EP_4 antagonist is AH22921(1) or AH23848(2) or pharmaceutically acceptable salts or solvates thereof.

5. The use according to any preceding claim wherein the EP_4 antagonist is combined with one or more therapeutic agents selected from an ergot derivative, a 5-HT_2 antagonist, a 5-HT_{1D} agonist, or a β-blocker.

6. The use according to claim 5 wherein the ergot derivative is dihydroergotamine.

7. The use according to claim 5 wherein the 5-HT_2 antagonist is ketanserin.

8. The use according to claim 5 wherein the 5-HT_{1D} agonist is selected from sumatriptan, naratriptan or zolmitriptan.

9. The use according to claim 5 wherein the β-blocker is propranolol.

10. The use of an EP_4 antagonist according to claim 1 substantially as herein described.

11. A combined preparation suitable for the treatment of a primary headache or drug-induced headache comprising a combination of an EP_4 antagonist and a second therapeutic agent selected from an ergot derivative, a 5-HT_2 antagonist, a 5-HT_{1D} antagonist, and a β-blocker.

12. A combined preparation according to claim 12 wherein the ergot derivative is dihydroergotamine.

13. A combined preparation according to claim 12 wherein the 5-HT_2 antagonist is ketanserin.

14. A combined preparation according to claim 12 wherein the 5-HT_{1D} antagonist is sumatriptan, naratriptan or zolmitriptan.

15. A combined preparation according to claim 12 wherein the β-blocker is propranolol.

16. A combined preparation according to any one of claims 11 to 15 for use in a method of treating a primary headache disorder or drug-induced headache.