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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 31/495

A1

(11) International Publication Number: WO 99/18963

(43) International Publication Date: 22 April 1999 (22.04.99)

(21) International Application Number: PCT/IT98/00266

(22) International Filing Date: 6 October 1998 (06.10.98)

(30) Priority Data:
RM97A000613 10 October 1997 (10.10.97) IT

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: USE OF FLUNARIZINE FOR THE TOPICAL TREATMENT OF GLAUCOMA

(57) Abstract

Use of flunarizine, a calcium channel blocking agent known for use as cerebral and peripheral vasodilator, in the treatment of glaucoma by topical administration. Differently from other calcium channel blockers already tested for use as antiglaucoma agents, flunarizine is highly active in lowering the intraocular pressure when administered by the topical ophthalmic route. The invention also comprises anti–glaucoma preparations containing flunarizine, or combinations of flunarizine with beta–blockers such as timolol.

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USE OF FLUNARIZINE FOR THE TOPICAL TREATMENT OF GLAUCOMA

SPECIFICATION

The present invention concerns the use of flunarizine for the topical treatment of glaucoma. More specifically, this invention relates to the use of flunarizine, a calcium channel blocking agent known and employed as cerebral and peripheral vasodilator, in a new indication as an antiglaucoma agent for topical ophthalmic treatment.

As it is known, glaucoma is a pathological ophthalmic condition the underlying causes of which are not well understood at present. This condition is usually shown by a progressive increase of the intraocular pressure, leading to severe impairment of the eye structures, in particular to damage to the optic nerve disc and to decrease in the visual field, finally resulting in optic atrophy. The disease is generally connected to an insufficient outflow of aqueous humour from the eye, although other causes, such as, e.g., the production of aqueous humour and the episcleral veins pressure, take part in the regulation of the intraocular pressure.

The rationale of the pharmacological therapy presently in use is to lower the intraocular pressure. The drugs currently used to that aim, divided into classes according to their mechanism of action, are beta-blockers (such as timolol, betaxolol, levobunolol), sympathomimetics (such as epinephrine and dipivephrine), parasympathomimetics or miotics (such as pilocarpine and acetylcholine) and carbonic anhydrase inhibitors (such as acetazolamide and dichlorphenamide). Besides the foregoing drugs well established in use, the search for agents having less side effects and longer lasting activity has lead to evaluate, more recently, the possibility of using for the treatment of glaucoma another class of drugs, i.e. the calcium blocking agents. The latter, also known as "calcium entry blockers" or "calcium antagonists", are currently used as vasodilators and in the treatment of cardiac affections. For such indications, the most widespread calcium antagonists are, e.g., nifedipine,

diltiazem and verapamil.

The role of calcium in the dynamics of aqueous humour and in the control of intraocular pressure has not yet been entirely clarified, although it is known that the production and the outflow of aqueous are modulated also by calcium. As concerns the formation of aqueous, it is to be noted, firstly, that the hydrostatic component due to the arterial pressure and to the pressure of the vessels feeding the ciliary body is calcium-dependent, as it is confirmed by the known systemic vascular action of calcium antagonists. Further, the osmotic pressure due to ionic secretion at the level of the non-pigmented ciliary epithelium is likely to be modulated by calcium, as hypothesised by Abelson et al. (Abelson M.B., Gilbert C.M., Smith L.M., Sustained reduction of intraocular pressure in humans with the calcium channel blocker verapamil, Am. J. Ophthamol. 105; 155 (1988)).

As far as the outflow of the aqueous humour is concerned, calcium ions play a direct role in modulating the pressure of episcleral veins, and some studies suggest that calcium influences the outflow capacity, by maintaining the structural integrity of the trabecuale and of the exterior wall of the Schlemm's canal.

In spite of the foregoing suggestions several experimental works, both on animal models and clinical, and involving both systemic and topical administration, reported contradictory results about the activity of calcium channel blockers in the therapy of glaucoma. For instance, Monica et al. (Monica M.L., Hesse R.J., Messerli F.H., The effect of a calcium-channel blocking agent on intraocular pressure, Am. J. Ophthalmol. 96, 814 (1983)) reports that the oral administration of nitrendipine to patients with moderate hypertension but with normal intraocular pressure slightly lowered the latter, while Beatty and co-workers (Beatty J.F., Krupin T., Nichols P.F., Elevation of intraocular pressure by calcium-channel blockers, Arch. Ophthalmol. 102; 1072, (1984)) did not evidence any effect upon oral administration of verapamil to rabbits, and did even report an increase in the intraocular pressure upon topical administration. More recently, for instance, Payene and co-workers (Payene, L.J., Slagle T.M., Cheeks L.T., Effect of calcium-channel

blockers on intraocular pressure, Ophthalmic Res. 22; 337, (1990)) obtained a reduction in the intraocular pressure upon systemic administration of verapamil or nifedipine to rabbits, but did not detect any significant effect upon topical administration of the same agents or of diltiazem by the topical route.

In general, however, at least as far as verapamil is concerned, it may be said that the administration of this drug to man normally results in a reduction of the intraocular pressure. A more consistent reduction upon topical administration has been explained, in particular, by a work of Ettl et al. (Ettl A., Daxer A., Hoffmann U., Calcium channel blockers in the management of low-tension and open-angle glaucoma, Am. J. Ophthalmol. 116; 778, (1993)). These authors have detected, in the rabbit eye, verapamil levels 200 times higher than the levels obtainable by systemic administration.

Accordingly, the use of verapamil in the treatment of ocular hypertension is the object of the international PCT application No. WO 92/07563, filed by Abelson (i.e., the first author cited above) et al.. A later publication in the name of the same author is the international application No. WO 96/03986, concerning the treatment of a particular form of glaucoma, referred to as low-tension glaucoma. This pathology is characterised by an intraocular pressure which is almost normal, in spite of the fact that all of the other symptoms of glaucoma are present. In the latter document the therapeutic proposal is generically extended to all calcium-antagonists, many representatives of which are mentioned in a preliminary list. However, the only example of active agent disclosed in the document and supported by experimental data is verapamil.

Another calcium blocking agent that was specifically proposed for use, in a patent document, in the treatment of intraocular hypertension is diltiazem (French patent No. 2593395, published in 1987), while a list of more than one hundred calcium antagonists is presented in the international PCT application No. WO 93/23082. The latter concerns, for use in the treatment of glaucoma, a combination of a compound which lowers the intraocular pressure (i.e., a conventional antiglaucoma agent) and a calcium channel blocking agent. The disclosure does not contain any specific example of preferred

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