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(54) **TOPICAL OPHTHALMIC FORMULATIONS CONTAINING OLOPATADINE FOR TREATING ALLERGIC EYE DISEASES**

FORMULIERUNG ZUR TOPISCHEN ANWENDUNG AM AUGE, DIE OLOPATADINE ENTHALTEN,
ZUR BEHANDLUNG VON ALLERGISCHEN AUGENERKRANKUNGEN

COMPOSITIONS OPHTHALMIQUES TOPIQUES CONTENANT OLOPATADINE DESTINEES AU
TRAITEMENT D'AFFECTIONS ALLERGIQUES DES YEUX

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- DATABASE CHEMABS CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US KAMEI, CHIAKI ET AL: "Effects of certain anti-allergic drugs on experimental conjunctivitis in guinea pigs" XP002021562 & ATARASHII GANKA, vol. 11, no. 4, 1994, pages 603-5,
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Remarks:

The file contains technical information submitted after the application was filed and not included in this specification

Description

BACKGROUND OF THE INVENTION

5 Field of the Invention

[0001] The present invention relates to topical ophthalmic formulations used for treating allergic eye diseases, such as allergic conjunctivitis, vernal conjunctivitis, vernal keratoconjunctivitis, and giant papillary conjunctivitis. More particularly, the present invention relates to therapeutic and prophylactic topical use of 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid for treating and/or preventing allergic eye diseases.

Description of the Related Art

[0002] As taught in U.S. Patent Nos. 4,871,865 and 4,923,892, both assigned to Burroughs Wellcome Co. ("the Burroughs Wellcome Patents"), certain carboxylic acid derivatives of doxepin, including 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepine-2-carboxylic acid and 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepine-2(E)-acrylic acid, have antihistamine and antiasthmatic activity. These two patents classify the carboxylic acid derivatives of doxepin as mast cell stabilizers with antihistaminic action because they are believed to inhibit the release of autacoids (i.e., histamine, serotonin, and the like) from mast cells and to inhibit directly histamine's effects on target tissues. The Burroughs Wellcome Patents teach various pharmaceutical formulations containing the carboxylic acid derivatives of doxepin; Example 8 (I) in both of the patents discloses an ophthalmic solution formulation.

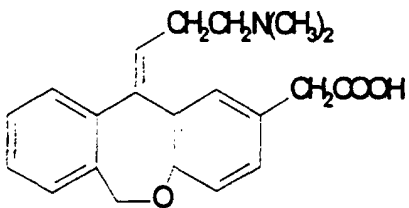
[0003] Although both of the Burroughs Wellcome Patents claim that the variety of pharmaceutical formulations disclosed are effective both for veterinary and for human medical use, neither patent contains an example demonstrating that the carboxylic acid derivatives of doxepin have activity in humans. Example 7 in the Burroughs Wellcome Patents demonstrates antihistamine activity in male guinea pigs and Example G demonstrates anaphylactoid activity in Wistar rats.

[0004] It is now well established, however, that the types of mast cells which exist in rodents are different from those in humans. See, for example, *THE LUNG: Scientific Foundations*, Raven Press, Ltd., New York, Ch. 3.4.11 (1991). Moreover, mast cell populations exist within the same species that differ in phenotype, biochemical properties, functional and pharmacological responses and ontogeny. These recognized differences in mast cells both between and within species are referred to as mast cell heterogeneity. See for example, Irani et al., "Mast Cell Heterogeneity," *Clinical and Experimental Allergy*, Vol. 19, pp. 143-155 (1989). Because different mast cells exhibit different responses to pharmacological agents, it is not obvious that compounds claimed to be anti-allergic ("mast cell stabilizers") will have clinical utility in specific mast cell populations. The assumption that mast cells are a homogeneous population and that therefore the effects of anti-allergic drugs observed in experiments in rat mast cells would be predictive of those in human cells is known to be incorrect. Church, "Is Inhibition of Mast Cell Mediator Release Relevant to the Clinical Activity of Anti-Allergic Drugs?," *Agents and Actions*, Vol. 18, 3/4, 288-293, at 291 (1986).

[0005] Examples exist in the art in which mast cell stabilizing drugs inhibit only select populations of mast cells. Disodium cromoglycate is an anti-allergic drug whose local effects are believed to be due to inhibition of mast cell degranulation (Church, *Agents and Actions*, at 288). This drug was shown to inhibit rodent mast cell degranulation. In human trials, 100 μ M of the drug inhibited mast cells obtained from bronchoalveolar lavage fluid. In dispersed human lung mast cell preparations, 1000 μ M of the drug was required to inhibit only 25% to 33% of histamine release. Finally, histamine release from human skin mast cells was not inhibited at all by disodium cromoglycate. Pearce et al., "Effect of Disodium Cromoglycate on Antigen Evoked Histamine Release in Human Skin," *Clinical Exp. Immunol.*, Vol. 17, 437-440 (1974); and Clegg et al., "Histamine Secretion from Human Skin Slices Induced by Anti-IgE and Artificial Secretagogues and the Effects of Sodium Cromoglycate and Salbutamol," *Clin. Allergy*, Vol. 15, 321-328 (1985). These data clearly indicate that classification of a drug as an anti-allergic does not predict that the drug possess inhibitory effects on all mast cell populations.

[0006] Topical ophthalmic formulations which contain drugs having conjunctival mast cell activity may only need to be applied once every 12-24 hours instead of once every 2-4 hours. One disadvantage to the ophthalmic use of reported anti-allergic drugs which in fact have no human conjunctival mast cell stabilizing activity is an increased dosage frequency. Because the effectiveness of ophthalmic formulations containing drugs which do not have conjunctival mast cell activity stems primarily from a placebo effect, more frequent doses are typically required than for drugs which do exhibit conjunctival mast cell activity.

[0007] U.S. Patent 5,116,863, assigned to Kyowa Hakko Kogyo Co., Ltd., ("the Kyowa patent"), teaches that acetic acid derivatives of doxepin and, in particular, the *cis* form of the compound having the formula



(i.e., Z-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid), have anti-allergic and anti-inflammatory activity.

[0008] The Kyowa patent demonstrates anti-allergic activity and anti-inflammatory activity in Wistar male rats. Medicament forms taught by the Kyowa patent for the acetic acid derivatives of doxepin include a wide range of acceptable carriers; however, only oral and injection administration forms are mentioned. In the treatment of allergic eye disease, such as allergic conjunctivitis, such administration methods require large doses of medicine.

[0009] What is needed are topically administrable drug compounds which have demonstrated stabilizing activity on mast cells obtained from human conjunctiva, the target cells for treating allergic eye diseases. What is also needed are local administration methods for the treatment of allergic eye disease.

Summary of the Invention

[0010] The present invention provides the use of a therapeutically effective amount of 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid (referred to as "Compound A" hereinafter) or of a pharmaceutically acceptable salt thereof for the preparation of a topical ophthalmic formulation for administering to the eye for treating an allergic eye disease. The formulation may contain the *cis* isomer of Compound A (Z-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid), the *trans* isomer of Compound A (E-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid), or a combination of both the *cis* and the *trans* isomers of Compound A, and unless specified otherwise, "11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid" or "Compound A" means the *cis* isomer, the *trans* isomer or a mixture of both. "Cis isomer" means the *cis* isomer substantially free of the *trans* isomer; "trans isomer" means the *trans* isomer substantially free of the *cis* isomer. One isomer is "substantially free" of the other isomer if less than about two percent of the unwanted isomer is present.

[0011] Compound A has human conjunctival mast cell stabilizing activity, and may be applied as infrequently as once or twice a day in some cases. In addition to its mast cell stabilizing activity, Compound A also possesses significant antihistaminic activity. Thus, in addition to a prophylactic effect, Compound A will also have a therapeutic effect.

Detailed Description of the Invention

[0012] Compound A is a known compound and both the *cis* and the *trans* isomers of Compound A can be obtained by the methods disclosed in U.S. Patent No. 5,116,863, the entire contents of which are hereby incorporated by reference in the present specification.

[0013] Examples of the pharmaceutically acceptable salts of Compound A include inorganic acid salts such as hydrochloride, hydrobromide, sulfate and phosphate; organic acid salts such as acetate, maleate, fumarate, tartrate and citrate; alkali metal salts such as sodium salt and potassium salt; alkaline earth metal salts such as magnesium salt and calcium salt; metal salts such as aluminum salt and zinc salt; and organic amine addition salts such as triethylamine addition salt (also known as tromethamine), morpholine addition salt and piperidine addition salt.

[0014] The inhibitory effects of reported anti-allergic, mast cell stabilizing drugs on mast cells obtained from human conjunctiva (the target cells for topical ophthalmic drug preparations claimed useful in treating allergic conjunctivitis) were tested according to the following experimental method. Human conjunctival tissues obtained from organ/tissue donors were weighed and transferred to petri dishes containing RPMI 1640 culture medium supplemented with heat inactivated fetal bovine serum (20%, v/v), L-glutamine (2mM), penicillin (100 units/ml), streptomycin (100 µg/ml), amphotericin B (2.5µg/ml) and HEPES (10mM) and equilibrated overnight at 37°C (5% CO₂).

[0015] Post equilibration, tissues were placed in Tyrode's buffer (in mM: 137 NaCl, 2.7 KCl, 0.35 Na H₂PO₄, 1.8 CaCl₂, 0.98 MgCl₂, 11.9 Na HCO₃, 5.5 glucose) containing 0.1% gelatin (TGCM) and incubated with 200U each of collagenase (Type IV) and hyaluronidase (Type I-S) per gram of tissue for 30 minutes at 37°C. Following enzyme digestion, tissues were washed with an equal volume of TGCM over Nitex® filter cloth (Tetko, Briarcliff Manor, NY). Intact tissues were placed in TGCM for further enzymatic digestions.

[0016] The filtrate obtained from each digestion was centrifuged (825 g, 7 minutes) and pelleted cells were resus-

5 pended in calcium/magnesium free Tyrode's buffer (TG). Pooled cells from all digestions were centrifuged (825 g, 30 minutes) over a 1.058 g/L Percoll® cushion. Mast cell enriched cell pellets were resuspended and washed in TG buffer. Viability and number of mast cells were determined by vital dye exclusion and toluidine blue 0 staining of the harvested cell suspensions. Mast cell containing preparations were placed in supplemented RPMI 1640 culture medium and allowed to equilibrate at 37°C prior to challenge with anti-human IgE (goat derived IgG antibody).

10 **[0017]** Cell suspensions containing 5000 mast cells were added to TGCM containing tubes and challenged with anti-human IgE. The final volume of each reaction tube was 1.0 mL. Tubes were incubated at 37°C for 15 minutes post challenge. The release reaction was terminated by centrifugation (500 g, 7 minutes). Supernatants were collected and stored (-20°C) until mediator analyses.

15 **[0018]** Initially, supernatants were analyzed for histamine content by both the automated fluorimetric method described by Siraganian, "An Automated Continuous Flow System for the Extraction and Fluorometric Analysis of Histamine," *Anal. Biochem.*, Vol. 57, 383-94 (1974), and a commercially available radioimmunoassay (RIA) system (AMAC, Inc., Westbrook, ME). Results from these assays were positively correlated ($r = 0.999$): therefore, the remainder of histamine analyses were performed by RIA.

20 **[0019]** Each experiment included an anti-human IgE (plus vehicle) positive release control, a spontaneous/vehicle release and a total histamine release control. Total histamine release was determined by treatment with Triton X-100® (0.1%). The experiments also included a non-specific goat IgG control. Test compounds are administered to the mast cell cultures either 1 or 15 minutes before stimulation with anti-human IgE. Inhibition of histamine release resulting from challenge of drug treated mast cells was determined by direct comparison with histamine release from vehicle treated, anti-IgE challenged mast cells using Dunnett's t-test (Dunnett, "A multiple comparison procedure for comparing treatments with a control," *J. Amer. Stat Assoc.*, Vol. 50, 1096-1121 (1955)). The results are reported in Table 1, below.

25 **[0020]** As Table 1 clearly shows, the anti-allergic drugs disodium cromoglycate and nedocromil failed to significantly inhibit human conjunctival mast cell degranulation. In contrast, Compound A (*cis* isomer) produced concentration-dependent inhibition of mast cell degranulation.

Tablet 1

Compound Effect on Histamine Release from Human Conjunctival Tissue Mast Cells upon anti-Human IgE Challenge.			
Compound	Dose (μM)	Treatment (min)	Inhibition (%)
Cromolyn sodium	1000	15	-15.4
	300	15	-6.9
	100	15	-1.2
	30	15	1.8
	10	15	10.6
Cromolyn sodium	1000	1	-9.4
	300	1	-1.8
	100	1	1.2
	30	1	0.1
	10	1	-0.9
Nedocromil sodium	1000	15	7.2
	300	15	11.3
	100	15	28.2*
	30	15	15.2
	10	15	9.2
	3	15	13.2

* $p < 0.05$, Dunnett's t-test

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