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(54) Title: INCREASING THE CHOROIDAL BLOOD FLOW

(57) Abrégé/Abstract:
The present invention is directed to a composition for increasing the choroidal blood flow which comprises administering to a subject in need of such treatment a 13,14-dihydro-15-keto-20-ethyl-prostaglandin F, a pharmaceutically acceptable salt thereof or a lower alkyl ester thereof.

ABSTRACT

The present invention is directed to a composition for increasing the choroidal blood flow which comprises administering to a subject in need of such treatment a 13,14-dihydro-15-keto-20-ethyl-prostaglandin F, a pharmaceutically acceptable salt thereof or a lower alkyl ester thereof.

INCREASING THE CHOROIDAL BLOOD FLOW

The present invention relates to a treatment for increasing the choroidal blood flow using 13,14-dihydro-15-keto-20-ethyl-prostaglandin Fs, salts or lower alkyl esters thereof.

The compounds used in the present invention, i.e. 13,14-dihydro-15-keto-20-ethyl-prostaglandin Fs, salts or lower alkyl esters thereof are known compounds and are described in EP-A-289349 (particularly in Examples 7, 11, 12, 13, 14 and 24) and EP-A-308135 (particularly in Example 8). In the former publication, the compounds are described as having a blood pressure increasing activity and in the latter publication, the compounds are described as having an ocular hypotensive activity. Nothing has been reported, however, concerning the activity of the above compounds on the choroidal blood flow. As a result of a study on the biological activity of 13,14-dihydro-15-keto-20-ethyl-prostaglandin Fs, salts or lower alkyl esters thereof, it has now been discovered that these compounds exhibit a choroidal blood flow increasing activity.

In a first aspect, the present invention provides a method for increasing the choroidal blood flow which comprises administering to a subject in need of such treatment a 13,14-dihydro-15-keto-20-ethyl-prostaglandin F, a pharmaceutically acceptable salt thereof or a lower alkyl ester thereof.

In a second aspect, the present invention provides a use of a 13,14-dihydro-15-keto-20-ethyl-prostaglandin F, a pharmaceutically acceptable salt thereof or a lower alkyl ester

thereof in the manufacture of a medicament for increasing choroidal blood flow.

In a third aspect, the present invention provides a pharmaceutical composition for increasing choroidal blood flow comprising a 13,14-dihydro-15-keto-20-ethyl-prostaglandin F, a pharmaceutically acceptable salt thereof or a lower alkyl ester thereof in association with a pharmaceutically acceptable carrier, diluent or excipient.

The present invention also provides a process for preparing the medicament or the pharmaceutical composition which comprises combining a 13,14-dihydro-15-keto-20-ethyl-prostaglandin F, a pharmaceutically acceptable salt thereof or a lower alkyl ester thereof with a pharmaceutically acceptable carrier, diluent or excipient.

The compounds used as the active ingredient in the present invention are compounds having the basic structure of the natural prostaglandin F and having a saturated carbon to carbon bond between positions 13 and 14, lacking the hydroxyl group at position 15, having an oxo group instead of said hydroxy group at position 15 and having an omega chain elongated by combining an ethyl group at position 20 (i.e. the terminal end of the omega chain), and salts or lower alkyl esters thereof.

The term "prostaglandin F" herein includes prostaglandin $F_1\alpha$, $F_2\alpha$ and $F_3\alpha$.

The salts of 13,14-dihydro-15-keto-20-ethyl-prostaglandin Fs are conveniently pharmaceutically acceptable salts.

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Suitable "pharmaceutically acceptable salts" include conventional non-toxic salts, and may be a salt with an inorganic base, for example a metal salt such as an alkali metal salt (e.g. sodium salt, potassium salt, etc.) and an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), ammonium salt, a salt with an organic base, for example, an amine salt (e.g. methylamine salt, dimethylamine salt, cyclohexylamine salt, benzylamine salt, piperidine salt, ethylenediamine salt, ethanolamine salt, diethanolamine salt, triethanolamine salt, tris(hydroxymethylamino)ethane salt, monomethylmonoethanolamine salt, procaine salt, caffeine salt, etc.), a basic amino acid salt (e.g. arginine salt, lysine salt, etc.), tetraalkylammonium salt and the like. These salts can be prepared by a conventional process, for example from the corresponding acid and base or by salt interchange.

The term "lower alkyl" in lower alkyl esters means alkyl groups having 1 to 6, preferably 1 to 4 carbon atoms, and include for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, etc.

Among the compounds used in the present invention, methods for the preparation of 13,14-dihydro-15-keto-20-ethyl-prostaglandin $F_2\alpha$ and its methyl ester, ethyl ester, isopropyl ester and n-butyl ester are described in Examples 24, 7, 11, 12 and 13 of EP-A-289,349, respectively. A method for the preparation of the isopropyl ester is also described in Example 7 of EP-A-30,135. A method for the preparation of 13,14-dihydro-

15-keto-20-ethyl-prostaglandin $F_1\alpha$ methyl ester is described in Example 14 of EP-A-289,349. Other compounds can be prepared analogously taking into consideration the other processes known for the preparation of prostaglandin compounds.

Choroid (Chorioidea) is the tissue present between the sciera and the retina with rich pigment and vascular, extending from the optic disk to the ora serrata. It is composed of four layers: supra-choroid (Stratum perichorioideum), layer of vessels (Lamina vasculosa), choriocapillaries (Lamina choriocapillaris) and Bruch's membrane (Lamina vitrea).

Since the compounds used in the invention exhibit a choroidal blood flow increasing activity, the compounds used in the invention, or medicaments or pharmaceutical compositions comprising said compounds, are useful in the treatment of, for example, ischemic disorder of choroid such as ischemic choroidal syndrome.

Such activity can be measured by conventional pharmacological assays which have been used to evaluate blood flow. The term "treatment" herein refers to any means of control of a disease including preventing the disease, curing the disease, relieving the disease and arresting or relieving the development of the disease.

The compounds used in the present invention may be used as a medicine for animals and human beings and is usually applied systemically or locally by such methods as ophthalmic administration, oral administration, intravenous injection

(including instillation), subcutaneous injection, suppository and the like. While the dosage will vary depending on the particular animal or human patient, age, body weight, symptom to be treated, desired therapeutic effect, administration route, term of treatment and the like, satisfactory effects will be obtained with a dosage of 0.01 - 100 μg/eye administered locally or 0.001 - 500 mg/kg administered systemically in 2 to 4 divided doses a day or as a sustained form.

The ophthalmic composition used according to the invention includes ophthalmic solution, ophthalmic ointment and the like. The ophthalmic solution can be prepared by dissolving an active ingredient in a sterile aqueous solution such as a physiological saline or a buffered solution, or as a combination of a solid and a solution for dissolving said solid to make a ready-to-use preparation. The ophthalmic ointment can be prepared by mixing an active ingredient with an ointment base.

The solid composition for oral administration used according to the invention includes tablets, troches, buccals, capsules, pills, powders, granules and the like. The solid composition contains one or more active substances in admixture with at least an inactive diluent, e.g. lactose, mannitol, glucose, hydroxypropyl cellulose, fine crystalline cellulose, starch, polyvinyl pyrrolidone, magnesium aluminate metasilicate. The composition may contain additives, in addition to the inactive diluent, for example, lubricants e.g., magnesium stearate, a disintegrator e.g. cellulose calcium gluconates, stabilizers e.g.

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α-, ß- or γ-cyclodextrins, etherated cyclodextrins (e.g. dimethyl-α-, dimethyl-ß-, trimethyl-ß-, or hydroxypropyl-ß-cyclodextrins), branched cyclodextrins (e.g. glucosyl- or maltosyl-cyclodextrins), formyl cyclodextrins, sulphur-containing cyclodextrins, misoprotols or phospholipids. Such cyclodextrins may increase the stability of the compounds by forming an inclusion compound. The stability may often be increased by forming a lyposome with phospholipids. Tablets and pills may be coated with an enteric or gastroenteric film e.g. white sugar, gelatin, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalates and the like, if necessary, and furthermore they may be covered with two or more layers. Additionally, the composition may be in the form of capsules made of a substance easily absorbed e.g. gelatin. The composition may be in the form of buccals, when an immediate effect is desired. For this purpose, a base e.g. glycerine, lactose, may be used.

Liquid compositions for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, elixirs and the like and contain a commonly used inactive diluent e.g. purified water or ethyl alcohol. The composition may contain additives e.g. wetting agents, suspending agents, sweeteners, flavours, perfumes and preservatives.

The composition of the present invention may be in the form of sprays which may contain one or more active ingredients and which can be prepared according to well known methods.

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An injection of this invention for non-oral administration includes sterile aqueous or nonaqueous solutions, suspensions, and emulsions. Diluents for the aqueous solution or suspension include, for example, distilled water for injection, physiological saline and Ringer's solution. Diluents for the nonaqueous solution and suspension include, for example, propylene glycol, polyethylene glycol, vegetable oils e.g. olive oil, alcohols, e.g. ethanol and polysorbates. The composition may contain other additives, e.g. preservatives, wetting agents, emulsifying agents, dispersing agents and the like. These are sterilized by filtration through, e.g. a bacteria-retaining filter, compounding with a sterilizer, gas sterilization or radiation sterilization. These can be prepared by producing a sterilized water or a sterilized solvent for injection before use.

Another formulation according to the present invention is a rectal or vaginal suppository. This can be prepared by mixing at least one active compound according to the invention with a suppository base e.g. cacao butter and optionally containing a nonionic surfactant for improving absorption.

A more complete understanding of the present invention can be obtained by reference to the following Formulation Examples and Test Examples which are provided herein for the purpose of illustration only and are not intended to limit the scope of the invention.

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Formulation Example 1

(Powders for injection)

(Parts by weight)

13,14-dihydro-15-keto-20-ethyl-prostaglandin $F_2\alpha$	1
mannitol	5
distilled water	0.4

The above ingredients are mixed, stirred, sterilized, filtered and lyophilized to give powders for injection.

Formulation Example 2

(Injectable solution)

(Parts by weight)

13,14-dihydro-15-keto-20-ethyl-prostaglandin $F_2\alpha$ methyl ester	0.2
nonionic surfactant	2
distilled water	98

The above ingredients are mixed and sterilized to give an injectable solution.

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Formulation Example 3

(Powders for oral administration)

	(Parts by weight)
13,14-dihydro-15-keto-20-ethyl-prostaglandin $F_2\alpha$ ethyl ester	5
light anhydrous silicic acid	5
Abicel*	20
lactose	70

The above ingredients are mixed to give powders for oral administration.

* Trademark

Formulation Example 4

(Soft gelatine capsules)

	(Parts by weight)
13,14-dihydro-15-keto-20-ethyl-prostaglandin $F_2\alpha$ propyl ester	1
Penasate*	899

The above ingredients are mixed and filled in soft gelatine capsules.

* Trademark

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Formulation Example 5

(Ophthalmic solution)

	(Parts by weight)
13,14-dihydro-15-keto-20-ethyl-prostaglandin $F_2\alpha$ isopropyl ester	1
Physiological saline	10

The above ingredients are placed in separate vials. The vials are combined to prepare a solution on actual use.

In the above formulation examples, the active ingredient can be replaced by any other compound within the compounds used in the invention.

Test Example 1

Six normal white rabbits (weight 2.1 - 3.2 kg) were anaesthetized by intraperitoneal administration of urethane (1.3 mg/kg). After 2 hours, experiments were conducted under stable depth of anaesthesia (room temperature: 25°C). The blood flow was measured by a heat gradient tissue blood flowmeter BTG-221* (Biomedical Science). Thus, an embedding type thermodiffusion sensor TGB-8R was fixed on the underlying membrane of a tenon capsule at a position between the medial rectus muscle and the superior rectus muscle and distanced by 10 mm from the dimbus. The tissue blood flow was measured continuously with an amplifier TGA-2. One eye was used as the treating eye and the other was used as the control. The treating

* Trademark

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eye received 50 μl of 0.06% aqueous solution of 13,14-dihydro-15-keto-20-ethyl-prostaglandin $F_2\alpha$ isopropyl ester and the control eye received 50 μl of physiological saline. Change in the tissue blood flow was measured over 5 hours.

The results are shown in Table 1 and also plotted in Figure 1, wherein * denotes $p<0.05$ and ** denotes $p<0.01$, according to the paired t-test (n=6, vs. control eye).

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Table 1

Treating eye						
Time	Rabbit					
(min)	A	B	C	D	E	F
30	100	103	97	102	104	102
60	108	108	103	108	111	109
90	114	112	107	110	113	111
120	113	110	108	107	110	107
150	116	108	107	108	113	110
180	117	105	105	106	110	107
210	112	103	102	105	108	106
240	111	103	101	105	107	104
270	105	101	101	105	106	103
300	100	98	99	104	103	101
Control eye						
Time	Rabbit					
(min)	A	B	C	D	E	F
30	102	98	97	98	101	98
60	105	98	96	99	102	98
90	104	100	99	101	102	101
120	110	99	98	100	103	101
150	112	100	98	101	102	103
180	105	97	94	97	98	99
210	108	98	96	100	97	102
240	108	96	95	98	96	99
270	104	96	95	98	97	98
300	102	95	95	96	96	95

(Values are shown in % taking the value at 0 minute as 100%.)

The above results clearly show that the compound used in the present invention had a choroidal blood flow increasing activity.

Claims:

1. A pharmaceutical composition for increasing choroidal blood flow comprising a 13,14-dihydro-15-keto-20-ethyl-prostaglandin F, a pharmaceutically acceptable salt thereof or a lower alkyl ester thereof in association with a pharmaceutically acceptable carrier, diluent or excipient.

2. A composition according to claim 1, wherein the 13,14-dihydro-15-keto-20-ethyl-prostaglandin is a 13,14-dihydro-15-keto-20-ethyl-prostaglandin $F_2\alpha$.

3. A composition according to claim 1, wherein the lower alkyl ester is isopropyl ester.

4. Use of a 13,14-dihydro-15-keto-20-ethyl-prostaglandin F, a pharmaceutically acceptable salt thereof or a lower alkyl ester thereof to increase choroidal blood flow.

Fig. 1