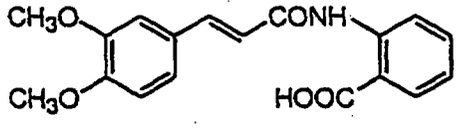
DESCRIPTION

SECONDARY CATARACT INHIBITOR

Technical Field

The present invention relates to a pharmaceutical composition being useful as a secondary cataract inhibitor.

More particularly, the present invention relates to an inhibitor for secondary cataract after cataract surgery which comprises as the active ingredient N-(3,4-dimethoxycinnamoyl)-anthranilic acid represented by the formula:



(I)

or a pharmaceutically acceptable salt thereof.

Background Art

Cataract is a refractory ocular disease which occurs and develops by various factors, and subsequently leads to lower vision due to lens opacity. Most of it is age-related senile cataract. The incidence of cataract is thought to be 60-70 % in the sixties and nearly 100 % in the eighties or more. In proceeding a society composed largely of elderly people, the prevention and treatment of cataract will become more important for the future. However, at the present time, there is no sure therapeutic agent having an inhibitory activity on the

development of cataract. Therefore, development of effective therapeutic agent has been desired. Accordingly, under the present situation, the treatment of cataract will be finally depended upon corrections of vision using eye glasses, contact lenses etc. or surgical operations such as insertion of the intraocular lens into capsula lentis after extracapsular cataract extraction.

In cataract surgery, secondary cataract after surgery is pointed out as a problem. This secondary cataract means opacity on the surface of the remaining posterior capsule following extracapsular cataract extraction. The mechanism of secondary cataract is mainly as follows. That is, after excising lens epithelial cells (anterior capsule), secondary cataract results from migration and proliferation of the residual lens epithelial cells, which are not completely removed at the time of extraction of the lens cortex, onto the posterior capsule leading to posterior capsule opacification. Also, secondary cataract results from abnormal proliferation of the residual lens epithelial cells in the equator followed by formation of Elschnig pearls.

In cataract surgery, it is impossible to remove lens epithelial cells completely, and consequently is difficult to prevent secondary cataract perfectly. It is said that the incidence of the above posterior capsule opacification is 40-50 % in aphakic eyes and 7-20 % in pseudophakic eyes.

On the other hand, in the field of the cataract medication,

extensive study has been actively promoted in order to find substances capable of inhibiting secondary cataract. Up to this time, for example, it was confirmed that metabolic antagonists such as mitomycin, daunomysin, 5-FU and colchicine are effective. However, theses drugs have been concerned about problems such as serious side effects [Atarashii Ganka, Vol.12, No.3, pp451-452 (1995); Japanese Journal of Ophthalmic Surgery, Vol.8, No.3, pp.439-446 (1995)] and are not enough to use clinically. In addition, it has been reported that the formation of secondary cataract was significantly inhibited when the inserted intraocular lens was coated with indometacin and that ethylenediaminetetraacetic acid (EDTA) is effective in secondary cataract [Japanese Journal of Ophthalmic Surgery, Vol.8, No.3, pp.439-446 (1995); IOL & RS, Vol.19, No.2, pp.78-82 (1995); Japanese Patent Application Publication (*kokai*) No.Hei.8-175984]. However, clinically satisfactory drugs preventing and inhibiting secondary cataract have not been developed yet.

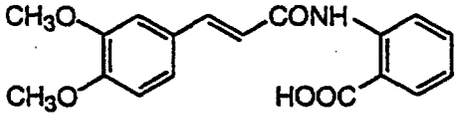
N-(3,4-dimethoxycinnamoyl)anthranilic acid (generic name: Tranilast) represented by the above formula (I) of the present invention has been widely used as medicines for the treatment of allergic disorders such as bronchial asthma, allergic rhinitis, atopic dermatitis and allergic conjunctivitis, and cutaneous disorders such as keloid and hypertrophic scar. For example, it has been known that Tranilast has inhibitory activities on chemical mediator release caused by an allergic reaction, excessive collagen accumulation by fibroblast cells

in cutaneous tissues and excessive proliferation of smooth muscle cells in coronary artery vessels.

However, it is disclosed in no way that Tranilast has an inhibitory activity on secondary cataract formation and it is not known at all that Tranilast is useful as an inhibitor for secondary cataract.

Disclosure of Invention

The present invention relates to a secondary cataract inhibitor which comprises as the active ingredient N-(3,4-dimethoxycinnamoyl)anthranilic acid represented by the formula:



(I)

or a pharmaceutically acceptable salt thereof.

The present invention relates to a method for the prevention or treatment of secondary cataract which comprises administering N-(3,4-dimethoxycinnamoyl)anthranilic acid represented by the above formula (I) or a pharmaceutically acceptable salt thereof.

The present invention also relates to a use of N-(3,4-dimethoxycinnamoyl)anthranilic acid represented by the above formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for the prevention or treatment of secondary cataract.

Furthermore, the present invention relates to a use of

N-(3,4-dimethoxycinnamoyl)anthranilic acid represented by the above formula (I) or a pharmaceutically acceptable salt thereof as a secondary cataract inhibitor.

The present inventors have been extensively studied to find compounds having an inhibitory activity on secondary cataract formation. As a result, it was found that N-(3,4-dimethoxy-cinnamoyl)anthranilic acid represented by the above formula (I) of the present invention has marked inhibitory effect on lens epithelial cell proliferation and is extremely useful as a secondary cataract inhibitor, thereby forming the basis of the present invention.

Accordingly, the present inventors confirmed that Tranilast significantly suppressed proliferation of lens epithelial cells in the *in vitro* test using rat lens epithelial cells to confirm inhibitory activity on cell proliferation.

As a consequence, Tranilast has excellent inhibitory effect on lens epithelial cell proliferation and is an extremely useful compound as a secondary cataract inhibitor.

Therefore, pharmaceutical compositions which are useful as secondary cataract inhibitors can be prepared by comprising as the active ingredient Tranilast or a pharmaceutically acceptable salt thereof.

Various methods for the preparation of Tranilast and salts thereof which are active ingredients are known and these compounds can be readily prepared according to methods described in

literatures and the like (Japanese Patent Application Publication (*kokoku*) No.Sho.56-40710; ibid. No.Sho.57-36905; ibid. No.Sho. 58-17186; ibid. No.Sho.58-48545; ibid. No.Sho.58-55138; ibid. No.Sho.58-55139; ibid. No.Hei.01-28013; ibid. No.Hei.01-50219; ibid. No.Hei.03-37539 etc.).

As examples of pharmaceutically acceptable salts of Tranilast, salts with inorganic bases such as a sodium salt and a potassium salt, salts formed with organic amines such as morpholine, piperazine and pyrrolidine and salts formed with amino acids can be illustrated.

When the pharmaceutical compositions of the present invention are employed in the practical treatment, various dosage forms of pharmaceutical compositions can be used depending upon usage. Preferably, eyedrops, injections, eye ointments or methods such as plantation after incorporating into pellet or microcapsule and insertion after pre-coating the intraocular lens can be illustrated.

These pharmaceutical compositions can be formulated by admixing, diluting or dissolving occasionally with appropriate pharmaceutical additives such as excipients, disintegrators, binders, lubricants, diluents, buffers, isotonicities, antiseptics, moistening agents, emulsifiers, dispersing agents, stabilizing agents and dissolving aids in accordance with conventional methods and formulating in the usual way depending upon the dosage forms.

For example, eyedrops can be formulated by dissolving

Tranilast or a pharmaceutically acceptable salt together with a basic substance with heating in sterilized water in which a surface active agent is dissolved, adding polyvinylpyrrolidone, optionally adding appropriate pharmaceutical additives such as a preservative, a stabilizing agent, a buffer, an isotonicity, an antioxidant and a viscosity improver, and dissolving completely.

Injections can be directly injected into diseased tissues such as cornea, crystalline lens and vitreous or their adjacent tissues by using a fine needle, and can be also used as intraocular perfusate.

The pharmaceutical compositions of the present invention can be administered as sustained release preparations. For example, Tranilast or a salt thereof is incorporated into pellet or microcapsule of a sustained release polymer as a carrier, and the pellet or microcapsule is surgically planted into tissues to be treated. Also, Tranilast or a salt thereof can be applied by inserting the intraocular lens pre-planted. As examples of sustained release polymers, ethylene-vinylacatate copolymer, polyhydrometacrylate, polyacrylamide, polyvinylpirrolidone, methylcellulose, lactic acid polymer, lactic acid-glycolic acid copolymer and the like can be illustrated, and preferably, biodegradable polymer such as lactic acid polymer and lactic acid-glycolic acid copolymer can be illustrated.

When the pharmaceutical compositions of the present invention are employed in the practical treatment, the dosage

of Tranilast or a pharmaceutically acceptable salt thereof as the active ingredient is appropriately decided depending on the body weight, age, sex, degree of symptoms of each patient to be treated. For example, when instillating to eyes, these compounds are administered approximately within the range of from 10 μg to 50 mg per day per adult human.

The dose of Tranilast or a pharmaceutically acceptable salt thereof can be appropriately increase and decrease depending on the degree of symptoms and therapeutic value of each patient to be treated.

Example

The present invention is further illustrated in more detail by way of the following Examples.

Example

Inhibitory activity on lens epithelial cell proliferation

① Culture of rat lens epithelial cells

Rat crystalline lens was harvested and cut into narrow strips. The strips were adhered to a culture plate and subcultured in Dulbecco's modified Eagle's Medium (DMEM) containing 10 % fetal calf serum (FBS) at 37 ℃ in an atmosphere of 5 % CO_2 in air for 4 days. On day 4 (at the point that lens epithelial cells were migrated and profilated from crystalline lens tissues), the medium was aspirated and cells were washed with phosphate-buffered saline (PBS(-)) gentlely. Then, the

PBS(-) was aspirated, an aliquot of 0.25 % trypsin solution containing 0.02 % EDTA was added to the culture plate, and the morphology of cells was observed under a phase-contrast microscopy. When cells were going to be round, an equal value of DMEM containing 10 % FBS was added to the trypsin solution to stop the action of trypsin. Attached cells were harvested from the plate by pipetting the medium using a slender pasture pipette. Cell suspension was transferred into spit, then medium was added to the spit, and the cell suspension was mixed about 20 times vigorously by pipetting with a pasture pipette and centrifuged at 100-110xg for 1 minute. After the supernatant was discarded, fresh medium was added to the precipitate, and lens epithelial cell suspension was prepared by pipetting using a pasture pipette. The suspension was further subcultured in DMEM containing 10 % FBS to use for experiment.

② Preparation of test drugs

Tranilast was added to 1 % aqueous sodium bicarbonate solution to prepare 1.0 % solution and dissolved by warming at 70 °C. The solution was sterilized with millipore filter and diluted with DMEM containing 10 % FBS to a final prescribed concentration.

③ Experimental method

Cell suspension (2×10^4 cells/0.1 ml) and DMEM medium (1.9 ml) containing various concentration of Tranilast and 10 % FBS

were added to a culture plate (60 mm), and cultured at 37 °C in an atmosphere of 5 % CO_2 in air. After 4 days, the medium was aspirated, the cells were washed with PBS(-), and 1 ml of 0.25 % trypsin solution containing 0.02 % EDTA was added to the plate. After harvesting cells from the plate by pipetting using a pasture pipette, number of viable cells was counted using a hemocytometer.

④ Assessment of effect

Mean and standard variation value of each group were calculated. Statistical analysis of significance was performed by a one-way analysis of variance and statistical significance was confirmed. Thereafter, analysis of significance between groups was performed by Dunnett's multiple test.

⑤ Results

As shown in Figure 1, Tranilast significantly suppressed the proliferation of lens epithelial cells in a concentration-dependent manner.

Brief Description of Drawings

Figure 1 is a graph illustrating an inhibitory activity on rat lens epithelial cell proliferation by Tranilast. The axis of the ordinates shows number of rat lens epithelial cells (x 10^4 cells), and the axis of the abscissas shows Tranilast concentrations to be added (μg/ml). The symbols * and ** in the

graph show the significantly difference at $p<0.05$ and $p<0.01$, respectively.

Industrial Applicability

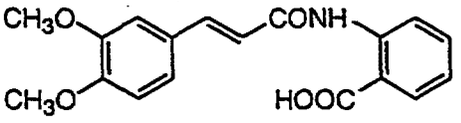
A pharmaceutical composition comprising as the active ingredient Tranilast or a pharmaceutically acceptable salt thereof has marked inhibitory activity on lens epithelial cell proliferation and is suitable as a secondary cataract inhibitor.

* C L M S *

THIS SHEET HAS BEEN REPLACED

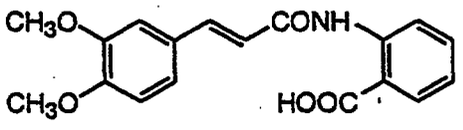
CLAIMS

1. A secondary cataract inhibitor which comprises as the active ingredient N-(3,4-dimethoxycinnamoyl)anthranilic acid represented by the formula:



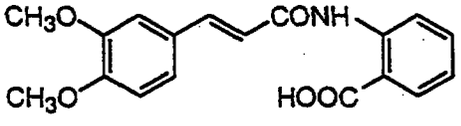
or a pharmaceutically acceptable salt thereof.

2. A method for the prevention or treatment of secondary cataract which comprises administering N-(3,4-dimethoxy-cinnamoyl)anthranilic acid represented by the formula:



or a pharmaceutically acceptable salt thereof.

3. A use of N-(3,4-dimethoxycinnamoyl)anthranilic acid represented by the formula:

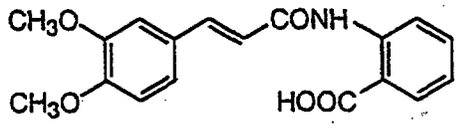


or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for the prevention or treatment of secondary cataract.

This Sheet Has Been Replaced

* C L M S *

4. A use of N-(3,4-dimethoxycinnamoyl)anthranilic acid represented by the formula:



or a pharmaceutically acceptable salt thereof as a secondary cataract inhibitor.