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(54) Title: **LOTEPREDNOL ETABONATE AGAINST VASCULAR DYSFUNCTION IN THE EYE**

(57) **Abstract:** This invention relates to the effect of Loteprednol etabonate on vascular dysfunction in the back of the eye. More specifically, this invention relates to methods of modifying a pathogenic angiogenesis in the back of an eye of a patient, the method comprising administering to a patient in need thereof a pathogenic angiogenesis modifying amount of Loteprednol etabonate. Moreover, this invention relates to methods of modifying pathologic vascular permeability manifested as retinal edema. The method comprises administering to a patient an amount of LE sufficient to reduce retinal edema.



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LOTEPREDNOL ETABONATE AGAINST VASCULAR DYSFUNCTION IN THE EYE

PRIORITY CLAIMS TO PRIOR APPLICATIONS

This application claims priority to US Provisional Application 60/730,277 filed October 26, 2005 the contents of which are incorporated by reference herein.

FIELD OF THE INVENTION

This invention relates to the effect of Loteprednol etabonate on vascular dysfunction in the back of the eye. More specifically, this invention relates to methods of modifying a pathogenic angiogenesis in the back of an eye of a patient, the method comprising administering to a patient in need thereof a pathogenic angiogenesis modifying amount of Loteprednol etabonate. Moreover, this invention relates to methods of modifying pathologic vascular permeability manifested as retinal edema. The method comprises administering to a patient an amount of LE sufficient to reduce retinal edema.

BACKGROUND AND SUMMARY

Compounds classified as corticosteroids, such as triamcinolone, can effectively treat some forms of neovascularization such as corneal neovascularization. In general, corticosteroids have been unsuccessful in treating neovascularization of the posterior segment. In many patients, these compounds cause undesirable side effects. These adverse affects include elevations in intraocular pressure and the formation of, or acceleration of the development of, cataracts. Elevations in intraocular pressure are of particular concern in patients who are already suffering from elevated intraocular pressure, such as glaucoma

patients. Moreover, a risk exists that the use of corticosteroids in patients with normal intraocular pressure will cause elevations in pressure that result in damage to ocular tissue. Since therapy with corticosteroids is frequently long term, i.e., several days or more, a potential exists for significant damage to ocular tissue as a result of prolonged elevations in intraocular pressure attributable to that therapy.

One approach to solving the foregoing problems has been to search for specific compounds which are effective in treating neovascularization without elevating intraocular pressure. Another approach has been to administer corticosteroids in conjunction with another drug to "block" or reduce the IOP elevating effects of the corticosteroids or to treat IOP elevation separately with another drug. A further approach has been to intravitreally inject corticosteroids to treat ocular neovascularization or retinal edema.

U.S. Patent No. 5,646,136 discloses methods for treating angiogenesis, tumors, and ocular hypertension with steroids including cortienic acid.

There still exists a need for an improved method for treating and/or preventing retinal diseases with corticosteroids.

Loteprednol etabonate (LE) is a predictably metabolized steroid that is being used as a topical anti-inflammatory agent. We have discovered that LE also has an anti-angiogenic effect in the eye by inhibiting the formation of VEGF (Vascular endothelial growth factor), a growth factor that stimulates new blood vessel growth and down regulating VEGF a potent endothelial cell specific mitogen and ICAM-1 (intracellular adhesion molecule -1) and VCAM-1 (vascular cell adhesion molecule -1).

Therefore provided herein is a method of modifying a pathogenic angiogenesis in the back of an eye of a patient, the method comprising administering to a patient in need thereof a pathogenic angiogenesis modifying amount of Loteprednol etabonate.

Also provided herein are methods for treating neovascular diseases of the back of the eye comprising administering to a patient in need thereof a therapeutically effective amount of Loteprednol etabonate in a pharmaceutically acceptable vehicle.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig.'s 1 A and B are graphical representations of the effect of LE on the expression of VEGF in HREC (human retinal endothelial cells) with (A) or without (B) LPS (lipopolysaccharide, a proinflammatory stimulant that has been shown to induce VEGF or upregulate VEGF induction) activation;

Fig.'s 2A and B are graphical representations of the effect of LE on the expression of sVCAM-1 (A) and sICAM-1 (B);

Fig. 3 depicts the physical appearance of 35% LE implants approximately 36 days after being placed in 2% FBS/PBS media;

Fig. 4 depicts the physical appearance of 35% LE implants approximately 36 days after being placed in PBS media;

Fig. 5 depicts the physical appearance of 10% LE implants approximately 36 days after being placed in 2% FBS/PBS media;

Fig. 6 depicts the release rates of the 35% LE implants.

DETAILED DESCRIPTION

Topical formulations comprising Loteprednol etabonate are commercially available under the trade names ALREX[®], LOTEMAX[®] and ZYLET[®] from Bausch & Lomb Incorporated and are described in US Patent No.'s 5,540,930 and 5,747,061 as well as US Patent Application Serial No. 10/698,322; the contents of each of which is incorporated by reference herein. Although there is currently no intraocular implants commercially available comprising LE, intraocular implants for the delivery of steroids such as Fluocinolone acetonide are available under the trade name RETISERT[®] from Bausch & Lomb Incorporated. Another intraocular implant for the delivery of steroids such as LE can be prepared by combining bioerodible PLGA with Loteprednol etabonate and preparing an implant sized and configured to deliver active LE to an intraocular region for an extended period of time.

Neovascular Diseases of the Eye

As noted above, the present invention provides methods for treating neovascular diseases of the back of the eye, including for example, proliferative diabetic retinopathy, retinopathy of prematurity, sickle cell disease, glaucoma associated with angiogenesis and macular degeneration.

Within one aspect of the present invention, methods are provided for treating proliferative diabetic retinopathy, comprising the step of administering to a patient a therapeutically effective amount of a Loteprednol etabonate composition to the eyes, such that the formation of blood vessels is inhibited. Methods of administration can include, for example, use of an intraocular implant containing LE.

In another aspect of the invention, it is contemplated that LE, for example in an implant, would be used the fellow eye when only one eye demonstrates a disease state as prophylaxis for the disease.

Briefly, background diabetic retinopathy is believed to convert to proliferative diabetic retinopathy under the influence of retinal hypoxia. Generally, neovascular tissue sprouts from the optic nerve (usually within 10 mm of the edge), and from the surface of the retina in regions where tissue perfusion is poor. Initially the capillaries grow between the inner modifying membrane of the retina and the posterior surface of the vitreous. Eventually, the vessels grow into the vitreous and through the inner modifying membrane. As the vitreous contracts, traction is applied to the vessels, often resulting in shearing of the vessels and blinding of the vitreous due to hemorrhage. Fibrous traction from scarring in the retina may also produce retinal detachment.

The conventional therapy of choice is panretinal photocoagulation to decrease retinal tissue, and thereby decrease retinal oxygen demands. Although initially effective, there is a high relapse rate with new lesions forming in other parts of the retina. Complications of this therapy include a decrease in peripheral vision of up to 50% of patients, mechanical abrasions of the cornea, laser-induced cataract formation, acute glaucoma, and stimulation of subretinal neovascular growth (which can result in loss of vision). As a result, this procedure is performed only when several risk factors are present, and the risk-benefit ratio is clearly in favor of intervention.

Therefore, within further embodiments of the invention, proliferative diabetic retinopathy may be treated by injection of a Loteprednol etabonate composition and/or intraocular implants comprising LE into the aqueous humor or the vitreous, in order to

increase the local concentration of Loteprednol etabonate in the retina. Preferably, this treatment should be initiated prior to the acquisition of severe disease requiring photocoagulation.

Within another aspect of the present invention, methods are provided for treating Retinopathy of prematurity, comprising the step of administering to a patient a therapeutically effective amount of a Loteprednol etabonate composition and/or intraocular implants comprising LE to the eye, such that the formation of blood vessels is inhibited.

Briefly, retinopathy of prematurity is a condition occurring in premature infants who receive oxygen therapy. The peripheral retinal vasculature, particularly on the temporal side, does not become fully formed until the end of fetal life. Excessive oxygen (even levels which would be physiologic at term) and the formation of oxygen free radicals are thought to be important by causing damage to the blood vessels of the immature retina. These vessels constrict, and then become structurally obliterated on exposure to oxygen. As a result, the peripheral retina fails to vascularize and retinal ischemia ensues. In response to the ischemia, neovascularization is induced at the junction of the normal and the ischemic retina.

In 75% of the cases these vessels regress spontaneously. However, in the remaining 25% there is continued capillary growth, contraction of the fibrovascular component, and traction on both the vessels and the retina. This results in vitreous hemorrhage and/or retinal detachment which can lead to blindness. Neovascular angle-closure glaucoma is also a complication of this condition.

As it is often impossible to determine which cases will spontaneously resolve and which will progress in severity, conventional treatment (i.e., surgery) is generally initiated

only in patients with established disease and a well developed pathology. This "wait and see" approach precludes early intervention, and allows the progression of disease in the 25% who follow a complicated course. Therefore, within one embodiment of the invention, topical administration of Loteprednol etabonate compositions, as described above may be accomplished in infants who are at high risk for developing this condition in an attempt to cut down on the incidence of progression of retrolental fibroplasia. Within other embodiments, intravitreal injections and/or intraocular implants of a Loteprednol etabonate composition may be utilized. Such methods are particularly preferred in cases of established disease, in order to reduce the need for surgery.

EXAMPLES

ELISA

HREC were treated with LE (10, 25 and 50 μ M) for 3 days. Supernatants were removed and microcentrifuge (Beckman Microfuge R) 1000 RPM for 10 min @ 4°C after which they were stored at -70°C until needed. ELISA kits (R&D systems) for human vascular endothelial growth factor (VEGF), soluble intracellular adhesion molecule (sICAM-1) and soluble vascular cell adhesion molecule (sVCAM-1) were used according to the manufacturer's instructions.

Protein Assay

Protein levels were measured using a Micro BCA protein assay kit (Pierce).

Western blot analysis

Cells were treated with LE (0, 10 & 50 μ M) for either 3 days or LE (0, 10 & 50 μ M) was replenished everyday for 3 days. Cells were lysed and protein levels determined/adjusted (see above). SDS PAGE was performed on cell lysates and then

separated proteins were transferred on to a nitrocellulose (NC) paper (Invitrogen). NC paper was blocked with 3% non-fat milk in phosphate buffered saline (PBS) for 1 hour and then probed with specific anti bodies to occludin (Rabbit anti-occludin polyclonal and monoclonal antibodies, Zymed); Goat anti-occludin (Santa Cruz). NC paper was then incubated with secondary horseradish peroxidase conjugated antibody for 1 hour and the bands were visualized using DAB (3, 3'-diaminobenzidine) (Vector Laboratories) or chemiluminescence (SuperSignal West Dura, Pierce).

Immunohistochemistry (HREC)

Human retina endothelial cells were seeded onto an 8-well glass chamber and allowed to become 80-90% confluent. Cells were treated with or without LE for 1 hour and then treated with VEGF (20 ng/ml) for 1 hour. HREC were immediately fixed and stained with specific antibodies to occludin and zonula occluden-1 (Zymed). FITC-conjugated secondary antibodies (R&D Systems) were used to visualize tight junction distribution/integrity.

Fabrication of LE/PLGA Sustained Release Implants

10% and 35% Loteprednol etabonate bioerodible implants were hot melt extruded through a lab mixing extruder Dynisco Instruments, Hickory, NC using the following formulations:

10% LE Implants

10% LE, Lot # 0208251158B

85% (50:50) PLGA, 0.17 I.V., Lot # D00120

5% (50:50) PLGA, 0.39 I.V., Lot # D01079

The process conditions used were as follows:

Rotor Temp: 72 C

Header Temp: 72 C

Rotor RPM: 40

Line Puller: 70-80 setting

35% LE Implants

35% LE, Lot # 0208251158B

60% (50:50) PLGA, 0.17 I.V., Lot # D00120

5% (50:50) PLGA, 0.39 I.V., Lot # D01079

The process conditions used were as follows:

Rotor Temp: 80 C

Header Temp: 85 C / Second Pass: Header Temp: 83 C

Rotor RPM: 20

Line Puller: 110 - 130 setting

The extruded LE/PLGA implants were stored in a Petri dish in a nitrogen dry box.

In vitro Release Study

Three implants were placed separately in individual vials containing 3 ml 2% Fetal Bovine Serum (FBS) HyClone, Logan, UT Phosphate Buffered Saline (PBS) Invitrogen,

Carlsbad, CA (pH = 7.4) and in PBS (pH = 7.4) release media. The various media were replaced fully twice a week (every 3 or 4th day). The release of LE from the implants as well as the physical appearance of the devices is shown in the figures 3-6. Implants containing 35% Loteprednol / 60% 50:50 PLGA (0.17 IV) / 5% 50:50 PLGA (0.39 IV) in PBS and 2% FBS/PBS were initiated. Fig. 3 depicts the 35% LE implants in 2% FBS/PBS implant approximately 36 days after initiation. Fig. 4 depicts the 35% LE implants in PBS media implant approximately 36 days after being placed in PBS media. The implant has severely degraded. The release rate study was abandoned using the PBS model. Implants in PBS and 2% FBS/PBS containing 10% Loteprednol / 85% 50:50 PLGA (0.17 IV) / 5% 50:50 PLGA (0.30 IV) were initiated. Fig. 5 depicts the 10% LE implant in PBS/2% FBS implant approximately 36 days after initiation. The implant has changed from a rod to a bead shape. The 10% LE implant in PBS completely eroded away during the first week of initiating the implant study. The release rate study for this formulation was abandoned due to the rapid erosion of the implant.

Fig. 6 depicts the release rates of the 35% Loteprednol Etabonate implants. The PLGA bioerodible polymers are known to erode in a bulk erosion fashion. This would imply that as the aqueous media penetrates the polymer the drug present in the matrix would be exposed to this environment. LE, which is known to hydrolyze very rapidly, would be rendered unstable. However, this formulation demonstrated that the drug is released in a sustained manner over a period of at least 13 weeks. This would facilitate the use of LE for various indications such as DME, uveitis, etc. for the posterior segment of the eye using long term sustained release implants. The content uniformity of the 35% LE implants was determined to be: 33.46 % (SD:4.9%)

Method and Treatment

A bioerodible device is prepared comprising DL-PLGA copolymers and Loteprednol etabonate. The device is cylindrical in form approximately 0.5 mm diameter by 10 mm in total length. The device is inserted into the vitreous body of the eye in a minimally invasive and sutureless form. The device is designed to provide for the release of active LE to the posterior chamber of the eye for an extended period of time.

Discussion

Loteprednol etabonate treatment (0, 10, 25 & 50 μ M) of HREC (with or without LPS activation) significantly down regulated the expression of VEGF ($p \leq 0.01$) (Fig.'s 1 A and B), sVCAM-1 ($p \leq 0.05$) and sICAM-1 ($p \leq 0.05$) (Fig.'s 2 A and B). There was no apparent cellular toxicity at the highest concentration of LE tested.

Loteprednol etabonate appears to regulate tight junction proteins by inhibiting VEGF-induced redistribution of ZO-1. Photomicrographs were taken to show the effect of LE on ZO-1 in VEGF-treated Human Retinal Endothelial Cells (HREC). HREC stained positively for ZO-1 when no VEGF was present, VEGF-treated cells did not react with ZO-1 and LE at concentration of 10 & 50 μ M reversed the effect of VEGF tight junction disruption.

Effect of steroids on vascular leakage and tight junctions has been reported before (Antonetti, D.A., et al.; Journal of Neurochemistry, 2002 80:667-677). In this study LE also inhibited the effect of VEGF-induced disruption of ZO-1 and increased the total content of occludin. However, this modulation of tight junction protein appears to be as a result of LE's steroid effect and not to its metabolites, since daily administration of LE was necessary to maintain its biological effect on occludin.

In conclusion LE is believed to be a good candidate for the treatment of vascular diseases of the eye such as diabetic macular edema and wet AMD.

The claims, as originally presented and as they may be amended, encompass variations, alternatives, modifications, improvements, equivalents, and substantial equivalents of the embodiments and teachings disclosed herein, including those that are presently unforeseen or unappreciated, and that, for example, may arise from applicants/patentees and others.

What is claimed is:

1. A method of modifying a pathogenic angiogenesis in the back of an eye of a patient, the method comprising:
administering to a patient in need thereof a pathogenic angiogenesis modifying amount of Loteprednol etabonate.
2. The method of claim 1 wherein the pathogenic angiogenesis is selected from the group consisting of proliferative diabetic retinopathy, retinopathy of prematurity, sickle cell disease, glaucoma associated with angiogenesis, macular degeneration and combinations thereof.
3. The method of claim 1 wherein the step of administering to a patient in need thereof a pathogenic angiogenesis modifying amount of Loteprednol etabonate is performed by injection of a Loteprednol etabonate composition and/or intraocular implant comprising LE into the aqueous humor or the vitreous of the patient.
4. The method of claim 1 wherein the step of administering to a patient in need thereof a pathogenic angiogenesis modifying amount of Loteprednol etabonate is performed by topically administering a Loteprednol etabonate composition.
5. The method of claim 1 wherein the step of administering to a patient in need thereof a pathogenic angiogenesis modifying amount of Loteprednol etabonate is performed by injection of a Loteprednol etabonate composition and/or intraocular implants comprising LE into the aqueous humor or the vitreous of the patient along with topically administering a Loteprednol etabonate composition.

6. The method of claim 1 wherein the step of administering to a patient in need thereof a pathogenic angiogenesis modifying amount of Loteprednol etabonate is performed to increase the local concentration of Loteprednol etabonate in the retina.
7. The method of claim 1 wherein the step of administering to a patient in need thereof a pathogenic angiogenesis modifying amount of Loteprednol etabonate is performed prior to the acquisition of a disease requiring photocoagulation.
8. A method comprising:

administering to a patient in need thereof a therapeutically effective amount of Loteprednol etabonate in a pharmaceutically acceptable vehicle for treating at least one neovascular disease of the back of the eye.
9. The method of claim 8 wherein the step of administering to a patient in need thereof a therapeutically effective amount of Loteprednol etabonate in a pharmaceutically acceptable vehicle is performed by injection of a Loteprednol etabonate composition and/or intraocular implant comprising LE into the aqueous humor or the vitreous of the patient.
10. The method of claim 8 wherein the step of administering to a patient in need thereof a therapeutically effective amount of Loteprednol etabonate in a pharmaceutically acceptable vehicle is performed by injection of a Loteprednol etabonate composition and/or intraocular implants comprising LE into the aqueous humor or the vitreous of the patient along with topically administering a Loteprednol etabonate composition.
11. The method of claim 8 wherein the neovascular disease of the back of the eye is selected from the group consisting proliferative diabetic retinopathy, retinopathy of prematurity, sickle cell disease, glaucoma associated with angiogenesis and macular degeneration and combinations thereof.

12. The method of claim 8 wherein the neovascular disease of the back of the eye is prophylactically treated by placing an implant in the fellow eye when only one eye demonstrates a neovascular disease state.
13. A method of modifying a pathogenic angiogenesis in the back of an eye of a patient, the method comprising:
administering to a patient in need thereof a pathogenic angiogenesis modifying amount of Loteprednol etabonate.
14. The method of claim 13 wherein the step of administering to a patient in need thereof a pathogenic angiogenesis modifying amount of Loteprednol etabonate is performed by injection of a Loteprednol etabonate composition and/or intraocular implant comprising LE into the aqueous humor or the vitreous of the patient.
15. The method of claim 13 wherein the step of administering to a patient in need thereof a pathogenic angiogenesis modifying amount of Loteprednol etabonate is performed by topically administering a Loteprednol etabonate composition.
16. The method of claim 13 wherein the step of administering to a patient in need thereof a pathogenic angiogenesis modifying amount of Loteprednol etabonate is performed by injection of a Loteprednol etabonate composition and/or intraocular implants comprising LE into the aqueous humor or the vitreous of the patient along with topically administering a Loteprednol etabonate composition.
17. The method of claim 13 wherein the step of administering to a patient in need thereof a pathogenic angiogenesis modifying amount of Loteprednol etabonate is performed to increase the local concentration of Loteprednol etabonate in the retina.

18. The method of claim 13 wherein the step of administering to a patient in need thereof a pathogenic angiogenesis modifying amount of Loteprednol etabonate is performed prior to the acquisition of a disease requiring photocoagulation.
19. A method comprising:
- administering to a patient in need thereof a therapeutically effective amount of Loteprednol etabonate in a pharmaceutically acceptable vehicle for treating at least one retinal edema disease of the back of the eye.
20. The method of claim 19 wherein the step of administering to a patient in need thereof a therapeutically effective amount of Loteprednol etabonate in a pharmaceutically acceptable vehicle is performed by injection of a Loteprednol etabonate composition and/or intraocular implant comprising LE into the aqueous humor or the vitreous of the patient.
21. The method of claim 19 wherein the step of administering to a patient in need thereof a therapeutically effective amount of Loteprednol etabonate in a pharmaceutically acceptable vehicle is performed by injection of a Loteprednol etabonate composition and/or intraocular implants comprising LE into the aqueous humor or the vitreous of the patient along with topically administering a Loteprednol etabonate composition.
22. The method of claim 19 wherein the retinal edema disease of the back of the eye is prophylactically treated by placing an implant in the fellow eye when only one eye demonstrates a retinal edema disease state.
23. A method of modifying a pathogenic macular edema in the back of an eye of a patient, the method comprising:
- administering to a patient in need thereof a pathogenic macular edema modifying amount of Loteprednol etabonate.

24. The method of claim 23 wherein the step of administering to a patient in need thereof a pathogenic macular edema modifying amount of Loteprednol etabonate is performed by injection of a Loteprednol etabonate composition and/or intraocular implant comprising LE into the aqueous humor or the vitreous of the patient.
25. The method of claim 23 wherein the step of administering to a patient in need thereof a pathogenic macular edema modifying amount of Loteprednol etabonate is performed by topically administering a Loteprednol etabonate composition.
26. The method of claim 23 wherein the step of administering to a patient in need thereof a pathogenic macular edema modifying amount of Loteprednol etabonate is performed by injection of a Loteprednol etabonate composition and/or intraocular implants comprising LE into the aqueous humor or the vitreous of the patient along with topically administering a Loteprednol etabonate composition.
27. The method of claim 23 wherein the step of administering to a patient in need thereof a pathogenic macular edema modifying amount of Loteprednol etabonate is performed to increase the local concentration of Loteprednol etabonate in the retina.
28. The method of claim 23 wherein the step of administering to a patient in need thereof a pathogenic macular edema modifying amount of Loteprednol etabonate is performed prior to the acquisition of a disease requiring photocoagulation.
29. A method comprising:
administering to a patient in need thereof a therapeutically effective amount of Loteprednol etabonate in a pharmaceutically acceptable vehicle for treating at least one macular edema disease of the back of the eye.

30. The method of claim 29 wherein the step of administering to a patient in need thereof a therapeutically effective amount of Loteprednol etabonate in a pharmaceutically acceptable vehicle is performed by injection of a Loteprednol etabonate composition and/or intraocular implant comprising LE into the aqueous humor or the vitreous of the patient.

31. The method of claim 29 wherein the step of administering to a patient in need thereof a therapeutically effective amount of Loteprednol etabonate in a pharmaceutically acceptable vehicle is performed by injection of a Loteprednol etabonate composition and/or intraocular implants comprising LE into the aqueous humor or the vitreous of the patient along with topically administering a Loteprednol etabonate composition.

32. The method of claim 29 wherein the neovascular disease of the back of the eye is prophylactically treated by placing an implant in the fellow eye when only one eye demonstrates a macular edema disease state.

33. A method of modifying a pathogenic macular edema in the back of an eye of a patient, the method comprising:
administering to a patient in need thereof a pathogenic systoid macular edema modifying amount of Loteprednol etabonate.

34. The method of claim 33 wherein the step of administering to a patient in need thereof a pathogenic systoid macular edema modifying amount of Loteprednol etabonate is performed by injection of a Loteprednol etabonate composition and/or intraocular implant comprising LE into the aqueous humor or the vitreous of the patient.

35. The method of claim 33 wherein the step of administering to a patient in need thereof a pathogenic systoid macular edema modifying amount of Loteprednol etabonate is performed by topically administering a Loteprednol etabonate composition.

36. The method of claim 33 wherein the step of administering to a patient in need thereof a pathogenic systoid macular edema modifying amount of Loteprednol etabonate is performed by injection of a Loteprednol etabonate composition and/or intraocular implants comprising LE into the aqueous humor or the vitreous of the patient along with topically administering a Loteprednol etabonate composition.

37. The method of claim 33 wherein the step of administering to a patient in need thereof a pathogenic systoid macular edema modifying amount of Loteprednol etabonate is performed to increase the local concentration of Loteprednol etabonate in the retina.

38. The method of claim 33 wherein the step of administering to a patient in need thereof a pathogenic systoid macular edema modifying amount of Loteprednol etabonate is performed prior to the acquisition of a disease requiring photocoagulation.

39. A method comprising:

administering to a patient in need thereof a therapeutically effective amount of Loteprednol etabonate in a pharmaceutically acceptable vehicle for treating at least one systoid macular edema disease of the back of the eye.

40. The method of claim 39 wherein the step of administering to a patient in need thereof a therapeutically effective amount of Loteprednol etabonate in a pharmaceutically acceptable vehicle is performed by injection of a Loteprednol etabonate composition and/or intraocular implant comprising LE into the aqueous humor or the vitreous of the patient.

41. The method of claim 39 wherein the step of administering to a patient in need thereof a therapeutically effective amount of Loteprednol etabonate in a pharmaceutically acceptable vehicle is performed by injection of a Loteprednol etabonate composition and/or

intraocular implants comprising LE into the aqueous humor or the vitreous of the patient along with topically administering a Loteprednol etabonate composition.

42. The method of claim 39 wherein the cystoid macular edema disease of the back of the eye is prophylactically treated by placing an implant in the fellow eye when only one eye demonstrates a neovascular disease state.

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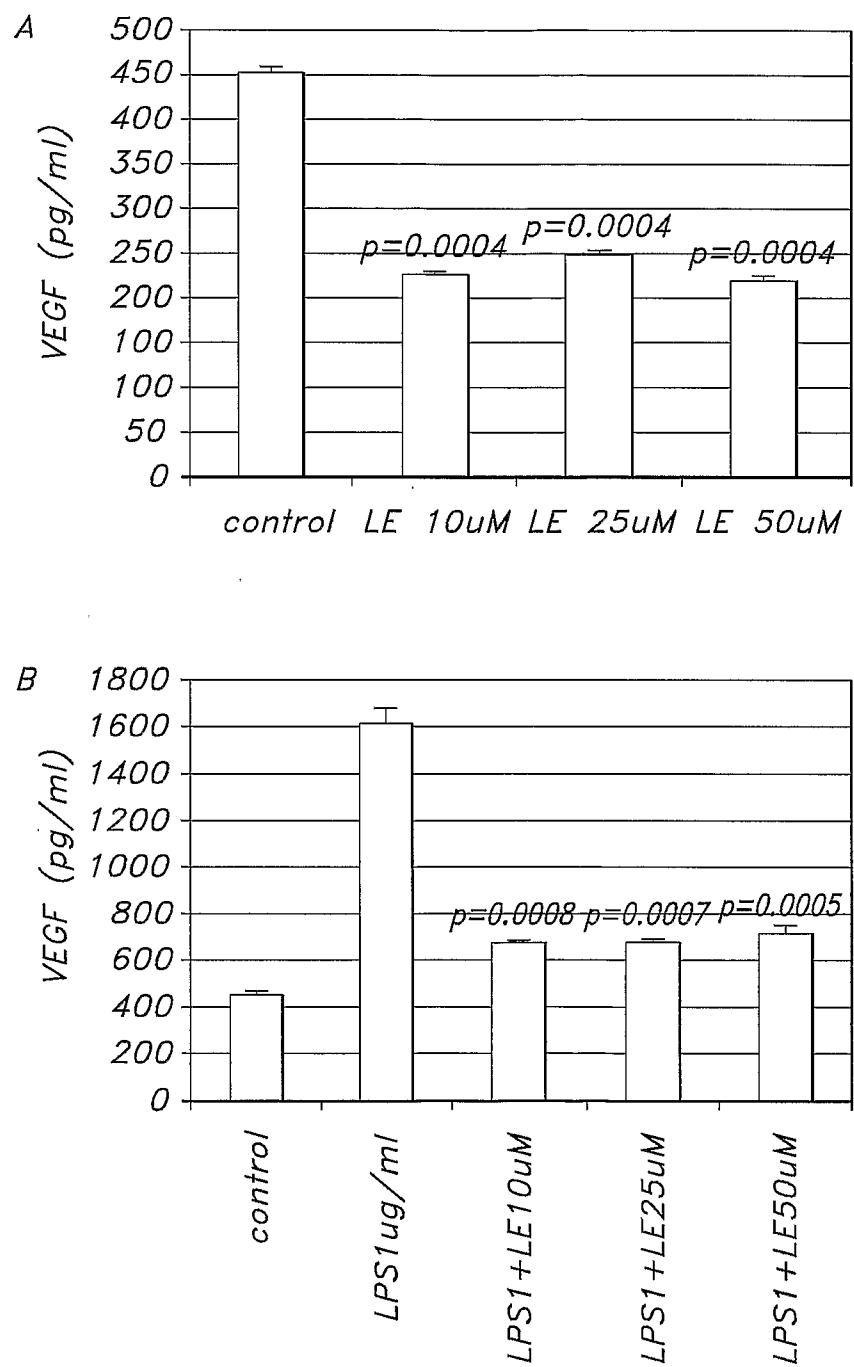


FIG. 1

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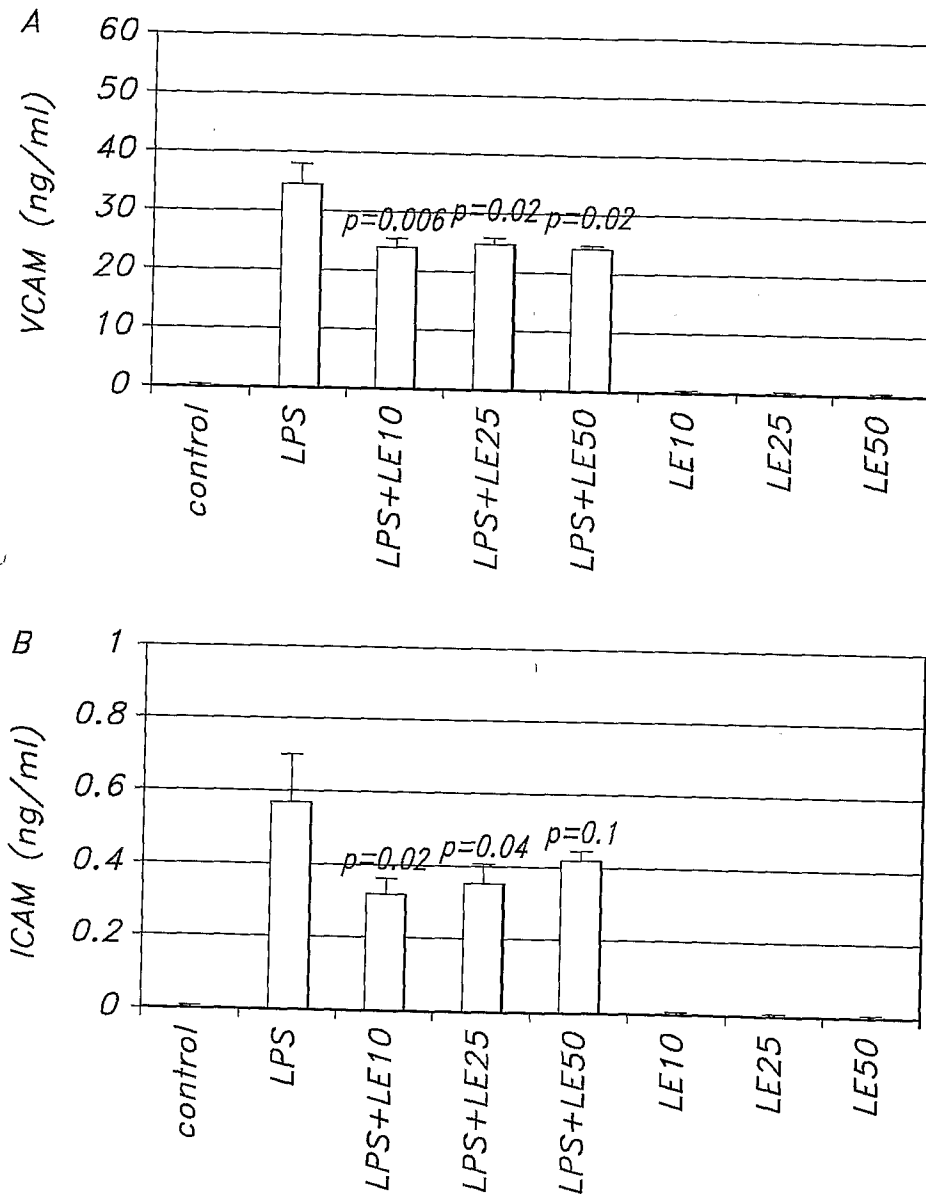


FIG. 2

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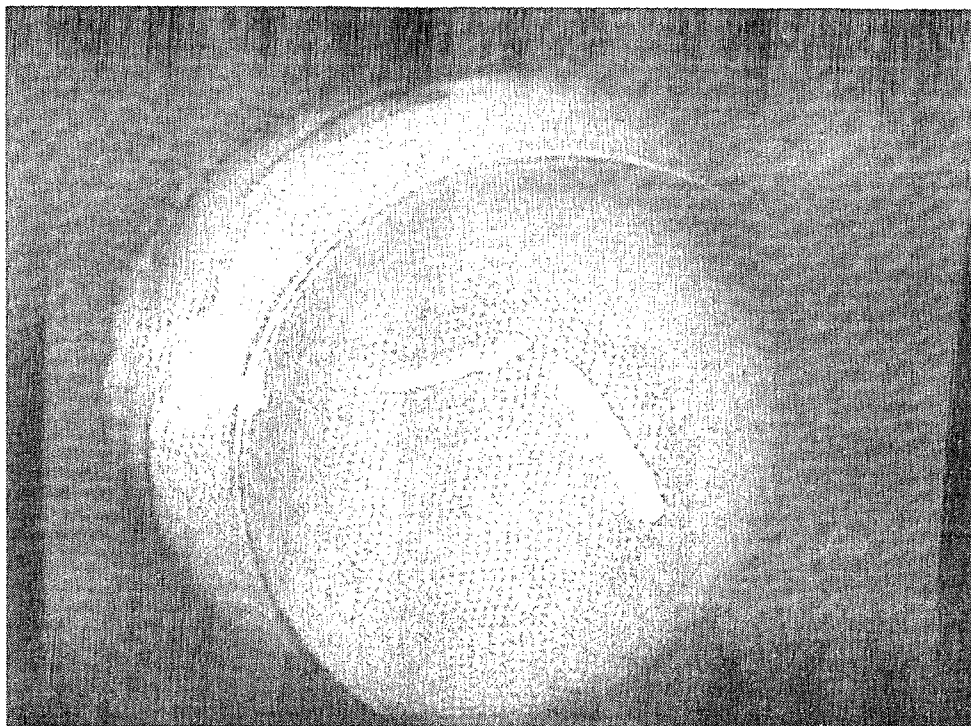


FIG. 3

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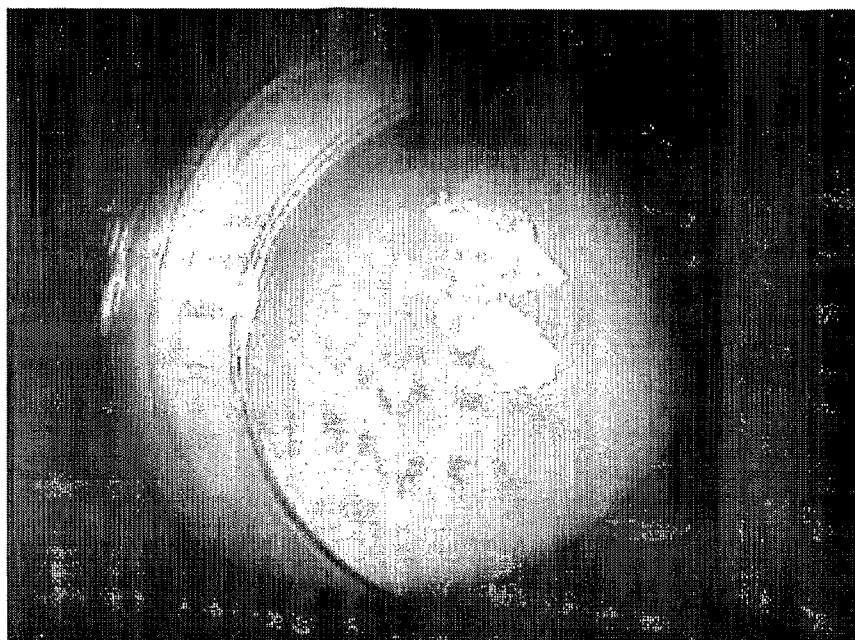


FIG. 4

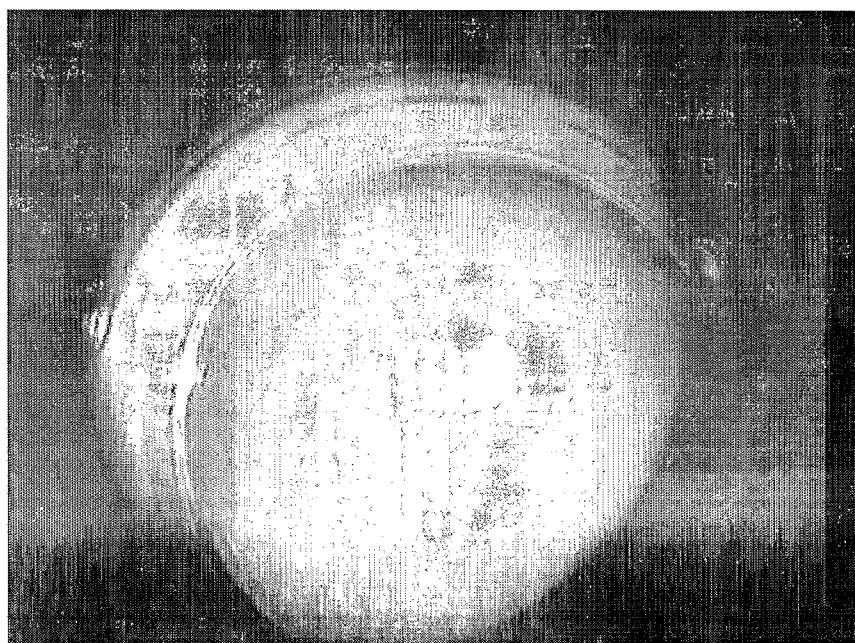


FIG. 5

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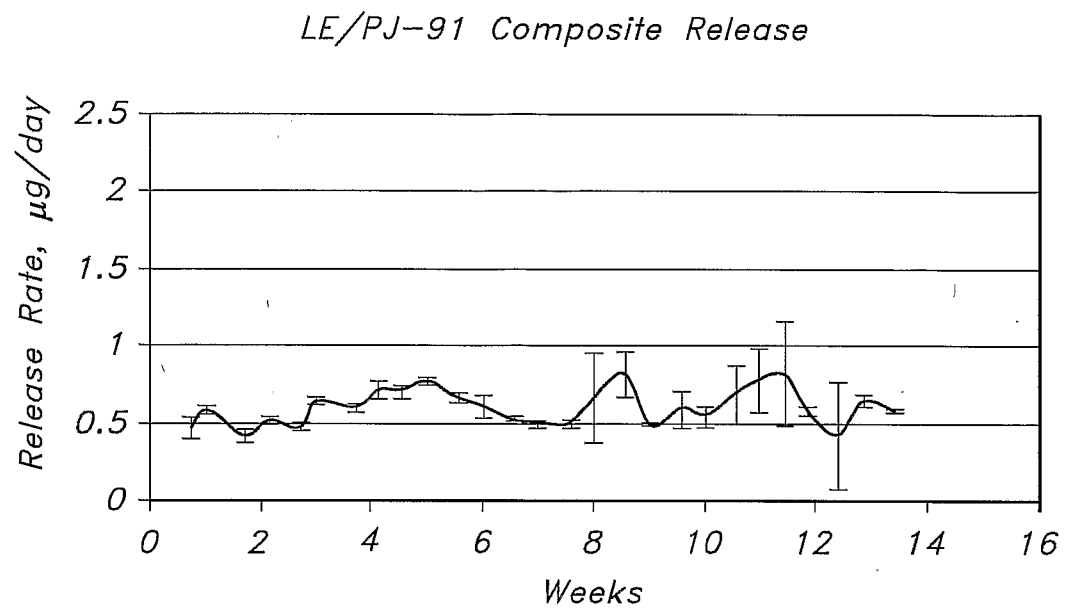


FIG. 6

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/041715

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/56 A61P27/02 A61P43/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, MEDLINE, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/058272 A (CONTROL DELIVERY SYSTEMS INC [US]; ASHTON PAUL [US]) 15 July 2004 (2004-07-15) page 2 - page 3 page 4, paragraph 2 page 12, paragraph 3 page 11, paragraph 2 page 13, paragraph 2 claims 1-25	1-42
X	HOWES J F: "LOTEPREDNOL ETABONATE: A REVIEW OF OPHTHALMIC CLINICAL STUDIES" PHARMAZIE, DIE, GOVI VERLAG, ESCHBORN, DE, vol. 55, no. 3, 2000, pages 178-183, XP008052947 ISSN: 0031-7144 abstract 2.5 Intraocular Pressure	1-42

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☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

14 March 2007

Date of mailing of the international search report

21/03/2007

Name and mailing address of the ISA/

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Authorized officer

Taylor, Mark

INTERNATIONAL SEARCH REPORT

international application No
PCT/US2006/041715

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2005/095205 A1 (KRISHNAMOORTHY RAMESH [US]) 5 May 2005 (2005-05-05) abstract paragraph [0012] claims 1-37	1-42
A	WO 95/18621 A (UNIV DUKE [US]) 13 July 1995 (1995-07-13) abstract page 3, line 28 - page 8, line 23 claims 1-14	1-42
A	WO 95/11669 A (PHARMOS CORP [US]; GUY YAACOV J [IL]; FRIEDMAN DORON [IL]) 4 May 1995 (1995-05-04) abstract page 1, line 26 - page 2, line 2 page 4, line 25 - page 5, line 5 claims 1-21	1-42

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/041715

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-42 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2006/041715

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