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(54) Title: METHOD FOR TREATING AND/OR PREVENTING RETINAL DISEASES WITH SUSTAINED RELEASE CORTICOSTEROIDS

(57) Abstract

The present invention relates to a method for administering a corticosteroid to a posterior segment of an eye. In the method, a sustained release device is implanted to deliver the corticosteroid to the eye. The aqueous corticosteroid concentration remains less than vitreous corticosteroid concentration during release of the corticosteroid from the device.

METHOD FOR TREATING AND/OR PREVENTING RETINAL DISEASES WITH SUSTAINED RELEASE CORTICOSTEROIDS

Field Of The Invention

The present invention relates to the field of controlled pharmaceutical delivery, particularly to corticosteroids.

Background Of The Invention

Compounds classified as corticosteroids, such as triamcinolone, effectively treat neovascularization and a number of other diseases including age related macular degeneration. In many patients, however, 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 without elevating intraocular pressure. Another approach has been to administer glucocorticoids in conjunction with another drug to "block" or reduce the IOP elevating effects of the glucocorticoid or to treat IOP elevation separately with another drug. A further approach has been to intravitreally inject corticosteroids to treat ocular neovascularization.

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

Disclosure of the Invention

An object of the present invention is to provide a method for treating and/or preventing ocular neovascularization with corticosteroids without the associated adverse side effects.

Additional objects, advantages and other features of the invention will be set forth in the description which follows and in part will become apparent to those having ordinary skill in the art upon examination of the following or may be learned from the practice of the invention. The objects and advantages of the invention may be realized and obtained as particularly pointed out in the appended claims.

According to the present invention, the foregoing and other objects are achieved in part by a method

for administering a corticosteroid to a posterior segment of an eye, the method comprising the step of:

implanting a sustained release device to deliver the corticosteroid to the vitreous of the eye wherein aqueous corticosteroid concentration is less than vitreous corticosteroid concentration during release.

In accordance with the present invention, the foregoing and other advantages are also achieved in part by an implantable, sustained release device for administering a corticosteroid to a posterior segment of an eye, the device comprising:

a corticosteroid, wherein the device is configured to provide sustained release of the corticosteroid to the vitreous of the eye such that aqueous corticosteroid concentration remains less than vitreous corticosteroid concentration during the release.

Additional objects and advantages of the present invention will become readily apparent to those skilled in this art from the following detailed description, wherein embodiments of the invention are described simply by way of illustrating of the best mode contemplated in carrying out the invention. As will be realized, the invention is capable of other and different embodiments, and its several details are capable of modifications in various obvious respects, all without departing from the invention. Accordingly, the drawings and description are to be regarded as illustrative in nature and not as restrictive.

Brief Description of Drawings

Fig. 1 shows the sustained release profile of a 2 mg fluocinolone acetonide implant in buffer.

Fig 2. shows the vitreous and aqueous levels of fluocinolone acetonide after implantation of a sustained release device.

Description of the Invention

The present invention provides for the use of a steroid in a medical device for treating ocular diseases, which can be adapted to be implanted into the vitreous of the eye. The device can further be adapted to establish a vitreous steroid concentration that is higher than an aqueous steroid concentrating during release of the steroid from the device.

The present invention is particularly effective in treating retinal diseases. Retinal diseases include, for example, ocular neovascularization, ocular inflammation and retinal degeneration. Specific examples of these disease states include diabetic retinopathy, chronic glaucoma, retinal detachment, sickle cell retinopathy, senile macular degeneration due to subretinal neovascularization); rubeosis iritis inflammatory diseases, chronic posterior and pan uveitis, neoplasms (retinoblastoma, pseudoglioma); neovascular glaucoma; neovascularization resulting following a combined vitrectomy and lensectomy; vascular diseases (retinal ischemia, choroidal vascular insufficiency, choroidal thrombosis); neovascularization of the optic nerve; diabetic macular edema, cystoid macular edema, macular edema, retinitis pigmentosa, retinal vein occlusion, and retinal artery occlusion; and, neovascularization due to penetration of the eye or ocular injury.

Examples of corticosteroids useful in the present invention include, for example, triamcinolone, dexamethasone, fluocinolone, cortisone, prednisolone, flumetholone, and derivatives thereof.

By "sustained release device" it is meant a device that releases drug over an extended period of time in a controlled fashion. Examples of sustained release devices useful in the present invention may be found in, for example, U.S. Patent No. 5,378,475 and U.S. Patent No. 5,773,019, and U.S. Serial No. 08/919,221 filed on August 28, 1997.

By "vitreous" of the eye, it is meant the vitreous or vitreal cavity of the eye. By "aqueous" of the eye, it is meant the aqueous humor of the eye.

In the present invention, a sustained release device is implanted into the eye such that it delivers corticosteroid to the posterior segment of the eye. In a preferred embodiment, the sustained release device is implanted intravitreally. However, the device may also be implanted in the choroidal space, sub-retinally, or in the sclera. These methods of administration and techniques for their preparation are well known by those of ordinary skill in the art. Methods of administration and techniques for their preparation are set forth in Remington's Pharmaceutical Sciences.

The aqueous corticosteroid concentration remains less than the vitreous corticosteroid concentration for substantially the lifetime of the sustained release device. Thus, during release of the corticosteroid, the aqueous corticosteroid concentration is about 0.002 μg/ml to about 0.01 μg/ml, such as from about 0.01 μg/ml to about 0.02 μg/ml. Preferably, the aqueous corticosteroid concentration is less than about 0.02 μg/ml.

In contrast, during release of the corticosteroid, the vitreous corticosteroid concentration remains therapeutic, that is, less than about 10 μg/ml. The exact concentration depends upon the disease and therapeutic index of the drug.

The sustained release device useful in the present invention is any device which can be implanted to deliver corticosteroid to the vitreous of the eye and can release a corticosteroid for a sustained period of time, that is, for about 1 month to about 20 years, such as from about 6 months to about 5 years.

The sustained release device can be prepared to release the corticosteroid by pseudo zero order kinetics with a mean release rate of about 1 μg/day to about 50 μg/day, such as, about 1 μg/day to about 10 μg/day.

The following non-limiting examples are given by way of illustration only.

Example 1

Sustained release fluocinolone acetonide devices were implanted into the vitreous of 4 rabbits while animals in the control group received a sham operation. After implantation, all rabbits received a sub-retinal injection of gelatin microspheres releasing basic fibroblast growth factor. All control animals developed neovascularization while 3/4 of the implant group showed no evidence of neovascularization. No animals showed any indication of ocular or systemic steroid-induced toxicity.

Example 2

Animals received intravitreal fluocinolone acetonide implants and were sacrificed at 1 month, 4 months, and 11 months. Samples of the vitreous and aqueous were collected for analysis by HPLC. Analysis was performed using a fully automated Hitachi HPLC system. The mobile phase was 40% acetonitrile buffered to a pH of 4.0. The flow rate was 1.0 ml/min with an Axxion C-18 column (25cm X 4mm X 5μm) and UV detection at 238nm. Intravitreal levels were found to be relatively constant throughout the study (0.1-0.2 μg/ml) while no steroid was detected in the aqueous humor (limit of detection 0.02 μg/ml).

Detailed Description of the Drawings

Fig. 1 shows the sustained release profile of a 2 mg flucinolone acetonide implant in buffer over 100 days. The mean release rate was 2.1 +/- 0.26 μg/day.

Fig. 2 shows the vitreous and aqueous levels of fluocinolone acetonide after implantation of a sustained release device. Animals were sacrificed at 1 month, 3 months, and 1 year. Fig. 2 shows that therapeutic levels are maintained in the vitreous while drug levels in the aqueous humor were below the detection limit of the assay.

In the previous descriptions, numerous specific details are set forth, such as specific materials, structures, chemicals, processes, etc., in order to provide a better understanding of the present invention. However, the present invention can be practiced without resorting to

the details specifically set forth. In other instances, well-known processing structures have not been described in detail in order not to unnecessarily obscure the present invention.

Only the preferred embodiment of the invention and but a few examples of its versatility are shown and described in the present disclosure. It is to be understood that the present invention is capable of use in various other combinations and environments and is capable of changes or modifications within the scope of the inventive concept as expressed herein. All patents, patent applications and publication cited herein are incorporated by reference in their entirety.

CLAIMS :

1. Use of a steroid in a medical device for treating ocular diseases, wherein the medical device is adapted to be implanted into the vitreous of the eye, and wherein the medical device is adapted to establish a vitreous steroid concentration that is higher than an aqueous steroid concentration during release of the steroid from the device.

2. The use according to claim 1, wherein the medical device is adapted to establish an aqueous steroid concentration of about 0.002 μg/ml to about 0.01 μg/ml.

3. The use according to claim 1, wherein the medical device is adapted to establish an aqueous steroid concentration of about 0.01 μg/ml to about 0.02 μg/ml.

4. The use according to claim 1, wherein the medical device is adapted to establish an aqueous steroid concentration of less than 0.02 μg/ml.

5. The use according to claim 1, wherein the medical device is adapted to release steroid for about 1 month to about 20 years.

6. The use according to claim 1, wherein the medical device is adapted to release steroid for about 6 months to about 5 years.

7. The use according to claim 1, wherein the vitreous steroid concentration is therapeutic.

8. The use according to claim 1, wherein the vitreous steroid concentration is less than about 10 μg/ml.

9. The use according to claim 1, wherein the medical device is adapted to be implanted intravitreally.

10. The use according to claim 1, wherein the medical device is adapted to treat a disease state selected from the group consisting of ocular neovascularization, ocular inflammation, and retinal degeneration.

11. The use according to claim 1, wherein the medical device is adapted to release the steroid with pseudo-zero order kinetics.

12. The use according to claim 1, wherein the medical device is adapted to provide a steroid release rate of about 1 μg/day to about 50 μg/day.

13. The use according to claim 12, wherein the medical device is adapted to provide a steroid release rate of about 1 μg/day to about 10 μg/day.

14. The use according to claim 1, wherein the medical device releases one drug only.

15. An implantable, sustained release medical device for administering a steroid to a posterior segment of an eye, the device comprising
a steroid, said device characterized in that the device is adapted to be implanted into the vitreous of the eye, and further wherein the device is configured to provide sustained release of the steroid to the vitreous of the eye such that aqueous steroid concentration remains less than vitreous steroid concentration during the release.

16. A device according to claim 15, wherein the device releases the steroid with pseudo zero order kinetics.

17. A device according to claim 15, wherein the device has a mean release rate of about 1 μg/day to about 50 μg/day of steroid.

18. A device according to claim 15, wherein the device releases only one drug.

19. The use according to any of claims 1-14, wherein the steroid is a corticosteroid.

20. The use according to claim 19, wherein the corticosteroid is selected from triamcinolone, dexamethasone, fluocinolone, cortisone, prednisolone, flumetholone, and derivatives thereof.

21. A device according to any of claims 15-18, wherein the steroid is a corticosteroid.

22. A device according to claim 21, wherein the corticosteroid is selected from triamcinolone, dexamethasone, fluocinolone, cortisone, prednisolone, flumetholone, and derivatives thereof.

23. Use of a steroid in a medical device for treating ocular diseases, wherein the medical device is adapted to be implanted into a posterior segment of the eye, and further wherein the medical device is adapted to establish a vitreous steroid concentration that is higher than an aqueous steroid concentration during release of the steroid from the device.

24. The use according to claim 23, wherein the medical device is adapted to establish an aqueous steroid concentration of about 0.002 μg/ml to about 0.01 μg/ml.

25. The use according to claim 23, wherein the medical device is adapted to establish an aqueous steroid concentration of about 0.01 μg/ml to about 0.02 μg/ml.

26. The use according to claim 23, wherein the medical device is adapted to establish an aqueous steroid concentration of less than 0.02 μg/ml.

27. The use according to claim 23, wherein the medical device is adapted to release steroid for about 1 month to about 20 years.

28. The use according to claim 23, wherein the medical device is adapted to release steroid for about 6 months to about 5 years.

29. The use according to claim 23, wherein the vitreous steroid concentration is therapeutic.

30. The use according to claim 23, wherein the vitreous steroid concentration is less than about 10 μg/ml.

31. The use according to claim 23, wherein the medical device is adapted to be implanted intravitreally.

32. The use according to claim 23, wherein the medical device is adapted to treat a disease state selected from the group consisting of ocular neovascularization, ocular inflammation, and retinal degeneration.

33. The use according to claim 23, wherein the medical device is adapted to release the steroid with pseudo-zero order kinetics.

34. The use according to claim 23, wherein the medical device is adapted to provide a steroid release rate of about 1 μg/day to about 50 μg/day.

35. The use according to claim 34, wherein the medical device is adapted to provide a steroid release rate of about 1 μg/day to about 10 μg/day.

36. The use according to claim 23, wherein the medical device releases one drug only.

37. An implantable, sustained release medical device for administering a steroid to a posterior segment of an eye, the device comprising:
a steroid, said device characterized in that the device is adapted to be implanted into a posterior segment of the eye, and further wherein the device is configured to provide sustained release of the steroid to the posterior of the eye such that aqueous steroid concentration remains less than vitreous steroid concentration during the release.

38. A device according to claim 37, wherein the device releases the steroid with pseudo zero order kinetics.

39. A device according to claim 37, wherein the device has a mean release rate of about 1 μg/day to about 50 μg/day of steroid.

40. A device according to claim 37, wherein the device releases only one drug.

41. The use according to any of claims 23-36, wherein the steroid is a corticosteroid.

42. The use according to claim 41, wherein the corticosteroid is selected from triamcinolone, dexamethasone, fluocinolone, cortisone, prednisolone, flumetholone, and derivatives thereof.

43. A device according to claim 37-40, wherein the steroid is a corticosteroid.

44. A device according to claim 43, wherein the corticosteroid is selected from triamcinolone, dexamethasone, fluocinolone, cortisone, prednisolone, flumetholone, and derivatives thereof.

45. A sustained release medical device including a corticosteroid disposed therein, which device is dimensioned for implantation in the vitreal cavity of a patient's eye and configured to have a release rate for said corticosteroid of 1 μg to 50 μg per day over a time course of at least 4 weeks after implantation, which release rate results in an aqueous humor corticosteroid concentration less than one tenth the vitreous corticosteroid concentration.

46. A sustained release medical device including a corticosteroid disposed therein, which device is dimensioned for implantation in the vitreal cavity of a patient's eye and configured to have a release rate for said corticosteroid to produce a sustained and therapeutic concentration of said corticosteroid over a time course of at least 4 weeks effective for reducing neovascularization, edema, or diabetic retinopathy, which release rate results in an aqueous humor corticosteroid concentration which does not cause an adverse increase in intraocular pressure over said time course.

47. The device of claim 45, wherein the corticosteroid is fluocinolone acetonide, said release rate for said fluocinolone acetonide is 1 μg to 10 μg per day over a time course of at least 4 weeks, and which release rate also results in an aqueous humor fluocinolone acetonide concentration of less than 0.05 μg/ml over said time course.

48. The device of claim 45 or 46, wherein said corticosteroid is selected from triamcinolone, dexamethasone, fluocinolone, cortisone, prednisolone, flumetholone, and derivatives thereof.

49. The device of claim 45 or 46, wherein said corticosteroid is fluocinolone acetonide.

50. The device of claim 45 or 46, wherein the aqueous humor corticosteroid concentration is about 0.002 μg/ml to about 0.01 μg/ml.

51. The device of claim 45, 46, or 47, wherein the corticosteroid is released with pseudo zero order kinetics.

52. The device of claim 45, 46, or 47, configured to have a release rate for said corticosteroid over said time course.

53. The device of claim 45, 46, or 47, wherein said time course is at least 100 days.

54. The device of claim 45, which release rate results in an aqueous humor corticosteroid concentration which does not cause an adverse increase in intraocular pressure over said time course.

55. The device of claim 45 or 54, wherein the release rate for said corticosteroid over said time course is effective for reducing one or more of ocular neovascularization, ocular inflammation and retinal degeneration.

56. The device of claim 45, 46, or 47, which release rate does not produce ocular steroid-induced toxicity.

57. A sustained release device including a steroid disposed therein, which device is dimensioned for implantation in the vitreal cavity of a patient's eye and configured to release a therapeutically effective amount of steroid, which amount does not produce ocular or systemic steroid-induced toxicity.

58. A sustained release device including a steroid disposed therein, which device is dimensioned for implantation in the posterior segment of a patient's eye and configured to release a therapeutically effective amount of steroid, which amount does not produce ocular or systemic steroid-induced toxicity.

59. The device of claim 57 or 58, wherein the steroid is released with pseudo zero order kinetics.

60. A sustained release device including a corticosteroid disposed therein, which device is dimensioned for implantation in the posterior segment of a patient's eye and configured to have a release rate for said corticosteroid of 1 μg to 50 μg per day over a time course of at least 4 weeks after implantation, which release rate results in an aqueous humor corticosteroid concentration less than one tenth the vitreous corticosteroid concentration.

61. A sustained release device including a corticosteroid disposed therein, which device is dimensioned for implantation in the posterior segment of a patient's eye and configured to have a release rate for said corticosteroid to produce a sustained and therapeutic concentration of said corticosteroid over a time course of at least 4 weeks effective for reducing neovascularization, edema, or diabetic retinopathy, which release rate results in an aqueous humor corticosteroid concentration which does not cause an adverse increase in intraocular pressure over said time course.

62. The sustained release device of claim 60, wherein the corticosteroid is fluocinolone acetonide, said release rate for said fluocinolone acetonide is 1 μg to 10 μg per day over a time course of at least 4 weeks, and which release rate also results in an aqueous humor fluocinolone acetonide concentration of less than 0.05 μg/ml over said time course.

63. The device of claim 60 or 61, wherein said corticosteroid is selected from the group consisting of triamcinolone, dexamethasone, fluocinolone, cortisone, prednisolone, flumetholone, and derivatives thereof.

64. The device of claim 60 or 61, wherein said corticosteroid is fluocinolone acetonide.

65. The device of claim 60 or 61, wherein the aqueous humor corticosteroid concentration is about 0.002 μg/ml to about 0.01 μg/ml.

66. The device of claim 60, 61, or 63, wherein the corticosteroid is released with pseudo zero order kinetics.

67. The device of claim 60, 61, or 63, configured to have a release rate for said corticosteroid over said time course.

68. The device of claim 60, 61, or 63, wherein said time course is at least 100 days.

69. The device of claim 60, which release rate results in an aqueous humor corticosteroid concentration which does not cause an adverse increase in intraocular pressure over said time course.

70. The device of claim 60 or 69, wherein the release rate for said corticosteroid over said time course is effective for reducing one or more of ocular neovascularization, ocular inflammation and retinal degeneration.

71. The device of claim 60, 61, or 63, which release rate does not produce ocular steroid-induced toxicity.

72. Use of flucinolone acetonide in a device for treating ocular diseases, wherein the device is adapted to be implanted into a posterior segment of an eye to provide sustained release of a therapeutic concentration of said fluocinolone acetonide in the vitreous of the eye while not exceeding a non-toxic concentration of fluocinolone acetonide in the aqueous of the eye.

73. Use of flucinolone acetonide in a device for treating ocular diseases, wherein the device is adapted to be implanted into a posterior segment of an eye to provide sustained release of a therapeutic concentration of said fluocinolone acetonide for a period of at least 1 month, wherein the aqueous concentration of fluocinolone acetonide is less than the vitreous concentration of fluocinolone acetonide during said period.

74. The use according to claim 72 or 73, wherein the aqueous concentration of fluocinolone acetonide is about 0.002 μg/ml to about 0.01 μg/ml.

75. The use according to claim 72 or 73, wherein the aqueous concentration of fluocinolone acetonide is about 0.01 μg/ml to about 0.05 μg/ml.

76. The use according to claim 72, wherein the aqueous concentration of fluocinolone acetonide is less than 0.05 μg/ml.

77. The use according to claim 73, wherein the aqueous concentration of fluocinolone acetonide is non-toxic and is less than 0.05 μg g/ml.

78. The use according to claim 72 or 73, wherein aqueous concentration of fluocinolone acetonide is about 0.01 μg/ml to about 0.02 μg/ml.

79. The use according to claim 72 or 73, wherein aqueous concentration of fluocinolone acetonide is less than 0.02 μg/ml.

80. The use according to claim 72 or 73, wherein said therapeutic concentration of fluocinolone acetonide persists for 1 month to 20 years.

81. The use according to claim 72 or 73, wherein said therapeutic concentration of fluocinolone acetonide persists for 6 months to 5 years.

82. The use according to claim 72 or 73, wherein the vitreous corticosteroid concentration is less than about 10 μg/ml.

83. The use according to claim 72 or 73, wherein a disease state to be treated is selected from the group consisting of ocular neovascularization, ocular inflammation and retinal degeneration.

84. The use according to claim 72, wherein fluocinolone acetonide is released with pseudo zero order kinetics

85. The use according to claim 72 or 73, wherein fluocinolone acetonide is released at a mean release rate of about 1 μg/day to about 50 μg/day.

86. The use according to claim 72 or 73, wherein fluocinolone acetonide is released at a mean release rate of about 1 μg/day to about 10 μg/day.

87. The use according to claim 72 or 73, wherein fluocinolone acetonide is released at a mean release rate of about 1 μg/day to about 50 μg/day over a time course of at least 4 weeks, which release rate results in an aqueous humor fluocinolone acetonide concentration of less than one tenth the vitreous fluocinolone acetonide concentration.

88. The use according to claim 72 or 73, wherein the release rate for fluocinolone acetonide produces a sustained and therapeutic concentration of fluocinolone acetonide over a time course of at least 4 weeks effective for reducing neovascularization, edema, or diabetic retinopathy, which release rate results in an aqueous humor fluocinolone acetonide concentration which does not cause an adverse increase in intraocular pressure over said time course.

89. The use according to claim 87, wherein the release rate for said fluocinolone acetonide is 1μg to 10μg per day over a time course of at least 4 weeks, and which release rate also results in an aqueous humor concentration of fluocinolone acetonide of less than 0.05μg/ml over said time course.

90. The use according to claim 87, wherein said time course is at least 100 days.

91. The use according to claim 88, wherein said time course is at least 100 days.

92. The use according to claim 89, wherein said time course is at least 100 days.

93. The use according to claim 72 or 73, wherein the aqueous concentration of fluocinolone acetonide does not cause an adverse increase in intraocular pressure over said time course.

94. The use according to claim 72 or 73, which does not produce ocular or systemic steroid-induced toxicity.