

VISCOELASTIC COMPOSITIONS AND METHODS OF USE

The present application is a continuation-in-part of U.S. patent application Ser. No. 08/362,718, filed Dec. 23, 1994, now U.S. Pat. No. 5,607,966.

BACKGROUND OF THE INVENTION

The present invention is directed to the provision of viscoelastic compositions containing compounds having potent anti-inflammatory, anti-oxidant and anti-proliferative activity. The present invention is also directed to various methods of using the compounds and compositions of the present invention in pharmaceutical applications including the treatment of inflammatory disorders such as ocular inflammation associated with ophthalmic disease and ophthalmic surgery.

Inflammation from cellular stress can cause excessive tissue damage. Numerous biochemical pathways are known to lead to inflammation. In general, these include the generation of locally produced or inflammatory cell derived proinflammatory cytokines (e.g., IL₁, IL₆, IL₈ and TNF_α), as well as products from the cyclooxygenase system, such as prostaglandins, and the lipoxygenase system, such as leukotrienes, "HETEs" and "HPETEs." Such agents have been associated with inflammation. See generally, *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, pages 600–617, Pergman Press, N.Y. (1990). Therapies designed to inhibit the production of these types of agents are therefore of great interest.

Non-steroidal anti-inflammatory agents (NSAIA) have been used for the treatment of inflammatory disorders. The following references may be referred to for further background concerning this use of NSAIA's:

Ophthalmoscope, volume 8, page 257 (1910);

Nature volume 231, page 232 (1971);

FASEB Journal, volume 1, page 89 (1987); and

Inflammation and Mechanisms and Actions of Traditional Drugs, Vol. I Anti-inflammatory and Anti-rheumatic drugs. Boca Raton, Fla., CRC Press, (1985).

However, there are some problems associated with NSAIA treatment including delivery to the appropriate site of action and side effects (*Goodman and Gilman's The Pharmacological Basis of Therapeutics* pages 638–669, Pergman Press, N.Y. (1990)).

Free radical molecules also play a major role in inflammation. These unstable chemical moieties lead to the oxidation of tissue resulting in damage. Such oxidative stress and damage has been described in *Biochemical Pharmacology*, 32(14), 2283–2286 (1983) and *Free Radicals in Biology and Medicine*, 4, 225–261 (1988). Agents that act as anti-oxidants can protect against oxidative damage. Such protection has been the subject of numerous scientific publications, including the following:

Archives of Pharmacology, volume 325, pages 129–146 (1992);

Journal of Photochemistry and Photobiology, volume 8, pages 211–224 (1991);

Free Radicals in Biology and Medicine, volume 11, pages 215–232 (1991); and

European Journal of Pharmacology, volume 210, pages 85–90 (1992).

The combination of anti-oxidant activity with other pharmacologically significant activities in a single molecule is discussed in JP 010484 A2 and EP 387771 A2; and com-

pounds with cyclooxygenase/5-Lipoxygenase and anti-oxidant activity are discussed in *Drug Research*, 39(II) Number 10, pages 1242–1250 (1989). However, these references do not disclose the compounds of the present invention.

Ocular inflammation is a condition which generally causes patient discomfort including red eye, conjunctival edema and congestion, ocular discharge as well as scratchiness and itchiness. Ocular inflammation can be initiated by various insults. For example, ocular inflammation can result from allergic response to various allergens, bacterial infections, trauma to the eye, dry eye and surgical complications. Various anti-inflammatory therapies are currently in use for the treatment of ocular inflammation including the topical administration of diclofenac.

Ocular surgery can result in various post-surgical complications to the eye. Such complications generally include: 1) loss of vascular blood barrier function; 2) neutrophil accumulation; 3) tissue edema including conjunctiva swelling, conjunctiva congestion and corneal haze; 4) cataract formation; 5) cellular proliferation; and 6) loss of membrane integrity including decrease in docosahexaenoic acid levels in membrane phospholipids.

Cataracts are opacities of the ocular lens which generally arise in the elderly. In order to improve eyesight, the cataractous lens is removed and an intraocular lens is inserted into the capsular bag. In order to maximize the procedure and post-surgical recovery, viscoelastic materials are injected in the anterior chamber and capsular bag to prevent collapse of the anterior chamber and to protect tissue from damage resulting from physical manipulation. Various inflammatory responses and tissue damage, however, may still occur from such surgeries, as described above. There is a need, therefore, for the provision of improved viscoelastic compositions and methods which aid in the amelioration of inflammation, tissue damage and trauma-induced complications resulting from anterior segment surgery (e.g., cataract surgery and trabeculectomy).

Trabeculectomy, i.e., glaucoma filtration surgery, involves the surgical creation of a fistula with a conjunctival flap which allows the direct drainage of aqueous humor from the anterior chamber into the conjunctival tissue. This procedure is used as an alternative to drug therapy, and allows for an increase in outflow of aqueous humor, thereby lowering the elevated intraocular pressure associated with glaucoma. In order to maintain a deep chamber and enhance visualization during the surgery, viscoelastic compositions have been injected into the anterior chamber of the eye. Inflammatory responses resulting from the surgery, however, may cause complications. For example, many patients exposed to prior inflammatory episodes (e.g., uveitis, cataract extraction) have an increased incidence of "bleb" failure due to fibroplasia. With such complications, the filtration bleb becomes scarred or heals over so that aqueous drainage can no longer occur. Thus, a need exists for the provision of improved viscoelastic compositions which further decrease the inflammatory response, cellular damage, and proliferation resulting from glaucoma filtration surgery, permitting an increased longevity of the filtration bleb following surgery.

Vitrectomy surgery can also induce a variety of post-surgical complications. Many of these complications are further potentiated in diabetic patients who are at risk for many ocular pathologies. Due to the severity of the surgical procedure, the posterior segment surgery process can cause extensive tissue damage at both the acute and chronic phases of the recovery. Tissue edema generally occurs during the post-surgical acute phase. This is caused by breakdown of