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Loteprednol etabonate: a review of ophthalmic clinical studies

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Loteprednol etabonate (LE) is a corticosteroid designed using the "soft drug" concept of Bodor. LE has been extensively evaluated as a treatment for ophthalmic inflammatory conditions. LE is administered as a sterile eye drop suspension and is commercially available as either a 0.5% or a 0.2% suspension. Lotemax® (0.5% LE) has been demonstrated as effective in reducing the signs and symptoms of giant papillary conjunctivitis (GPC), acute anterior uveitis and inflammation following cataract extraction with intraocular lens (IOL) implantation. It is also effective for the prophylaxis of seasonal allergic conjunctivitis (SAC) in patients with a history of that condition. Alrex® (0.2% LE) is effective for the treatment of the signs and symptoms of SAC. In comparison with other steroids LE has a superior safety profile which has been attributed to its "soft drug" characteristics.

1. Introduction

Loteprednol etabonate (LE) is currently approved in the US as an ophthalmic anti-inflammatory agent and is available commercially in two separate strengths. Lotemax® (0.5% LE) is approved for steroid responsive ocular inflammatory conditions and for the treatment of the signs and symptoms of inflammation following cataract removal and intraocular lens (IOL) implantation. Alrex® (0.2% LE) is approved for the treatment of seasonal allergic conjunctivitis (SAC).

LE is a corticosteroid that was designed according to the "soft drug" concept of Bodor [1]. It is derived from Δ_1-cortienic acid and is the 17β-chloromethyl ester of Δ_1-cortienic acid etabonate. LE undergoes a predictable hydrolysis to Δ_1-cortienic acid etabonate [2]:

LE has a high lipophilicity (Table 1) which was determined using an HPLC method and relative retention times [3].

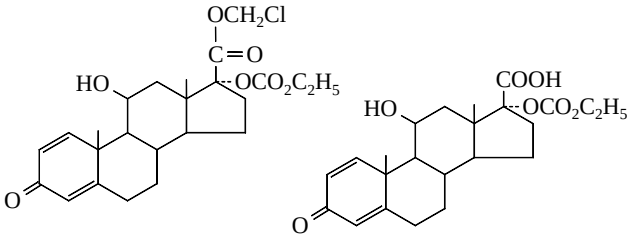
The high lipophilicity of LE combined with the lability of the molecule in ocular tissues of the rabbit [2] suggested that LE might be useful as an ophthalmic steroid with a superior safety profile than those already available. Preclinical studies in animal models of ocular inflammation supported this assumption [4].

2. Therapeutic efficacy in ophthalmic disease

For any ophthalmic anti-inflammatory agent to gain acceptance it must demonstrate efficacy in a range of ophthalmic conditions that include the external tissues (conjunctivae) and the internal tissues of the anterior segment of the eye. Further it must be safe when used over a reasonable period of time. LE was evaluated in a variety of ophthalmic inflammatory conditions. Most studies were carried out over a 42-day period and assessed safety as well as efficacy. LE was studied in two major external conditions (giant papillary conjunctivitis and seasonal allergic conjunctivitis) and in two major inflammatory conditions of the anterior chamber of the eye (post-operative surgery and acute anterior uveitis).

2.1. Giant papillary conjunctivitis (GPC)

GPC is an inflammatory condition associated with the wearing of contact lenses [5, 6]. The primary sign of contact lens associated GPC is papillary hypertrophy of the superior tarsal conjunctivae (i.e. the inner surface of the eyelid). These are the giant papillae that give the condition its name. The condition causes itching and redness of both the bulbar and palpebral conjunctivae. The condition, when untreated, is self-perpetuating by continuous movement of the eyelid against the contact lens. The result is contact lens intolerance and patients either have to reduce contact lens wear time or suffer discomfort. While the precise cause of the condition is unknown, it is thought to result from antigenic deposits on the lens. Non-pharmacological treatment involves the discontinuation of lens wear for the duration of the disease. This option is frequently unacceptable to the patient. Prior to the approval of Lotemax® there were no drugs that had been studied systematically in the condition. Therapy consisted of mast cell stabilizers or non-steroidal agents, neither of which is very effective in the condition or the use of the available corticosteroids, which have the potential for serious adverse events [7, 8].



loteprednol etabonate Δ_1-cortienic acid etabonate

GPC is an excellent model for the evaluation of an ophthalmic inflammatory agent since the condition has well defined signs and symptoms that can be evaluated including itching and redness, which are characteristic of allergic conditions in the eye. Reduction in the papillae size is an excellent measure of anti-inflammatory activity. An end point specific to the disease itself is contact lens tolerance.

LE was evaluated in three separate clinical studies. In a small phase II study [9] it was demonstrated that LE

Table 1: Lipophilic indices of loteprednol etabonate and other corticosteroids

	Log
Loteprednol etabonate	3.04
Hydrocortisone 17-valerate	2.34
Dexamethasone	2.19
Hydrocortisone	1.95

effectively reduced the primary sign (enlarged papillae) of the disease when compared to a vehicle placebo. Most of the patients discontinued contact lenses wear during the study with the result that itching and redness rapidly resolved in both treatment groups. In order to evaluate the effects of LE on these parameters the phase III studies were designed to allow the continuation of contact lenses during the study.

Both Phase III studies followed identical protocols and have been reported in detail [10, 11]. The two studies enrolled a total of 443 evaluable patients of whom 220 received LE qid, and 223 received vehicle control qid for a period of 42 days. The primary efficacy variables were the severity of the papillae, using the scale shown in Table 2. This four point scale was accompanied by photographs representative of each unit on the scale. Itching was evaluated on a five point scale where 4 = severe (a desire to constantly scratch or rub the eyelids), 3 = moderate (frequent desire to rub or scratch the eyelids), 2 = mild (occasional desire to rub or scratch the eyelids), 1 = trace (rare need to scratch the eyelids) and 0 = no desire.

Lens tolerance was evaluated on a four point scale (Table 3) based on the patients diary reports.

A priore, clinical significance was set as the proportion of patients showing an improvement of one grade for each of the three primary efficacy variables. This represents a 25% change and the clinicians involved in the study felt that a change of this magnitude would be clinically relevant for the patient. The results of both studies are summarized in Fig. 1.

A treatment differential was observed even though the population continued to wear their lenses. The patients receiving placebo showed improvement compared to baseline. This placebo effect is probably due to the lubricating and rinsing effect of the vehicle. The statistical difference in favor of LE for all parameters suggests a substantial therapeutic effect of the molecule beyond the mechanical lubrication afforded by the product.

Throughout the studies intraocular pressure (IOP) was measured. The incidence of clinically significant IOP increases was low and will be discussed in a later section of this review.

The rapid therapeutic response and the low incidence of adverse effects indicate that LE is an appropriate treatment for GPC especially if the patients choose to continue wearing their contact lenses.

Table 2: Criteria used for the scoring of papillae

Score	Description
0	Smooth normal translucent appearance of superior conjuctiva of upper lid; papillae <0.3 mm in diameter
1	Uniform "velvety" papillary appearance with 4–8 papillae per mm^2; area surrounding papillae opaque but not red or inflamed; papillae >0.3 mm in diameter
2	Nonuniform appearance with papillae covering the superior conjunctival surface; areas surrounding the papillae red and opaque; papillae range in diameter from 0.4 – 1.0 mm.
3	Nonuniform appearance with giant papillae scattered over the conjunctival surface; areas surrounding papillae red and opaque.

Table 3: Scale for determining lens intolerance

Score	Description
0	Fully controlled; able to comfortably wear lenses for longer than 6 h
1	Reasonably controlled; able to comfortably wear lenses longer than 3 h but less than 6 h
2	Partially controlled; able to comfortably wear lenses for longer than 45 min but less than 3 h
3	Uncontrolled; able to comfortably wear lenses for less than 45 min

2.2. Seasonal allergic conjunctivitis (SAC)

(SAC) is one of the most common forms of ocular allergy and following exposure to airborne antigens, sensitive individuals typically develop ocular signs such as redness (conjunctival injection) and symptoms such as itching. Agents used to treat this condition tend to treat only one of the signs or symptoms [12] e.g. antihistamines reduce itching while vasoconstrictors reduce only redness. Mast cell stabilizers and non-steroidal anti-inflammatory are weak agents [13]. While corticosteroids are the most effective treatment for SAC they have not been used extensively because of their side effect profile.

The low side effect profile of LE that was observed in early clinical studies suggested that it might be a safe ster-

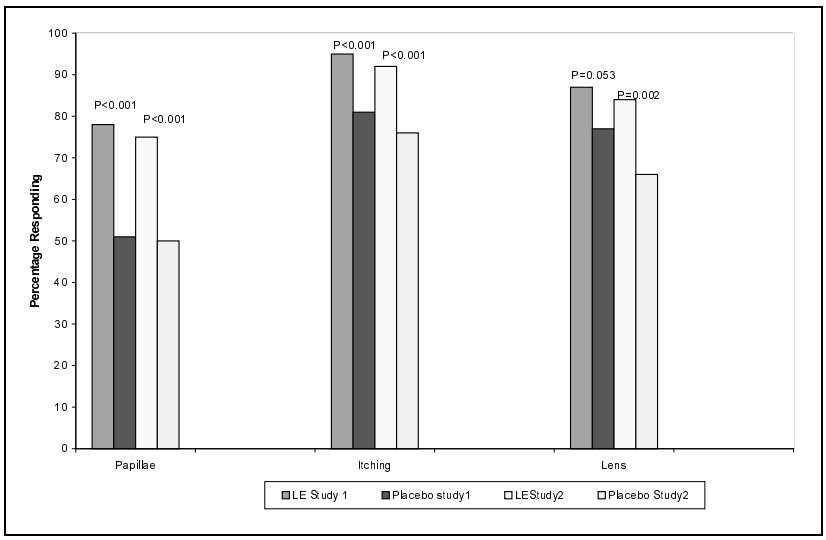


Fig. 1:
Primary measures of efficacy: the proportion of patients at final visit with a decrease in severity of at least one unit in papillae, itching and lens intolerance (lens)

oid for use in the treatment of SAC. Initially Lotemax® (0.5% LE) was evaluated as a prophylaxis of SAC.

The prophylactic study of SAC using 0.5% LE was a double-masked placebo-controlled study that was carried out during the late summer allergy season in the US Midwest and the winter mountain cedar allergy season in Central Texas [14]. In this study 293 patients with a documented history of SAC were enrolled, of whom, 288 were evaluable. One hundred and forty five (145) patients received LE (0.5%) qid and 143 received the vehicle placebo qid for up to 42 days. Dosing started approximately 14 days prior to the anticipated start of the pollen season in the geographical area. Pollen records from previous years were reviewed to determine this date. During the course of the study data on pollen counts was collected. The primary parameters measured in this study were itching, using the same 5 point scale as described above for GPC studies and redness (bulbar conjunctival injection) using a four point scale where 0 = absent, 1 = mild, 2 = moderate and 3 = severe. The data were reported as a composite of the itching and redness scores. Other parameters such as tearing and chemosis were evaluated on four point scales to add supporting data to the study. Intraocular pressure, was measured at baseline and throughout the study. The changes in the composite score from baseline to the peak pollen period are summarized in Fig. 2.

LE was more effective than placebo in the prophylactic treatment of the primary efficacy variable of SAC. The mean composite score in the LE treated patients was lower during the peak pollen period than at baseline, whereas in the vehicle placebo treated group there was an increase in the score. A low incidence of adverse events was reported especially the IOP effects. This will be discussed later.

Based upon the efficacy and safety observed with Lotemax® a product with a lower concentration of LE was developed specifically for the treatment of SAC. The concentration used was 0.2% and the product is now commercially available as Alrex®. The selection of the 0.2% concentration was made following the results of a dose ranging study using the conjunctival provocation test model [15].

Two separate studies were carried out using SAC patients during the mountain cedar pollen season in Central Texas [16, 17]. A total of 268 patients suffering from severe signs and symptoms of SAC were enrolled of whom 133 received LE 0.2% qid and 135 who received vehicle placebo qid for up to 42 days during the peak pollen season. Throughout the study the pollen levels were recorded. IOP was measured at baseline and throughout the study. The primary endpoints were itching and redness using the scales described above. In these studies the individual parameters were calculated and not a composite. A clinically relevant response was the complete resolution of a sign or symptom during the time that pollen was detectable. The results from Study 1 are shown in Fig. 3 and for study 2 in Fig. 4.

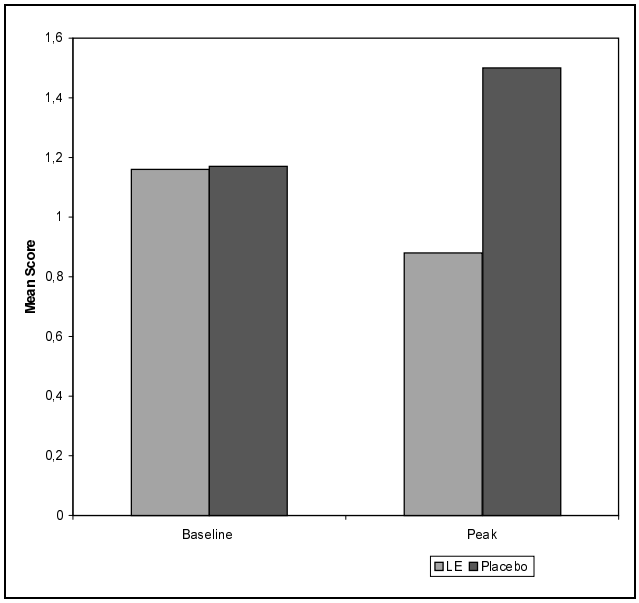


Fig. 2: Mean scores for primary composite score.

In both studies there was a substantial improvement in both treatment groups within the first few hours of the study. This initial improvement is probably due to the demulcent effect and frequent rinsing of the conjunctivae with the eye drops. At later times the LE-treated patients experienced greater improvement suggesting a substantial therapeutic action beyond that of the vehicle. Over the two studies there was no difference in the incidence of clinically relevant changes in IOP, indicating that this lower concentration of LE is both safe and effective for the treatment of SAC.

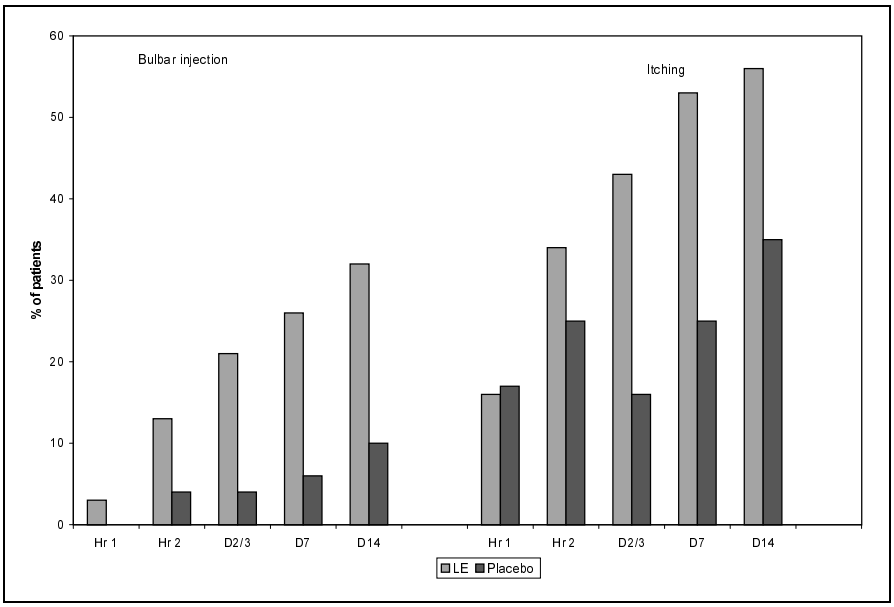


Fig. 3:
Resolution for bulbar injection and itching. Resolution is defined as the proportion of patients with a 0 score.

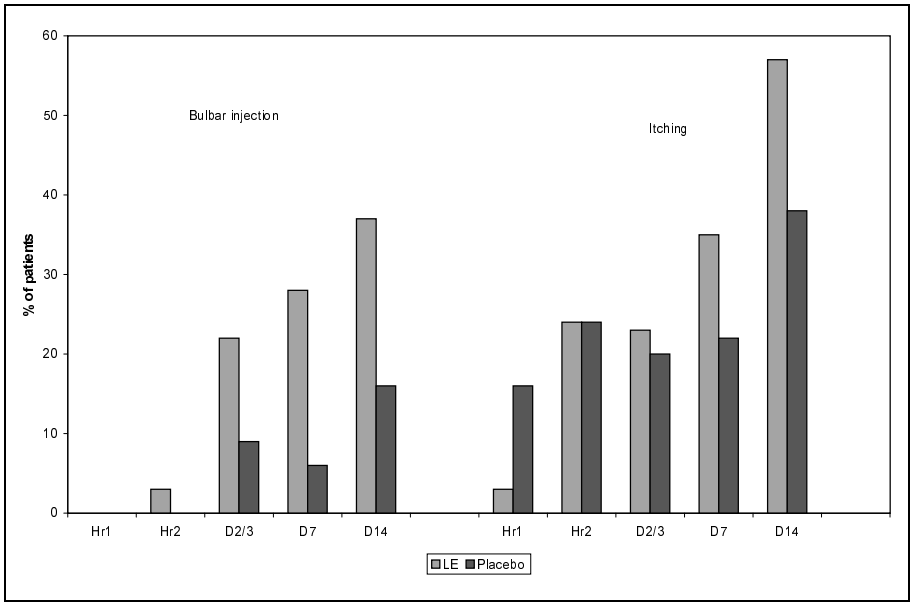


Fig. 4:
Resolution for bulbar injection and itching. Resolution is defined as the proportion of patients with a 0 score.

2.3. Post operative inflammation

The surgical removal of cataracts combined with the implantation of intraocular lenses is a common procedure. The procedure may result in a mild inflammation or iritis. Subjectively the patient experiences discomfort for a number of days following the surgery. During this time an increase in protein (flare) and the number of white cells in the anterior chamber of the eye is observed. The condition is generally self-limiting but anti-inflammatory agents are used in the post-operative period to improve the comfort and well being of the patient.

Lotemax® was evaluated in two separate but identical studies [18, 19]. Between the two studies a total of 430 patients undergoing a unilateral procedure were enrolled of which 424 were evaluable. Two hundred and eleven (211) of these patients receive LE (0.2%) qid and 213 received vehicle placebo qid for 14 days following the surgery. Efficacy was evaluated using the cell and flare reaction. Cells were determined using a slitbeam at 1.0 mm height with maximum luminescence. The number of cells in the field was scored where 0 = 5 cell or less, 1 = 6–10 cells, 2 = 11–20 cells, 3 = 21–40 cells, 4 = >40 cells and 5 = hypopyon. Flare was evaluated on a five point scale where 0 = none to trace, 1 = mild (clearly noticeable, visible), 2 = moderate (without plastic aqueous), 3 = marked (with plastic aqueous) and 4 = severe (with fibrin deposits and/or clots). The total anterior cell inflammatory score was determined by adding the cell and the flare scores. A clinically significant outcome was considered as the complete resolution of anterior chamber inflammation (ACI) and the percentage of patients in each group achieving this was determined at the final on-study visit. IOP was measured throughout the study in both the treated and the control eye. The data from these studies are summarized in Table 4.

The difference or treatment effect was 33% in study 1 and 27% in study 2. LE was considerably better than its vehicle placebo in controlling anterior chamber inflammation following surgery for cataract removal and intraocular lens implantation. Combining the data from the two studies a total of 126/221 patients (57%) receiving LE had complete resolution of ACI compared to 61/223 (27%) of those treated with the vehicle placebo. If patients with mild ACI (i.e. a combined cell or flare score of 1 or 2) are included a total of 89% of LE patients were treatment successes compared to only 57% of the vehicle placebo group. There were no changes in IOP that were considered related to the drug.

It was concluded from these studies that treatment of post-surgical inflammation with LE (0.5%) led to a clinically meaningful reduction of the signs and symptoms of post-surgical inflammation when compared to the vehicle placebo.

2.4. Acute anterior uveitis

Acute anterior uveitis is an autoimmune condition that generally occurs unilaterally in patients. Patients experi-

Table 4: Proportion of patients achieving resolution of ACI in two clinical studies of post-surgical inflammation

Visit	Treatment Group	Study 1		Study 2	
		Proportion resolved	P =	Proportion resolved	P =
2	LE	16/109	0.003	10/102	0.834
(Day2–6)	Placebo	4/111		9/100	
3	LE	44/102	<0.001	33/96	0.005
(Day 7–12)	Placebo	17/92		14/83	
4	LE	69/98	<0.001	54/93	0.008
(Day 12–20)	Placebo	30/76		27/70	
Final visit*	LE	70/109	<0.001	56/102	<0.001
	Placebo	33/113		28/100	

* Patients with resolved signs and symptoms were discontinued early

Table 5: Dosing regimens for uveitis studies

Day	Study 1	Study 2
0–7	8 times per day	16 times per day
8–14	6 times per day	8 times per day
15–21	4 times per day	4 times per day
22–25	As required	2 times per day
26–28	As required	Once a day
>28	As required	Not applicable

ence pain, redness and photophobia. The condition is characterized by the presence of white cells and protein (flare) in the anterior chamber of the affected eye.

Lotemax® was evaluated in two studies in the US, which have been reported in a single publication [20]. In both studies the efficacy and safety of LE was compared to prednisolone acetate (1.0%). In both the studies the primary endpoints were the reduction of the cell and flare scores in the affected eyes. The studies used a tapering dosage regimen, which was different for each study (Table 5).

The measurement scale for the flare was identical to the one described above for the post surgery studies. Differences in the measurement of the cells are outlined in Table 6.

In both studies LE and prednisolone acetate substantially reduced the cell and flare (Table 7). The data are the mean changes from baseline.

Although both corticosteroids were effective, prednisolone acetate was more effective in some measures. This slight advantage in efficacy was offset by the higher incidence of clinically significant IOP elevation observed in the prednisolone acetate treated group.

2.5. Intraocular pressure

The elevation of IOP following the chronic use of steroids is a well-recognized phenomenon. It was studied extensively in the 1960s by Becker [21] who treated subjects four times daily with topical betamethasone for 6 weeks.

Table 6: Measurement scales for the cell reaction

	Study 1	Study 2
Grade	Cells per field	Cells per field
0	<5cells	<6 cells
0.5	5–7 cells	–
1.0	8–10 cells	6–10 cells
1.5	11–15 cells	–
2.0	16–20 cells	11–20 cells
2.5	21–30 cells	–
3.0	31–40 cells	21–40 cells
3.5	41–50 cells	–
4.0	>50 cells	>40 cells
5.0	Hypopyon	Hypopyon

Using absolute IOP as the criterion with 20 mm being the lower limit he found that approximately 42% of subjects responded to corticosteroid treatment. His criterion paid no attention to the baseline score however. In a similar study Armaly [22] treated subjects with 0.1% dexamethasone for four weeks and classified patients according to their response. He found that approximately 35% of his patients had a response of at least 6-mm Hg during this treatment. Later studies by Stewart [23] established that a clinically meaningful response was an increase of 10 mm Hg.

LE was evaluated in a double-masked study [24] designed to evaluate its potential to elevate IOP in patients with a history of responding to corticosteroids. The study was designed as a crossover study versus prednisolone acetate. The proportion of patients in the prednisolone acetate group with significant elevations of IOP was 5/9 or 55% whereas in the LE group this was only 1/9 or 11%. The median time to significant elevation was 42 days in the PA group and could not be estimated in the LE group. The mean endpoint IOP in the LE group was 20 mm Hg whereas in the prednisolone acetate group this was 27 mm Hg. Based on this small study the safety of LE appeared to be superior to other drugs in the class and further development of the product was warranted.

Throughout all of the clinical studies, which have been described for LE, the measurement of IOP was one of the main considerations. A total of 2210 subjects were involved in clinical studies of LE. Of these 1648 were treated for 28 days or longer with either LE (0.5% or 0.2%), prednisolone acetate (1.0%) or vehicle placebo [25]. Overall 15 of the 901 (1.7%) patients on LE had a significant IOP elevation. The incidence was 3/583 (0.5%) in those treated with vehicle placebo and 11/164 (6.7%) in the prednisolone acetate group.

Of the 15 patients with an IOP elevation on LE, 11 were GPC patients and continued to wear contact lenses throughout the study. The contact lenses may have prevented the removal of the drug from the eye thereby increasing the contact times and allowing more corticosteroid to reach the anterior chamber. The incidence of a significant IOP elevation in patients without contact lenses was only 4/634 or 0.6% an incidence that was not different from the placebo group. In studies with the 0.2% formulation there was one patient in the LE treated group and one patient in the vehicle placebo treated group with a significant IOP elevation.

The results of these studies confirm that LE had a lower incidence of IOP elevation than has been reported for any other similar product.

3. Discussion

Loteprednol etabonate (LE) has been demonstrated as effective in a wide variety of ophthalmic inflammatory conditions. It is the only drug that has been extensively stu-

Table 7: Comparison of LE and prednisolone acetate (PA) in the treatment of the signs and symptoms of acute anterior uveitis (Mean changes in baseline scores)

	Study 1			Study 2		
	LE	PA	P	LE	PA	P
Cell	-1.8 ± 0.2	-2.0 ± 0.2	0.767	-1.5 ± 0.2	-1.9 ± 0.1	0.154
Flare	-1.4 ± 0.2	-1.4 ± 0.2	0.977	-1.1 ± 0.1	-1.3 ± 0.1	0.173
Pain	-1.4 ± 0.2	-1.3 ± 0.2	0.838	-1.5 ± 0.1	-1.6 ± 0.1	0.793
Photophobia	-1.3 ± 0.2	-1.6 ± 0.2	0.828	-1.4 ± 0.1	-1.6 ± 0.1	0.207

died against giant papillary conjunctivitis. It was effective in this condition even though the patients continued to wear contact lenses. It is also effective for the treatment of seasonal allergic conjunctivitis a condition, which has not traditionally been treated with corticosteroids. The safety of LE on the eye removes the stigma associated with this class of drugs and allows for the first time the use of a fully effective product for those patients who suffer from SAC. LE was also effective in the treatment of inflammatory conditions of the anterior portion of the eye, including acute anterior uveitis. Although its efficacy was not as good as prednisolone acetate, it proved to be a safer alternative. LE was very effective for the treatment of inflammation following cataract surgery.

LE has less effect on IOP than all other ophthalmic corticosteroids. While the precise reason for this has not been investigated it has been speculated that the "soft drug" nature of the molecule would account for the lower toxicity. It has been demonstrated in the rabbit eye that LE is hydrolyzed to an inactive metabolite in the anterior tissues. If this also occurs in the human eye then the levels of active steroid leaving the eye in the aqueous humor will be low. This would expose the trabecular meshwork to lower concentrations of an active corticosteroid than would occur with other drugs such as dexamethasone, which is not metabolized in the eye. It is changes in the trabecular meshwork that result in the decreased outflow of aqueous from the eye and this results in an elevation of IOP. In this hypothesis LE retains activity in the eye due to its high lipophilicity. Studies in rabbits demonstrated high levels of the drug in the ciliary body.

LE therefore represents a new and useful product to treat ophthalmic inflammation and validates the soft drug concept.

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