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Comparison of lodoxamide 0.1% ophthalmic solution and levocabastine 0.05% ophthalmic suspension in vernal keratoconjunctivitis

Ph. VERIN[1], R. ALLEWAERT[2], J.C. JOYAUX[3], E. PIOZZI[4], J. KOLIOPOULOS[5], E. BLOCH-MICHEL[6], and the LODOXAMIDE STUDY GROUP

[1] Service d'Ophtalmologie, Centre Jean Abadie, Bordeaux - France
[2] Saint Martin - French West Indies
[3] Fort de France, Martinique - French West Indies
[4] Oculistica Pediatrica, Ospedale Ca' Granda, Milano - Italy
[5] Department of Ophthalmology, Medical School of Patras University, Regional University Hospital of Patras, Rion Patras - Greece
[6] Paris - France

PURPOSE. *To compare the clinical efficacy and safety of lodoxamide 0.1% ophthalmic solution with levocabastine 0.05% ophthalmic suspension, each given four times daily (QID) for three months to patients with vernal keratoconjunctivitis (VKC).*

METHODS. *The study was conducted multinationally according to a triple-masked parallel design in 95 VKC patients, with assessments at baseline then monthly during the three months of treatment. The primary efficacy variables were a Physician's Clinical Judgement Scale and a Patient's Overall Judgement Scale of improvements from baseline. Signs and symptoms of VKC were also assessed.*

RESULTS. *Both primary efficacy variables showed significantly greater overall improvement of VKC from baseline with lodoxamide than levocabastine. The superiority of lodoxamide was demonstrated by the Physician's Clinical Judgement Scale at months 2 and 3, with a trend at month 1, and by the Patient's Overall Judgement Scale at months 1, 2 and 3. All signs and symptoms of VKC improved significantly from baseline at all time points, regardless of treatment ($p<0.001$). However, relative to levocabastine, conjunctival discharge, photophobia and lacrimation were significantly reduced by lodoxamide at months 1, 2 and 3, itching at months 2 and 3, and bulbar conjunctiva at month 3. The temporal improvement of superior tarsal papillae did not differ significantly between treatments. Both were well tolerated.*

CONCLUSIONS. *Lodoxamide 0.1% and levocabastine 0.05% eye drops, instilled four times daily for three months, were effective, safe and well tolerated by patients with VKC, but lodoxamide was significantly superior to levocabastine. (Eur J Ophthalmol 2001; 11: 120-5)*

KEY WORDS. *Mast cell stabilisers, Antihistamines, Vernal keratoconjunctivitis*

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INTRODUCTION

Vernal keratoconjunctivitis (VKC) is an uncommon, severe allergic disease of unknown etiology that may last 4-10 years. It mostly affects males younger than 20 years old with a family history of atopy. Preventive or palliative remedies may minimise exacerbations, but severe cases of VKC may need intensive topical or systemic corticosteroids to control itching, inflammation, lacrimation, mucus production and

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photophobia (1, 2). However, chronic steroids can cause serious adverse effects (e.g., glaucoma or cataract), so dosages must be reduced as soon as possible (2).

In less severe cases mast cell stabilisers such as disodium cromoglycate, N-acetyl aspartyl glutamic acid and lodoxamide trometamol 0.1% ophthalmic solution ('lodoxamide') may prevent inflammation. Lodoxamide is effective in various forms of non-infective allergic conjunctivitis (3-5). It has no intrinsic vasoconstrictor, antihistaminic, cyclooxygenase inhibitory, or other anti-inflammatory activity (6). Lodoxamide was significantly superior to placebo and disodium cromoglycate in relieving primary symptoms and signs of VKC (7-9).

Topical antihistamines play a significant role in the treatment of allergic ocular disorders. Levocabastine 0.05% ophthalmic suspension ('levocabastine') is a new, highly specific histamine-H_1 receptor blocker that is effective in allergic conjunctivitis (10, 11). It was equivalent or superior to disodium cromoglycate (12, 13) and equivalent to lodoxamide (5) in this condition. This study compared the clinical efficacy and safety of lodoxamide and levocabastine in patients with VKC.

METHODS

Patients

Patients aged 4 years or more, of either sex and any race were eligible if diagnosed with VKC, with severity meeting the following two criteria: first, a rating of at least 'moderate itching' (intermittent sensation with desire to rub); second, on slit-lamp inspection, a grading of at least moderate papillae (prominent scattering of papillae, evenly throughout the middle two thirds of the superior tarsal conjunctiva, to the extent that the vascular pattern was significantly obscured, with mild thickening of the conjunctiva). Patients were excluded for any of the following: known sensitivity to any component of the study medications; participation in another drug study during the previous month; inability to discontinue contact lenses for two weeks before the study and throughout its duration; pregnant or nursing women, and women of child-bearing age not using adequate contraception. Current topical or systemic anti-allergy medication was withdrawn one week before participation, and topical or systemic steroids three weeks before, except when symptoms required immediate trial medication. The study was approved by an appropriate Ethics Committee and written informed consent was obtained from patients or their legal guardians.

Procedures

Eligible patients were randomly assigned (triple-masked) to recommended dosages of lodoxamide (Alomide® Eye Drops) or levocabastine (Livostin® Eye Drops) i.e., one drop per eye (with a second drop if the first missed) approximately every 4h between 08.00h and 20.00h (QID) for three months.

Primary efficacy assessments comprised a "Physician's Clinical Judgement Scale" (PCJS) and a "Patient's Overall Judgement Scale" (POJS) which rated the overall improvement relative to baseline (screening visit), using the same definitions of clinical cure (0), satisfactory response (1), slight improvement (2), unchanged (3), slightly worse (4), or significantly worse (5) (3). Itching, lacrimation and photophobia were rated as absent (0), mild (1), moderate (2), or severe (3), with levels defined per symptom. Likewise, ocular signs (slit-lamp examination) were rated by a "Conjunctival discharge (mucopurulent exudate) scale" as absent (0), mild (1), moderate (2), or severe (3); a "Superior Tarsal Conjunctival Papilla Scale" as normal (0), mild (1), moderate (2), severe (3), or very severe (4); and by a Bulbar conjunctiva (erythema, hyperemia) scale as normal (0), minimal (1), mild (2), moderate (3), moderately severe (4), or severe (5). Measurements were repeated monthly for three months. Ocular safety comprised Snellen visual acuity, with 'best' corrected scores (maximum change in the worst eye) taken at all visits.

Statistical methods

The primary variables were the PCJS and POJS. Treatment was declared equivalent if the 95% confidence limits (two-sided) of the difference between treatment means of either scale lay within one score unit, i.e. the smallest increment measured. The power to detect this difference was greater than 90% with 60 evaluable patients (30 per treatment group) and a two-tailed t-test ($\alpha = 0.05$). Patients who met the selection criteria and received treatment for at least 14 days were evaluable for the primary efficacy analysis. Intent-to-

treat and safety analyses were done on all patients who received at least one dose of a study drug. Average scores of both eyes were analysed. The last observation value was carried forward for evaluable patients withdrawn because of treatment failure. A repeated measures analysis of variance model was applied to treatment differences. Tabulated values are least-square means. Fisher's exact test was applied to changes of visual acuity between baseline and the last visit.

RESULTS

In total, 95 patients were randomised to either treatment at 12 centres in four countries. Twenty-eight patients were ineligible for the primary efficacy analysis because they did not meet the selection criteria (lodoxamide 13; levocabastine 15) which left 67 eligible patients. Intent-to-treat efficacy and safety analyses were done for all patients. Treatment was discontinued for 25 patients (lodoxamide 6; levocabastine 19); nine of these were excluded from the primary efficacy analysis. Reasons for discontinuation were treatment failure (12), adverse events (2), patient's decision (1), noncompliance (3), lost to follow-up (5), and 'other' (1).

Treatment failure was accepted if, after at least 14 days of treatment, signs or symptoms of VKC had worsened significantly for at least three days (PCJS score 5). Twelve cases of treatment failure were identified (levocabastine 11; lodoxamide 1). There were no significant demographic differences between the treatment groups (Tab. I), but approximately 25% of patients in each group were aged 26 years or more.

Both primary efficacy variables showed an overall improvement of VKC from the baseline state, but this was significantly greater after lodoxamide than levocabastine (Tab. II), evident with the PCJS at months 2 and 3 (with a trend at month 1: $p = 0.06$), and with the POJS every month (Fig. 1).

All six VKC signs and symptoms improved significantly from baseline under both treatments. The effect was significantly greater for five of the variables with lodoxamide, i.e., conjunctival discharge, photophobia and lacrimation at months 1, 2 and 3, itching at months 2 and 3, and bulbar conjunctivitis at month 3 only (Tab. III). Also, superior tarsal papillae decreased

TABLE I – PATIENT'S MAIN DETAILS

	Treatments				
Parameter	**Lodoxamide**		**Levocabastine**		**p ≤**
	n. 46	**%**	**n. 49***	**%**	
Age (years)					
3-6	3	6.5	7	14.6	
7-12	17	37.0	19	39.6	
13-16	8	17.4	8	16.7	
17-25	6	13.0	2	4.1	
≥ 26	12	26.1	12	24.5	
Mean	21.4		19.4		0.500[1]
SD	17.10		18.58		
Sex					
Male	27	58.7	28	57.1	0.878[2]
Female	19	41.3	21	42.9	
Race					
Caucasian	30	65.2	31	63.3	0.977[2]
Black	15	32.6	17	34.7	
Other	1	2.2	1	2.0	

[1] Two-sample t-test
[2] Chi-square or Fisher's exact tests
* The date of birth of one levocabastine patient was not known

by 43% at month 3 after lodoxamide, compared to 34% after levocabastine.

The superiority of lodoxamide over levocabastine was unchanged when demographic factors were analysed and by the intent-to-treat analysis. Three patients were withdrawn for non-compliance (lodoxamide 2; levocabastine 1). However, compliance could not be assessed accurately because the amount of fluid used depended on the instillation technique. One ocular adverse event (mild ocular hyperemia) was related to levocabastine. It resolved without treatment, but led to withdrawal from the study. Changes from baseline of visual acuity were clinically unimportant and did not differ significantly between the treatment groups.

DISCUSSION

Both primary efficacy variables (Physician's and Patient's Judgement Scales) showed significantly greater responses of VKC to lodoxamide than to levocabastine. Physicians recorded significantly more recovery at months 2 and 3 following lodoxamide; and patients noted a corresponding difference even earlier, from month 1 onwards. In another study of VKC, significant global improvement was reported by physicians after 3, 7 and 28 days of lodoxamide, as compared to 4.0% disodium cromoglycate (7).

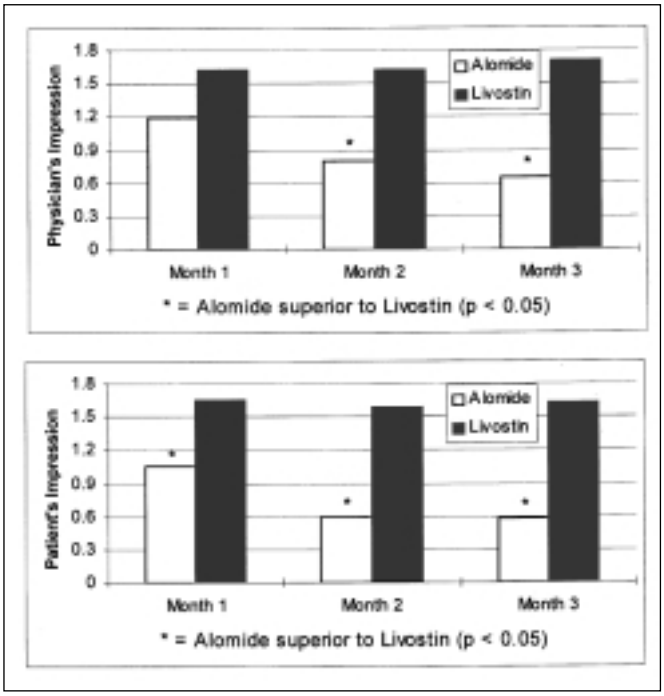

Fig. 1 - *Physician's and patient's impressions.*

The present global evaluations were supported by specific improvements in conjunctival discharge, lacrimation, photophobia, bulbar conjunctivitis and itching, where lodoxamide was again significantly superior to levocabastine, and by the

TABLE II - RESPONSES RELATIVE TO BASELINE RATED FROM 0 (CURE) TO 5 (SIGNIFICANTLY WORSE)

	Months of treatment		
	1	**2**	**3**
Lodoxamide			
Physicians' impression	1.19	0.80°	0.65‡
(SD)	*(0.74)*	*(0.76)*	*(0.66)*
Patients' impression	1.06*	0.60†	0.58‡
(SD)	*(0.91)*	*(0.72)*	*(0.76)*
no.	32	30	31
Levocabastine			
Physicians' impression	162	1.62	1.70
(SD)	*(0.85)*	*(1.15)*	*(1.26)*
Patients' impression	165	1.59	1.63
(SD)	*(1.12)*	*(1.32)*	*(1.40)*
no.	34	29	30

Lodoxamide versus levocabastine: * = $p \leq 0.05$; ° = $p \leq 0.01$; † = $p \leq 0.001$; ‡ = $p \leq 0.0001$

literature. Thus conjunctival discharge was less after lodoxamide at all three monthly visits. Similarly in VKC lodoxamide reduced conjunctival discharge relative to placebo (8) and 4.0% disodium cromoglycate in one study (9), but not in another (7).

Lacrimation was less after lodoxamide at all three monthly visits. In three other VKC studies lodoxamide reduced lacrimation significantly more than 4% disodium cromoglycate after 10 (7) and 28 days of treatment (9). Photophobia was less after lodoxamide at all three monthly visits. In previous studies, lodoxamide reduced photophobia significantly more than disodium cromoglycate after 10 (7) and 28 days (9) of treatment. Bulbar conjunctivitis was less after lodoxamide at month 3. Lodoxamide also reduced bulbar conjunctival hyperemia (7, 9) and chemosis (9) in VKC significantly more than sodium cromoglycate. Lastly, itching was reduced by lodoxamide at months 2 and 3. Three other studies found lodoxamide significantly more effective against itching than disodium cromoglycate (7, 9) or placebo (8).

Both lodoxamide and levocabastine significantly reduced upper tarsal papillae relative to baseline (by respectively 43% and 34%), but the difference between treatments was not significant. In a previous study lodoxamide significantly reduced the number and size of tarsal papillae in VKC by 32% versus 18% after placebo (8).

An interesting feature of this study was the high

TABLE III – EFFECTS OF TREATMENT ON OCULAR SIGNS AND SYMPTOMS

		Months of treatment		
	Baseline	**1**	**2**	**3**
Lodoxamide				
Conjunctival discharge	1.41	0 34*†	0.17*†	0.06*‡
(SD)	*(0.82)*	*(0.64)*	*(0.46)*	*(0.25)*
Papillae	2.48	1.86*	1.67*	1.42*
(SD)	*(0 55)*	*(0.69)*	*(0.87)*	*(0.89)*
Bulbar conjunctivitis	1.61	0.69*	0.53*	0.31*°
(SD)	*(1.26)*	*(0.83)*	*(0.87)*	*(0.72)*
Itching	2.26	0.78*	0.37*Δ	0.32*†
(SD)	*(0.60)*	*(0.72)*	*(0.54)*	*(0.53)*
Photophobia	1.65	0.48*Δ	0.22*‡	0.18*‡
(SD)	*(0.69)*	*(0.56)*	*(0.45)*	*(0.42)*
Lacrimation	1.56	0.42*°	0.17*‡	0.10*‡
(SD)	*(0 74)*	*(0.61)*	*(0.38)*	*(0.30)*
no.	33	32	30	31
Levocabastine				
Conjunctival discharge	1.46	0.94*	0.76*	0.75*
(SD)	*(0.93)*	*(0.85)*	*(0.84)*	*(0.80)*
Papillae	2.54	1.84*	1.72*	1.65*
(SD)	*(0.58)*	*(0.83)*	*(0.95)*	*(1.03)*
Bulbar conjunctivitis	1.69	1.00*	0.93*	0 77*
(SD)	*(1.42)*	*(1.13)*	*(1.07)*	*(1.10)*
Itching	2.26	1.01*	0.91*	0.97*
(SD)	*(0.50)*	*(0.87)*	*(0.82)*	*(0.84)*
Photophobia	1.79	0.99*	0.95*	0.95*
(SD)	*(0.76)*	*(0.78)*	*(0.89)*	*(0.93)*
Lacrimation	1.60	0.85*	0.98*	0.98*
(SD)	*(0.84)*	*(0.85)*	*(0.83)*	*(0.86)*
no.	34	34	29	30

Versus baseline: * $p \leq 0\ 001$. Lodoxamide versus levocabastine: ° $p \leq 0.05$; Δ $p \leq 0.01$; † $p \leq 0.001$; ‡ $p \leq 00001$

proportion (approx. 25%) of patients in each group aged 26 years or more. Fifty-percent of these older patients (6 per group) were black; others described as 'Caucasian' in the West Indies may have been mulattos. A persistent (tardive) form of VKC has been described in such populations, especially in tropical countries where Spring is permanent (14).

In conclusion, lodoxamide 0.1% and levocabastine 0.05% eye drops instilled four times daily for three months were effective, safe and well tolerated by patients with VKC, but lodoxamide showed significantly greater efficacy.

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Reprint requests to:
Prof. Philippe Vérin
Centre d'Ophtalmologie
19, rue Thiac
F-33077 Bordeaux, France

Lodoxamide Study Stroup:

P. TRAJANNIDES, MD, Thessalonikis - Greece;
D. DROUTSAS, MD, Cholargos, Athens - Greece;
P. VADALÀ, MD, Passo Scuro, Roma - Italy;
L. HELLEBOID, MD, Orleans - France;
A.D. PETOUNIS, MD, Athens - Greece;
P. COULON, MD, Saint Martin - French West Indies;
R. GROSS, MD, Alcon Laboratories - Fort Worth, USA.

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