

Absence of central effects with levocabastine eye drops

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Twelve healthy volunteers were randomly allocated to receiving in a double-blind cross-over fashion levocabastine eye drops (0.5 mg/ml solution) and placebo. They were advised to instill 2 drops per eye, four times daily. Each treatment was administered for a period of 1 week. Before and after each treatment period psychomotor function was assessed using Critical Flicker Fusion Test and the Choice Reaction Time Test. At the same time intervals a subjective evaluation of sedation was given using a Visual Analogue of Sedation. Both objective and subjective measurements showed that no significant treatment effects could be detected. It is concluded that repeated instillations of levocabastine eye drops are devoid of any sedative side effects.

Key words: eye-drops; levocabastine; psychoperformance; sedation; topical antihistamines.

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Levocabastine is a potent, specific and fast-acting histamine-H₁-receptor antagonist (1, 10, 11). In clinical studies using topical administration (eye drops and nasal spray), its efficacy in the treatment of allergic conjunctivitis and allergic rhinitis has been established (2, 9).

Many oral antihistamines are known to produce sedation but information about their sedative potential when given by ocular route appears to be non-existent. It therefore seemed interesting to investigate whether repeated instillations of levocabastine eye drops (up to steady state plasma levels) would induce any CNS-related side effects (3).

MATERIAL AND METHODS

Twelve healthy volunteers (5 men and 7 women) were selected for this study. They ranged in age from 22 to 57 (median: 28 years), and their weights from 72.5 to 48 (median 61) kg. Exclusion criteria for participation were: eye lenses, organic or psychiatric disorders, alcohol abuse or addiction to other drugs, concomitant medication of any kind (except oral contraceptives),

pregnancy, lactation, and (in the case of non-sterile women) absence of contraceptive measures.

The study was placebo-controlled and conducted in a double-blind cross-over fashion, consisting of 2 phases (I and II) with no wash-out in between. The volunteers were randomly allocated to receiving active eye drops either during phase I (Group 1) or phase II (Group 2), and placebo during the alternate phase. The duration of each phase was 1 week.

The levocabastine bottles (containing 10 ml at 0.5 mg/ml) were indistinguishable to the placebo bottles. The active bottles contained benzalkoniumchloride as a preservative. The volunteers were instructed to instill, per eye, 2 drops of the double-blind medication, four times daily. Medication administration was supervised by a qualified assistant, except for the final night-time administration (at home).

Evaluations were performed on day 0 (start), day 7 (end phase I) and day 14 (end phase II), at fixed times and under identical conditions. Each session consisted of a combination of ob-

Table 1

Mean values (SD) of Groups 1 and 2, at start, and after weeks 1 and 2

	Start		Week 1		Week 2	
	Group 1 (-)	Group 2 (-)	Group 1 (L)	Group 2 (P)	Group 1 (P)	Group 2 (L)
CFF (hertz)	28.82 (3.97)	29.26 (1.67)	29.31 (2.45)	30.65 (1.50)	30.20 (2.99)	31.07 (1.49)
CRT						
TRT (secs)	684.7 (56.1)	683.8 (87.6)	675.7 (65.2)	640.8 (79.0)	647.3 (47.2)	662.0 (104.7)
VAS (cm)	4.98 (1.71)	4.45 (1.01)	5.82 (1.06)	5.28 (0.42)	5.17 (0.67)	5.52 (0.69)

(-): no treatment; (L): levocabastine; (P): placebo.

jective assessments using the Leeds Psychomotor Tester (4) and a subjective evaluation by means of a Visual Analogue for Sedation. The Leeds Psychomotor Tester includes two tests: Critical Flicker Fusion (CFF), and Choice Reaction Time (CRT).

The CFF (5, 6) is a means of measuring the ability to distinguish discrete sensory data and is taken as an index of overall CNS activity. The subject is required to discriminate flicker fusion in a set of four light-emitting diodes held in foveal fixation at 1 m. Individual thresholds are determined by the psychophysical methods of limits on three ascending and three descending scales (12).

The CRT (5, 6) is a measure of sensorimotor performance. The subject is required to extinguish one of six red lights illuminated at random, by touching the appropriate response button. The Leeds Psychomotor Tester enables the recognition (RRT) and motor (MRT) components to be separated from the total reaction time (TRT). The response measure used is the mean reaction time for 20 stimulus presentations.

The Visual Analogue for Sedation (VAS) consists of a 100 mm line with the extremes “completely awake” versus “very sleepy”. The subject is required to mark the line at a point which corresponds to his present state (7).

Volunteers were asked to report any untoward effects they experienced during the study.

Blood samples for routine biological examination and determination of plasma levels were taken on day 7 (end phase I) and day 14 (end phase II).

RESULTS

All volunteers completed the trial.

The results obtained with the objective measurements (CFF and CRT) were in complete agreement with the subjective evaluation (VAS). Table 1 shows that, at none of the time intervals was there any indication of relevant changes in alertness, in any of the three tests. This was confirmed statistically by a cross-over analysis according to Koch (8) using the Mann-Whitney U-test with two-tailed probabilities: in the absence of any significant interaction and/or period effects, no significant treatment effects could be detected for any of the parameters tested.

Four volunteers reported adverse effects during the study: burning and pruritus of the left eye during placebo and during levocabastine treatment (1 volunteer), drowsiness during levocabastine (1 volunteer), headache during placebo (1 volunteer), and headache and drowsiness during levocabastine (1 volunteer).

Plasma levels after 7 days of levocabastine treatment were low, as expected, ranging from 0.57 ng/ml to 4.19 ng/ml (median: 1.48). Results of the routine laboratory tests were all within normal range.

CONCLUSION

After 7 days of instillation of levocabastine eye drops, 2 drops per eye, q.i.d., no drug-related changes could be detected in any of the tests

which evaluated possible central effects: both objective measurements (CFF and CRT) and subjective evaluation (VAS) remained unchanged throughout the study.

It is concluded that repeated instillations of levocabastine eye drops are devoid of any sedative side effects.

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