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H1-ANTIHISTAMINES SUPPRESS WHEAL-AND-FLARE REACTION AND SKIN BLOOD PERFUSION MEASURED BY LASER DOPPLER FLOWMETRY: RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, CROSSOVER DESIGN STUDY

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The aim of our study was to compare the influence of pre-treatment with H1-antihistamines (levocetirizine, desloratadine, clemastine, quifenadine, and sequifenadine) and a placebo on the histamine-induced weal and flare reaction, increase of skin blood perfusion and sedation. Thirty healthy volunteers were enrolled in the study. The study design was a prospective, randomised, double-blind, placebo-controlled, crossover, balanced clinical trial. Volunteers in randomised and double-blind order were treated with oral levocetirizine 5 mg, desloratadine 5 mg, clemastine 1 mg, quifenadine 50 mg, sequifenadine 50 mg or a placebo. Two hours after intake of medication, the histamine skin prick test was performed and skin blood perfusion was registered with further evaluation of sedative effect. We conclude that levocetirizine induced a significant and pronounced decrease of weal and flare reaction and skin blood perfusion compared to the placebo and the other H1-antihistamines. The effect of quifenadine and sequifenadine on weal reaction area was similar to desloratadine and clemastine. Regarding the sedative effect, we can conclude that second generation antihistamines appear to be not non-sedative but the least impairing, and the first generation antihistamines appear to be the most impairing on central nervous system function. There is a necessity to consider the sedating potential of antihistamines, along with other factors such as efficacy, when prescribing antihistamines to patients.

Key words: *H1-antihistamines, laser Doppler flowmetry, skin blood perfusion, sedation.*

INTRODUCTION

H1-antihistamines are divided into the first generation drugs, which often have sedative side-effects, and the newer second-generation, non-sedating histamine receptor antagonists. Although first-generation antihistamines have been widely used in clinical practice for many decades, the studies performed on these drugs mostly do not comply with the accepted standards. This can also be attributed to some non-sedative H1-antihistamines, which are quiniclidine derivatives, designed in the late 1970s: quifenadine (xinuclidil-3-diphenilcarbinol hydrochloride) and sequifenadine ((xinuclidil-3)-di-(ortho-tolil)-carbinol hydrochloride) (Kaminka, 1977; Mashkovskij *et al.*, 1981). Paradoxically, double-blind and placebo-controlled studies have not been performed on these pharmacological agents, which have been widely used in clinical practice, for more than twenty years.

Effectiveness of the new second generation H1-antihistamines in treating rhinitis and chronic urticaria has been well studied by many randomised, double-blind, placebo-controlled studies. Nevertheless, it is not easy to make the best possible choice from all available H1-antihistamines. Particularly little is known about the comparative efficacy of these drugs.

The potency of H1-antihistamines in earlier studies is usually assessed by establishing the capacity to inhibit wheal and flare reaction caused by the histamine or allergen (Simons *et al.*, 1990; Grant *et al.*, 1999; Hindmarch *et al.*, 2001).

In the late 1980s, measurement of the blood perfusion in the skin with the aid of laser Doppler flowmetry method was found to be useful for continuous evaluation of vascular changes and quantification of wheal and flare reaction induced after skin prick tests (Serup *et al.*, 1985; Hovell *et al.*, 1987; Olsson *et al.*, 1988). Laser Doppler flowmetry can be used to evaluate comparative effectiveness of various medical products, including H1-antihistamines (Rihoux *et al.*, 1989; Hammarlund *et al.*, 1990; Clough *et al.*, 1998; Leroy *et al.*, 1998; Clough *et al.*, 2001).

However, the claims of pharmaceutical companies that second generations H1-antihistamines do not have sedative effect data, which are based on clinical trials, are controversial (Hindmarch *et al.*, 2001; Bender *et al.*, 2003; Verster *et al.*, 2003; Ng *et al.*, 2004; Takahashi *et al.*, 2004). In real life second-generation antihistamines may induce sedation and also impair driving performance. The magnitude and the extent of impairment depend on the administered dose, sex, and time between testing and treatment administration. Tolerance develops after 4 to 5 days of administration, but impairment is not fully absent (Verster *et al.*, 2004).

The potency to induce sedation is directly dependent to permeability of the haematoencephalic barrier and H1-receptor occupancy in central nervous system (Tagawa *et al.*, 2001). Occurrence of sedation in clinical trials varies from 0% for fexofenadine to 30% for cetirizine (Tashiro *et al.*, 2002).

We have not been able to find publications regarding the onset time of sedative reaction in the available literature.

The aim of our study was to compare the influence of pretreatment with H1-antihistamines (levocetirizine, desloratadine, clemastine, quifenadine, and sequifenadine) and a placebo on histamine induced weal and flare reaction, increase of skin blood perfusion and sedation.

MATERIALS AND METHODS

Subjects. Thirty healthy volunteers of 18 to 60 years of age, 17 females and 13 males, were enrolled in the study.

Study design and treatment. The study design was a prospective, randomized, double-blind, placebo-controlled, crossover, balanced clinical trial. Patients in randomised and double-blind order were treated with oral levocetirizine 5 mg, desloratadine 5 mg, clemastine 1 mg, quifenadine 50 mg, sequifenadine 50 mg or placebo. Two hours after intake of medication the histamine skin prick test was performed and skin blood perfusion was registered with further evaluation of sedative effect.

The interval between trial visits was at least two weeks to provide a sufficient wash-out period for the study medications. At a period of at least one week before visits, the patients were prohibited to use other H1-antihistamines, systemic or topical glucocorticoids, sedatives and other vasoactive medication that could affect the results of the skin prick tests, blood perfusion measurements and evaluation of sedation.

Evaluation of wheal and flare reaction. The skin prick test was performed with a standardised 10 mg/ml histamine HCl solution (Stallergens, France) in the typical place on the volar surface of the forearm. Reaction to histamine was evaluated 15 minutes after the prick test. The area of wheal and flare response was calculated from measurements of two perpendicular diameters in mm according to the formula: π ((d1 + d2)/4).

Laser Doppler flowmetry. Blood perfusion was registered with a laser Doppler flowmeter Periflux System 4001 (Perimed AB, Sweden). The probe tip was fixed in a position about 1–2 mm above the skin. It has been previously demonstrated that a varying distance between the probe tip and the tissue surface from 0 to 3.5 mm does not significantly affect the output signal (Olsson *et al.*, 1985).

As recommended previously (Serup *et al.*, 1985; Hammarlund *et al.*, 1991; Kruszewski *et al.*, 2005), recording of blood perfusion was made at a distance of 5 mm from the center of the prick test. Basal perfusion was measured for 2 min before the prick test. Registration of blood perfusion after the histamine prick test was made continuously for 15 min.

Percentage of blood perfusion change and area under curve during the peak perfusion period (AUC_{max}) were calculated using a special computer programme (Perisoft Perimed AB, Sweden). Average blood perfusion curves in perfusion units (PU) were calculated for the active treatment and placebo using the raw data of the Perisoft programme.

Evaluation of sedative effect. Sedative effect was evaluated by the Stanford sleepiness scale (SSS) two hours after drug intake. After instruction, the subjective sedation was evaluated by the patient himself, without active involvement of the researcher.

The visual analogue scale (VAS) is a valuable tool for assessment of dynamic change of subjective senses, like pain or sedation. Evaluation by VAS started at the moment before intake of study medication and proceeded hourly up to 12 hours. In the VAS test, the volunteer was given a 100 mm long line, entitled "How sleepy am I?" The rating "Not at all" was placed on the left hand side, and "Explicitly sleepy", on the right hand side. The volunteer marked his subjective sensations at any given moment. In the analysis, researchers measured the distance from the beginning of the line at the left hand side till the point marked by the volunteer.

Using SSS, an Introspective Measure of Sleepiness was performed, following the scale on (Table 1). The scale consists of eight statements. Every statement has a relevant numerical evaluation, or the level of sleepiness. The volunteers had to choose the statement that expressed most precisely their sensations at the moment. In the data analysis, the numbers from the scale were used.

Table 1

STANFORD SLEEPINESS SCALE

Degree of sleepiness	Scale rating
Feeling active, vital, alert, or wide awake	1
Functioning at high levels, but not at peak; able to concentrate	2
Awake, but relaxed; responsive but not fully alert	3
Somewhat foggy, let down	4
Foggy; losing interest in remaining awake; slowed down	5
Sleepy, woozy, fighting sleep; prefer to lie down	6
No longer fighting sleep, sleep onset soon; having dream-like thoughts	7
Asleep	X

Since it is easy to express the change in subjective sensations with the aforementioned methods, the patients were asked to mark the dynamics of their sleepiness every hour within a 12 hour period after drinking the medicine.

Statistical analysis. Data processing was carried out using the software Statistica 6.0 (StatSoft, Inc., USA). Data were expressed as mean ±95% confidence interval. Square or logarithmic transformation was made for data that did not correspond to criteria of normal distribution. Analysis of the study results was done by multifactorial analysis of variance (ANOVA). Differences was considered a statistically significant if $P < 0.05$.

Ethical aspects. The study was approved by the local ethics committee. Before inclusion in the trial, volunteers signed an informed consent. The clinical study was supported by an unrestrictive grant from the pharmaceutical company AS Olainfarm.

RESULTS

The main results of the study are summarized in Table 2.

A statistically significant difference was observed in wheal reaction area between the active treatment and placebo ($P < 0.05$), and levocetirizine and other H1-antihistamines ($P < 0.001$) (Fig. 1).

A significant decrease of blood perfusion was observed after pre-treatment with levocetirizine and desloratadine vs. placebo ($P < 0.05$) and levocetirizine vs. quifenadine, sequifenadine and clemastine ($P < 0.05$) (Fig. 2).

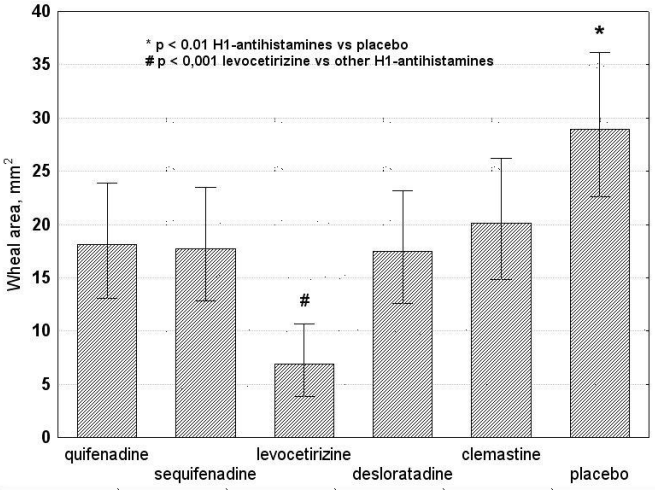

Fig. 1. Statistically significant difference of wheal reaction area mm2 between H1-antihistamines and the placebo ($P < 0.05$), and levocetirizine and other H1-antihistamines ($P < 0.001$).

Perfusion AUC_{max} was significantly lower after pre-treatment with levocetirizine vs. placebo and levocetirizine vs. other antihistamines ($P < 0.05$). Desloratadine, clemastine,

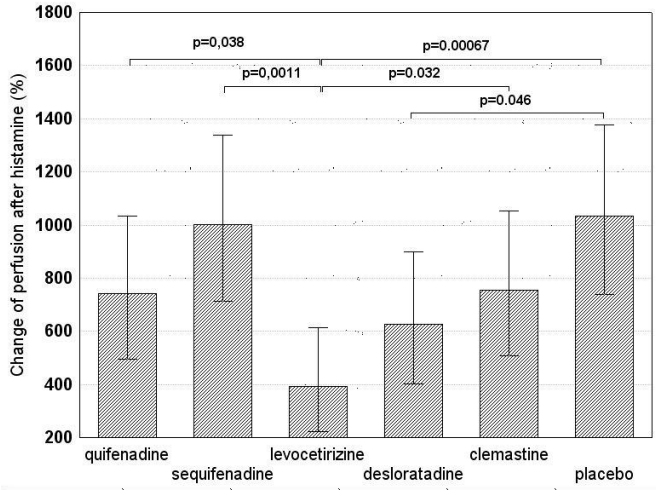

Fig. 2. A significant decrease of blood perfusion after pre-treatment with levocetirizine and desloratadine vs. placebo ($P < 0.05$), and levocetirizine vs. quifenadine, sequifenadine and clemastine ($P < 0.05$).

Table 2

MAIN STUDY RESULTS

H1-antihistamines	Study medication (mean ± 95% CI)					
	quifenadine	sequifenadine	levocetirizine	desloratadine	clemastine	placebo
Wheal area, mm^2	18.1 (-13.1; + 23.9)	17,8 (-12.8; + 23.5)	6.9 (-3.9; + 10.7)	17.5 (-2.6; + 23.1)	20.2 (-4.9; + 26.2)	29.0 (-2.6; + 36.1)
Increase of blood perfusion, %	741.2 (-496.2; +1035.1)	1001.5 (-712.8; + 1339.1)	393.1 (-221.3; + 613.8)	626.2 (-403.0; + 898.3)	756.5 (-508.8; + 1053.2)	1033.2 (-739.6; + 1375,8)
Blood perfusion, AUC_{max}, kU*s	2.6 (-1.9; + 3.5)	2.6 (-1.8; + 3.4)	1.3 (-7.8; + 1.9)	2.2 (-1.5; + 3.0)	2.5 (-1.7; + 3.3)	3.2 (-2.3; + 4.1)
Sedation Stenford scale (1 – 7)	2.22 (-1.99; +2.44)	2.28 (-2.06; +2.50)	2.69 (-2.47; +2.92)	2.33 (-2.11; +2.55)	2.67 (-2.45; +2.89)	2.33 (-2.11; +2.55)

qiifenadine and sequifenadine induced a decrease of AUC_{max}, but the difference compared to placebo was not statistically significant (Fig. 3).

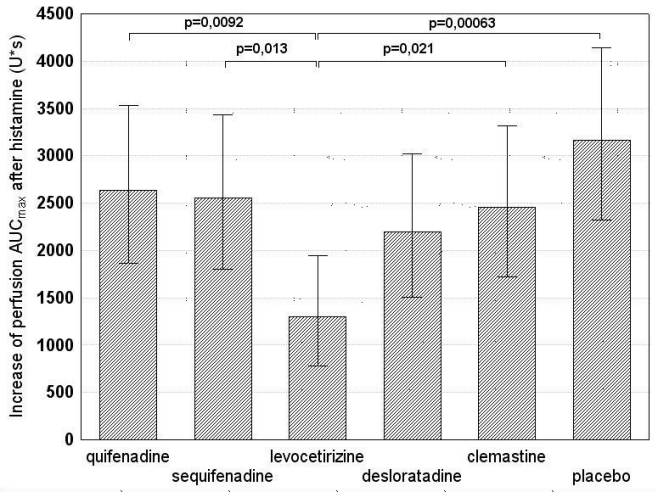

Fig. 3. Significant lower change in blood perfusion AUC_{max} U*s after pre-treatment with levocetirizine vs. placebo and levocetirizine vs. other H1-antihistamines ($P < 0.05$).

The ANOVA test of blood perfusion curves demonstrated significantly less histamine-induced skin reaction in patients after intake of H1-antihistamines compared to placebo and levocetirizine compared to other H1-antihistamines ($P < 0.001$) (Fig. 4) .

The sedative effect evaluated by the Stenford sleepeness scale two hours after the drug intake was significantly higher after pre-treatment with clemastine and levocetirizine, compared to other H1-antihistamines and the placebo ($P < 0.05$) (Fig. 5). We observed a significant increase of the sedation level evaluated by VAS in volunteers pre-treated with clemastine, compared to the placebo, in the

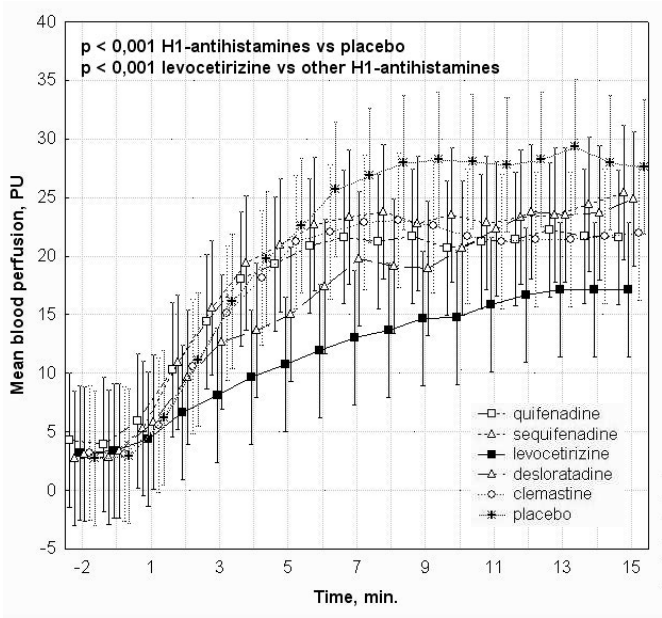

Fig. 4. Blood perfusion curves PU after intake of H1-antihistamines compared to placebo, and levocetirizine compared to other H1-antihistamines ($P < 0.001$).

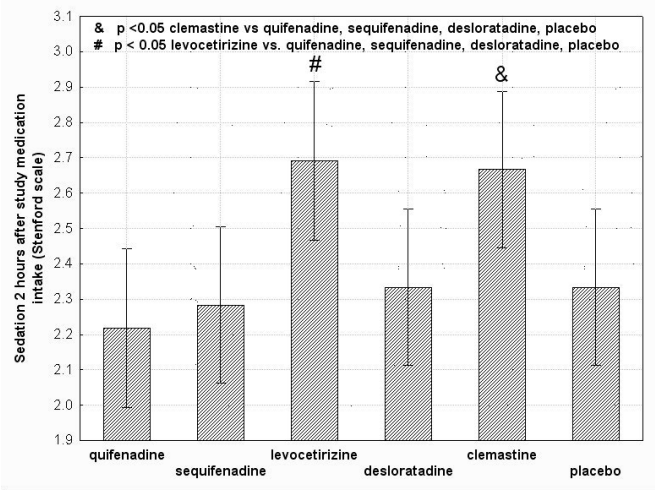

Fig. 5. Sedative effect evaluated by Stenford sleepiness scale two hours after drug intake after pre-treatment with clemastine and levocetirizine, compared to other H1-antihistamines and placebo ($P < 0.05$).

time interval 5 to 11 hours after drug intake ($P < 0.01$) (Fig. 6). The sedative profile of quifenadine and sequifenadine did not differ from the placebo.

One patient refused to participate in the study due to a severe sedative reaction after intake of levocetirizine. Statistical analysis demonstrated significant individual variability of treatment efficacy and sedation.

DISCUSSION

Histamine is one of the main mediators that can be used to ensure vasodilatation and increase of permeability of blood vessels during allergic reaction. Treatment with H1-antihistamines induced decrease of the wheal and flare reaction. The effect of levocetirizine in decreasing wheal diameter

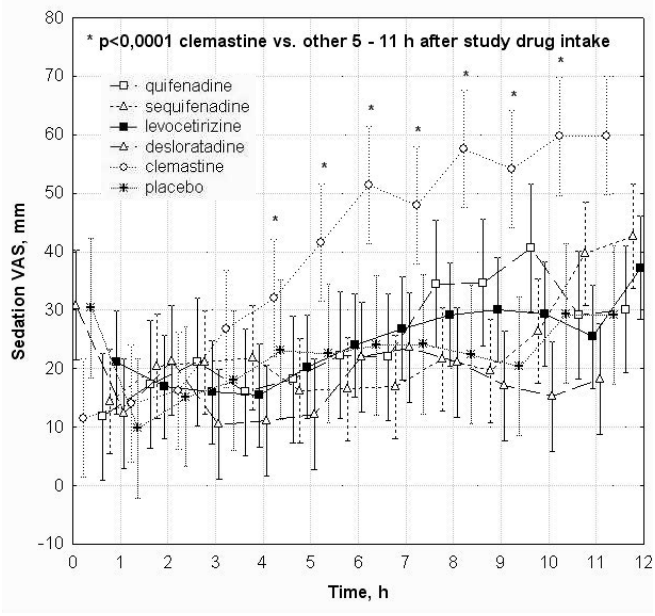

Fig. 6. Sedation evaluated by VAS in volunteers pre-treated with H1-antihistamines and placebo, significant difference between H1-antihistamines, placebo and clemastine, in time interval of 5 to 11 hours after study drug intake ($P < 0.01$).

and blood perfusion was significantly higher than of other H1-antihistamines. We demonstrated comparable efficacy of the older non-sedative H1-antihistamines (quifenadine and sequifenadine) with desloratadine and the first generation histamine receptor antagonist clemastine. Sedative effect was the most pronounced in a definite time interval after intake of the first generation antihistamine clemastine.

Numerous studies have compared the efficacy of single dose of antihistamines on histamine-induced wheal and flare reaction. In other studies levocetirizine reduced wheal and flare reaction to a greater extent than desloratadine, as well as other second generation antihistamines (Hindmarch *et al.*, 2001; Grant *et al.*, 2002; Denham *et al.*, 2003; Purohit *et al.*, 2003). A greater suppressive effect of cetirizine on the wheal and flare reaction compared to loratadine was demonstrated after histamine iontophoresis under physiological conditions differing from skin prick tests (Leroy *et al.*, 1998). General trends for wheal and flare reaction obtained in our study were consistent with previous studies.

Antihistamines, as in previous studies, induced a decrease of the blood flow intensity; however, in our study the differences were not very prominent.

The reasons why differences in the effect of the H1-antihistamines on skin blood perfusion are not very large may be due to the following:

1) high variability in estimated perfusion by laser doplerography;

2) pronounced differences of antihistamine effect on various individuals;

3) changes of blood perfusion are caused not only by reactions related to H1-receptors, but also by the effect of histamine on H3-receptors in the arteriole walls;

4) excretion of other mediators, for example, cystenyl-leucotrienes, prostaglandins, and bradikinine, under the influence of histamine;

5) irritation of terminal buttons of sensory neurons by histamine and excretion of substance P, and development of neurogenic inflammation;

6) evaluation of the blood perfusion by laser doplerography and papulae and erythema reaction reflect different manifestations of local reaction.

The increase of blood perfusion in the peripapular erythema area is significantly higher than in the wheal area (Olsson *et al.*, 1988). As reported by Hammarlund *et al*., there is a distance-related increase in blood flow intensity from wheal center to the periphery up to 30 mm from the prick test site (Hammarlund *et al.*, 1991).

Increased permeability of the microcirculation vessels is the cause of edema, increased intra-tissue pressure in the wheal area and subsequent decrease of local blood perfusion. Therefore, location of the detector in the fixed distance from the prick test site may give different results depending on the radius of wheal reaction. In our case, a significant decrease of wheal diameter might not been followed by equal change of blood perfusion.

The obtained laser results using laser Doppler scanning are consistent with results of other studies in which cetirizine with loratadine, or their optic isomers (levocetirizine with desloratadine) were similarly compared (Van Neste *et al.*, 1992; 1993; Klos *et al.*, 2006; Popov, 2006). In these studies, like in our trial, the effect of levocetirizine was more stable and predictable.

Relatively poorer effectiveness of desloratadine, compared to levocetirizine, can be explained also by the delayed effect — two hours after taking the medicine comparing to the optic isomer of cetirizine, which developed the therapeutic effect already within one hour.

Thus, does the higher effect of levocetirizine over other antihistamines in histamine-induced wheal and flare studies translate into a measurable benefit in terms of symptom control in clinical setting? Can we use evaluation of wheal and flare reaction and blood perfusion measurements as surrogate markers of H1-antihistamines potency?

H1-antihistamines can directly block wheal and flare reaction. Also, changes of blood perfusion in the skin during a skin prick test are probably not directly related to their clinical effectiveness and decrease of symptoms of allergic rhinitis or chronic urticaria.

The study results are therefore controversial. A lack of difference in clinical efficacy was demonstrated in a review article published by Devillier *et al.* (Devillier *et al.*, 2007). Two clinical trials assessing suppression of both histamine-induced wheal and flare reaction and the clinical efficacy on allergic rhinitis did not find a significant difference between antihistamines (Bousquet *et al.*, 1998; Persi *et al.*, 1999).

Mechanisms of pathogenesis during allergic reactions in real life are related to excretion of many inflammation mediators — histamine, eicosanoids, bradykinin, cytokines. Use of supra-physiological histamine concentrations during skin testing, development of late phase allergic reaction and specifics of individual anatomic differences, for example, of the skin and nasal mucous membrane, may give different results in antihistamine comparative trials. However, such testing allows obtaining certain information about the course of early allergic reaction, where the dominating mediator is histamine.

A recently published comparative study in patients with chronic idiopathic urticaria demonstrated significant superiority of a standard dose of levocetirzine over desloratadine (Potter *et al.*, 2009). In another study levocetirizine improved nasal obstruction and more significantly modulated cytokine pattern than desloratadine in patients with seasonal allergic rhinitis (Ciprandi *et al.*, 2004). Deruaz and coworkers observed better protective effect of levocetirizine

versus desloratadine in a nasal provocation test with pollen allergen (Deruaz *et al.*, 2004).

Nevertheless, it is of great interest to assess whether there is a relationship between inhibition of histamine-induced wheal and flare reaction or blood perfusion scanning, and the control of symptoms of allergic rhinitis or chronic urticaria in the clinical setting.

A credible evaluation of the sedation effect is difficult because there is no standardized method of how to evaluate the sedative effect exclusively on its own. The method most commonly used is general evaluation of psychomotor activity. This method is not specific for sedation, it is biased and has weak correlation between the sedation and test results. Lack of significant differences most probably can be explained by deficiencies of testing methods. Testing of the sedation effect over a longer period of time, for example, 12–24 hours after medication has been taken, could be significantly better.

The most prominent sedative effect, as found in other studies, was observed after intake of the first generation antihistamine clemastine (Frolund *et al.*, 1990; Hagermark *et al.*, 1992). Quifenadine and sequifenadine did not demonstrate any significant sedative effect compared to the placebo. This observation confirms the results of previously published studies about the lack of sedative potency of quinuclidine derivatives (Kaminka *et al.*, 1980; 1990).

Testing of sedation using the Stenford scale demonstrated, as expected, more prominent sedation after intake of clemastine, and, surprisingly, after levocetirizine. Cetirizine and its optical isomer levocetirizine are derivatives of the first generation antihistamine hydroxazine with significant sedative potential. For example, in the post-marketing study published by Layton and co-workers, levocetirizine is more likely to induce drowsiness and sedation in the first month after starting treatment, compared to desloratadine (Layton *et al.*, 2006). This study demonstrated a small but significantly higher frequency of sedation in the patient group treated with levocetirizine.

In conclusion, levocetirizine induced a significant and most pronounced decrease of weal and flare reaction and skin blood perfusion compared to the placebo and other H1-antihistamines. The effect of quifenadine and sequifenadine on weal reaction area was similar to desloratadine and clemastine. Regarding the sedative effect, we can conclude that second generation antihistamines appear to be sedative, but the least impairing, and the first generation drugs appear to be the most impairing on the function of the central nervous system. There is a necessity to consider the sedating potential of antihistamines, along with other factors, such as efficacy, when prescribing antihistamines to patients.

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H1-ANTIHISTAMĪNI SAMAZINA PAPULAS UN ERITĒMAS REAKCIJU UN ASINS PERFŪZIJAS PIEAUGUMU ĀDĀ, IZVĒRTĒJOT AR LĀZERA DOPLERA PLŪSMAS ANALĪZES METODI: RANDOMIZĒTS, DUBULTAKLS, PLACEBO KONTROLĒTS KRUSTOTA DIZAINA PĒTĪJUMS

Mūsu pētījuma mērķis bija salīdzināt ietekmi, kāda piemīt pirms testa lietotiem H1-antihistamīniem — levocetirizīnam, desloratadīnam, klemastīnam, kvifenadīnam, sekvifenadīnam — un placebo uz histamīna izraisītu papulas un eritēmas reakciju, asins perfūzijas pieaugumu ādā un sedāciju. Pētījumā tika iesaistīti 30 veseli brīvprātīgie. Šis bija prospektīvs, randomizēts, dubultakls, placebo kontrolēts, krustota dizaina un balansēts klīnisks pētījums. Brīvprātīgajiem randomizētā un dubultaklā veidā tika doti perorāli 5 mg levocetirizīna, 5 mg desloratadīna, 1 mg klemastīna, 50 mg kvifenadīna, 50 mg sekvifenadīna vai placebo. Divas stundas pēc kapsulas lietošanas tika veikts ādas dūriena tests ar histamīnu, tika reģistrētas asins perfūzijas izmaiņas ādā, kā arī sedatīvā efekta izvērtēšana. Mēs secinājām, ka levocetirizīns izraisa visnozīmīgāko un visizteiktāko ādas papulas un eritēmas reakcijas samazinājumu, kā arī visievērojamāko asins perfūzijas samazinājumu ādā, salīdzinot ar placebo un citiem H1-antihistamīniem. Kvifenadīna un sekvifenadīna ietekme uz papulas reakciju bija līdzīga desloratadīna un klemastīna ietekmei. Attiecībā uz sedatīvo efektu var secināt, ka otrās paaudzes antihistamīni ir nevis bez sedatīvas ietekmes, bet to sedatīvā ietekme atstāj vismazāko iespaidu un sekas uz organisma funkcijām, savukārt pirmās paaudzes antihistamīni visvairāk pasliktina centrālās nervu sistēmas funkciju. Jāievēro, ka, izrakstot pacientam kādu H1-antihistamīna preparātu, jāatceras arī par to sedatīvo ietekmi, ne tikai tiešo efektu uz alerģiskās reakcijas patoģenētiskajiem faktoriem.