

Short communication

Evaluation of a composite scoring system in conjunctival challenge with allergen: reproducibility and evolution during loratadine treatment

Bousquet J, Chanal I, Czarlewski W, Michel FB. Evaluation of a composite scoring system in conjunctival challenge with allergen: reproducibility and evolution during loratadine treatment. Allergy 1995; 50: 841–843. © Munksgaard 1995.

The reproducibility of any challenge and its sensitivity to change during therapeutic interventions should always be examined before any drug trial is conducted. Conjunctival challenge has been widely used to assess objectively the efficacy of antiallergic treatments. A double-blind, placebo-controlled, crossover study was carried out in 26 patients allergic to grass pollen to test the reproducibility of a composite symptom score during placebo and control days, and to check the ability of loratadine to increase the provocative dose inducing a positive challenge. Conjunctival challenge was carried out with increasing concentrations of a standardized orchard grass pollen extract until a composite symptom score of 5 was reached. The provocative dose inducing a positive challenge was similar for the baseline (6.94 ± 8.7 index of reactivity (IR)) and placebo days (20.0 ± 32.5 IR) and was significantly increased ($P < 0.01$ and $P < 0.001$) when patients received loratadine (117.3 ± 136.8 IR). This study shows that the composite score used was reproducible and sensitive to change, making it possible to use in drug trials.

J. Bousquet¹, I. Chanal¹, W. Czarlewski²,
F. B. Michel¹

¹ Service des Maladies Respiratoires, Hôpital Arnaud de Villeneuve, Centre Hospitalier Universitaire, 34059-Montpellier-Cedex;

² Schering-Plough, Rue Baudin, Levallois-Perret, France

Dr J. Bousquet
Service des Maladies Respiratoires
Hôpital Arnaud de Villeneuve
Centre Hospitalier Universitaire
34295-Montpellier-Cedex 5
France

Accepted for publication 14 June 1995

Conjunctival provocation tests (CPT) are being used to assess the efficacy of various antiallergic treatments (1–11). The positivity of the challenge may be assessed by symptoms (3, 12, 13) or composite symptom scores (14, 15), and more recently by the measurement of inflammatory mediators released in tears (14, 16) or the enumeration of cells obtained by scraping (7, 17, 18). It has been shown that symptoms induced by CPT are reproducible (3, 10, 11, 13), but the reproducibility of the test using a composite symptom score has not been fully examined yet. Aichane et al. have shown that the provocative dose (PD) inducing a positive CPT in both eyes challenged the same day is reproducible (14). However, the reproducibility of CPT carried out on different days has not been assessed. Moreover, the changes in PD inducing a positive CPT have not been studied using such a composite symptom score.

A double-blind, placebo-controlled, crossover

study was carried out in 26 patients allergic to grass pollen to test the reproducibility of a composite symptom score during placebo and control days, and to check the ability of loratadine to increase the PD inducing a positive CPT.

Material and methods

Patients

Twenty-six subjects (21–32 years old) were studied after informed consent and approval by the ethics committee of the hospital. They were selected as previously published (14) on a history of seasonal allergic rhinoconjunctivitis, positive prick test to a standardized orchard grass pollen extract (Staller-gènes Laboratories, Fresnes, France), and the presence of orchard grass pollen-specific IgE (Phade-bas® RAST or CAP System, Pharmacia Diagnostics, Uppsala, Sweden). None of the patients had

perennial allergic symptoms, and none of them had received any antiallergic or anti-inflammatory treatment for the previous 2 months.

Methods

Orchard grass pollen extract. A standardized extract from orchard grass (*Dactylis glomerata*) pollens (Stallergènes SA, Fresnes, France) was used. Details of preparation and standardization have been published previously (19). Extracts were labeled in biologic units (IR: index of reactivity) using methods derived from the proposals of the Nordic Countries' Guidelines on Allergen Standardization and codeine phosphate as a positive control. The freeze-dried extracts were stored at 4°C and reconstituted the day of the test with a diluent specifically prepared for conjunctival application. The same batch of allergen was used throughout the study. Each test day, a new vial was diluted in the sterile isotonic saline which was prepared without preservatives.

Conjunctival provocation test. Conjunctival provocation tests were performed as previously described (14). None of the patients had suffered from any form of allergic conjunctivitis for at least 2 months before the study. On entering the clinic, all subjects were examined to establish that no visible ocular symptoms were present at the time of the challenge. CPTs were performed by applying inside the conjunctival cul de sac 20 µl of the diluent and then 20 µl of threefold increasing allergen solutions ranging in concentration from 0.14 to 100 IR/ml to the eyelid every 10 min until a composite symptom score of at least 5 was reached. This composite score was derived from Abelson et al. (3) and includes redness, tearing, chemosis, and itching (Table 1).

Design of the study

Day 1 consisted of a baseline challenge without any treatment to assess the positivity of the test. A double-blind, placebo-controlled, crossover study was then performed. After a washout period of 7 days, loratadine (10 mg OD) or placebo was administered for 1 week and a second challenge was carried out. After a washout period of 1 week, the crossover product was administered for 1 week and a third challenge was carried out.

Statistical analysis of the data were done by non-parametric tests when possible. The Kruskal-Wallis test was used to compare the three groups and Dunn-Bonferroni's post test was used to compare the individual groups. The Wilcoxon W test was used to compare placebo and control days and placebo and loratadine days.

Table 1. Scoring system to measure signs and symptoms of allergic conjunctivitis (from Abelson et al. (3))

Redness, eyelid swelling
0: none
1: mild
2: moderate
3: severe
Chemosis
0: none
1: mild, detectable with slit lamp, conjunctiva separated from sclera
2: moderate (visually evident, raised conjunctiva, especially at limbal area)
3: severe (ballooning of conjunctiva)
Tearing
0: none
1: mild (eyes feel slightly watery)
2: moderate (blows nose occasionally)
3: severe (tears rolling down cheeks)
Itching (to be graded by subject)
0: none
1: mild (intermittent tickling sensation)
2: moderate (continual awareness but without desire to rub)
3: severe (continual awareness with desire to rub eyes)
4: incapacitating (subject insists on rubbing eyes)

Results

The provocative dose inducing a positive challenge was similar for the baseline (6.94 ± 8.7 IR) and placebo days (20.0 ± 32.5 IR), and was significantly increased ($P < 0.01$ and $P < 0.001$) when patients received loratadine (117.3 ± 136.8 IR) (Fig. 1). Overall symptoms were similar on different days of challenge without treatment. With the Wilcoxon W tests, there was no significant difference between placebo and control days and there was a highly significant difference between placebo and loratadine days ($P < 0.001$).

Discussion

This study shows that the composite score derived from Abelson et al. (3) can be used to monitor the

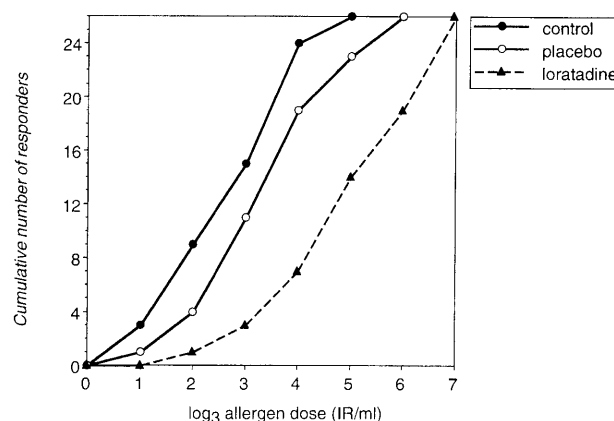


Fig. 1. Results of nasal provocation test with grass pollen extract. Statistical analysis by Kruskal-Wallis test ($P < 0.0001$) and Dunn's multiple comparison: placebo/control: NS; placebo/loratadine: $P < 0.01$; control/loratadine: $P < 0.01$.

efficacy of an antiallergic drug since there is no significant difference between baseline and placebo days, and loratadine was effective in increasing the PD inducing a positive CPT with allergen.

CPT are considered to be highly reproducible, but few studies have examined this parameter (3, 8, 10, 13). Moreover, in these studies, various symptoms were considered, including itching and chemosis (13); itching and hyperhemia (8, 10); or hyperhemia, itching, tearing, and chemosis (3). However, a composite symptom score had never been validated. We propose to use a composite score since hyperhemia, itching, tearing, and chemosis are cardinal symptoms of allergic conjunctivitis, but they are not always present in the same patient during the natural exposure to allergens. Moreover, we have previously shown that this composite score was correlated with the release of inflammatory mediators in tears during CPT (14). The present study was designed to assess the possible use of a composite symptom score in CPT, and a high reproducibility was observed when CPT was performed on subsequent days.

Another parameter to be examined in the evaluation of any provocative challenge is its sensitivity to change during a therapeutic intervention. Several treatments have been found effective in improving CPT (1, 2, 4–6, 8–11, 20). Loratadine is a non-sedative H₁-blocker with antiallergic properties that was shown to be effective in the treatment of allergic rhinitis and conjunctivitis (21). This drug was selected because Ciprandi et al. had shown its efficacy in CPT studies (2, 22). The present study confirmed these data and showed that the PD inducing a positive CPT was significantly increased.

This study shows that a composite score derived from the cardinal symptoms of allergic conjunctivitis can be used during clinical trials since it is both reproducible and sensitive to change both during treatment with oral (present study) or topical antiallergic drugs (23).

Acknowledgment

This work was supported by Schering-Plough, France.

References

1. CIPRANDI G, BUSCAGLIA S, IUDICE A, CANONICA GW. Protective effect of different doses of terfenadine on the conjunctival provocation test. *Allergy* 1992; 47: 309–12.
2. CIPRANDI G, BUSCAGLIA S, PESCE GP, MARCHESI E, CANONICA GW. Protective effect of loratadine on specific conjunctival provocation test. *Int Arch Allergy Appl Immunol* 1991; 96: 344–7.
3. ABELSON MB, CHAMBERS WA, SMITH LM. Conjunctival allergen challenge. A clinical approach to studying allergic conjunctivitis. *Arch Ophthalmol* 1990; 108: 84–8.
4. ABELSON M, GEORGE M, SCHAEFER K, SMITH L. Evaluation of a new ophthalmic antihistamine, 0.05% levocabastine, in the clinical allergen challenge model of allergic conjunctivitis. *J Allergy Clin Immunol* 1994; 94: 458–64.
5. CIPRANDI G, BUSCAGLIA S, IUDICE A, PESCE GP, BAGNASCO M, CANONICA GW. Protective effects of deflazacort on allergen-specific conjunctival challenge. *Eur J Clin Pharmacol* 1993; 45: S35–41.
6. JANSSENS M. Efficacy of levocabastine in conjunctival provocation studies. *Doc Ophthalmol* 1992; 82: 341–51.
7. BONINI S, BONINI S, BERRUTO A, et al. Conjunctival provocation test as a model for the study of allergy and inflammation in humans. *Int Arch Allergy Appl Immunol* 1989; 88: 144–8.
8. SCHOENEICH M, PÉCOUD AR. Effect of cetirizine in a conjunctival provocation test with allergens. *Clin Exp Allergy* 1990; 20: 171–4.
9. PÉCOUD A, ZUBER P, KOLLY M. Effect of a new selective H₁ receptor antagonist (levocabastine) in a nasal and conjunctival provocation test. *Int Arch Allergy Appl Immunol* 1987; 82: 541–3.
10. ZUBER P, PÉCOUD A. Effect of levocabastine, a new H₁ antagonist, in a conjunctival provocation test with allergens. *J Allergy Clin Immunol* 1988; 82: 590–4.
11. KJELLMAN NI, ANDERSSON B. Terfenadine reduces skin and conjunctival reactivity in grass pollen allergic children. *Clin Allergy* 1986; 16: 441–9.
12. RIMÁS M, GUSTAFSSON PM, KJELLMAN NI, BJÖRKSTÉN B. Conjunctival provocation test: high clinical reproducibility but little local temperature change. *Allergy* 1992; 47: 324–6.
13. MÖLLER C, BJÖRKSTÉN B, NILSSON G, DREBORG S. The precision of the conjunctival provocation test. *Allergy* 1984; 39: 37–41.
14. AICHANE A, CAMPBELL AM, CHANAL I, et al. Precision of conjunctival provocation tests in right and left eyes. *J Allergy Clin Immunol* 1993; 92: 49–55.
15. CAMPBELL AM, DEMOLY P, MICHEL FB, BOUSQUET J. Conjunctival provocation tests with codeine phosphate. Effect of disodium cromoglycate. *Ann Allergy* 1993; 71: 51–5.
16. PROUD D, SWEET J, STEIN P, et al. Inflammatory mediator release on conjunctival provocation of allergic subjects with allergen. *J Allergy Clin Immunol* 1990; 85: 896–905.
17. BONINI S, VECCHIONE A, NAIM DM, ALLAN-SMITH MR, BALSANO F. Inflammatory changes in conjunctival scrapings after allergen provocation in humans. *J Allergy Clin Immunol* 1988; 82: 462–9.
18. CIPRANDI G, BUSCAGLIA S, PESCE G, VILLAGGIO B, BAGNASCO M, CANONICA GW. Allergic subjects express intercellular adhesion molecule-1 (ICAM-1 or CD54) on epithelial cells of conjunctiva after allergen challenge. *J Allergy Clin Immunol* 1993; 91: 783–92.
19. BOUSQUET J, DJOUKADAR F, HEWITT B, GUERIN B, MICHEL FB. Comparison of the stability of a mite and a pollen extract stored in normal conditions of use. *Clin Allergy* 1985; 15: 29–35.
20. RIMÁS M, KJELLMAN NI, BLYCHERT LO, BJÖRKSTÉN B. Topical levocabastine protects better than sodium cromoglycate and placebo in conjunctival provocation tests. *Allergy* 1990; 45: 18–21.
21. CLISSOLD SP, SORKIN EM, GOA KL. Loratadine. A preliminary review of its pharmacodynamic properties and therapeutic efficacy. *Drugs* 1989; 37: 42–57.
22. CIPRANDI G, BUSCAGLIA S, MARCHESI E, DANZIG M, CUSS F, CANONICA GW. Protective effect of loratadine on late phase reaction induced by conjunctival provocation test. *Int Arch Allergy Immunol* 1993; 100: 185–9.
23. CHANAL I, BOUSQUET J, ARNAUD B, DUPIN O, TRINQAND C. Comparaison d'un nouveau collyre anti-allergique, la lévocabastine versus NAAGA, dans le test de provocation conjonctivale. *Rev Fr Allergol* 1994; 34: 420–3.