

ORIGINAL PAPER

Inhibition of the histamine-induced weal and flare response: a valid surrogate measure for antihistamine clinical efficacy?

P. Devillier* and J. Bousquet†

*Hôpital Foch, Suresnes, France and †Hôpital Arnaud de Villeneuve, Montpellier, France

Clinical and Experimental Allergy

Summary

Histamine plays a central role in allergic responses. Inhibition of the weal and flare response to histamine is a traditional pharmacodynamic tool to measure the activity of H₁-receptor antagonists. The time course and duration of cutaneous weal and flare inhibition are often used as surrogate measures of clinical efficacy. Pharmacodynamic differences among antihistamines are often interpreted to indicate differences in clinical efficacy. A systematic review of literature from 1980 to 2006 regarding the histamine induced weal and flare was undertaken. Search terms included 'histamine', 'skin test', 'weal', 'flare', and 'antihistamine'; retrieved articles were searched for relevant studies not identified initially. Data from human studies on the inhibition of the weal and flare by second-generation antihistamines were extracted and assessed. A literature search from 1980 to 2006 was undertaken for comparative studies of second-generation antihistamines in the clinical settings of allergic rhinitis (AR) and chronic idiopathic urticaria; data extracted from these studies underwent systematic review. Differences were noted among second-generation antihistamines in terms of their ability to inhibit the histamine-induced weal and flare. Corresponding differences in terms of clinical efficacy in AR and chronic urticaria were not identified following a systematic review. The reasons for the disconnect between pharmacodynamic effects and clinical efficacy may include differences between the route and concentration of histamine, the involvement of mediators other than histamine in the allergic response, and the short time course of pharmacodynamic studies. The histamine-induced weal and flare response is a pharmacodynamic test that should not be used to compare the clinical efficacy of different antihistamines, and is not an adequate alternative to clinical end-point assessments in AR or chronic idiopathic urticaria.

Correspondence:

Prof. Philippe Devillier, Biologie
Clinique, UPRES EA220, Hôpital Foch,
40, rue Worth, F-92150 Suresnes,
France.
E-mail: p.devillier@hopital-foch.org

Introduction

Allergic rhinitis (AR) and chronic idiopathic urticaria (CIU) are associated with a significant burden in terms of symptoms, disease-related quality-of-life impairment, and related costs [1–9]. While the symptomatology of AR and CIU differs due to the organs affected, both conditions involve activation of allergic cells, such as mast cells and basophils, which subsequently release inflammatory mediators. Histamine plays an important role in the symptomatology of AR and CIU, particularly following the initial degranulation of mast cells [7, 10]. However, histamine is only one of a variety of preformed (e.g. tryptase) and rapidly synthesized (eicosanoid) mediators, inflammatory cytokines, chemokines, and adhesion molecules that are involved in the initiation and propagation of allergic inflammatory responses [11–15].

Given the relatively important role played by histamine in the pathophysiology of AR and CIU, histamine H₁-receptor antagonists/inverse agonists are first-line therapy for both conditions [7, 16]. First-generation oral H₁-antihistamines, although effective in symptom relief, have been largely superseded by second-generation agents due to their improved adverse event (AE) profile. Second-generation antihistamines that have an AE profile similar to placebo and that do not exhibit potentially harmful interactions with concomitantly administered medications are now widely available [7]. The European Academy of Allergology and Clinical Immunology/Allergic Rhinitis and its Impact on Asthma (EAACI/ARIA) criteria for oral H₁-antihistamines call for the use of clinical trial data to assess the efficacy and safety of these compounds; however, few adequately powered comparative studies have been reported for newer agents [17]. Indeed, changes

in subjectively rated symptom severity scores may not be sufficiently sensitive to determine clinically relevant differences between second-generation antihistamines. For more recently developed antihistamines, methodologies other than clinical efficacy estimates have been used to compare their activities in the short-term. Among these surrogate measures, the pharmacodynamic test of the inhibition of the weal and flare response to histamine administration has been used most frequently. The results obtained from these histamine-induced weal and flare studies are commonly used to ascribe potential benefits to one agent over another. The validity of ascribing clinical superiority to an antihistamine based on pharmacodynamic data derived from histamine-induced weal and flare studies remains unproven [18]. The purpose of this review is to evaluate comprehensively the methodology involved in histamine-induced weal and flare studies, and to examine the role and validity of the histamine-induced weal and flare response as a predictor of clinical outcomes in patients with AR or CIU.

Histamine-induced weal and flare test: methodology

The histamine-induced weal and flare test is based on the measurement of local swelling caused by plasma extravasation (weal) and reflex vasodilatation (flare) after histamine challenge [18]. The test is used in the study of the pharmacodynamics of antihistamines, with responses measured at intervals to evaluate suppression of the response as a function of time and/or dose. Variables that can be calculated include maximal suppression of the weal and flare responses, the time to maximal suppression, and the onset and duration of weal and flare suppression. These pharmacodynamic measurements may be useful for assessing aspects of drug activity during the early clinical development of a new antihistamine. Correlations between plasma/cutaneous drug levels and inhibition of histamine-induced skin reactions can be undertaken, although description of pharmacokinetics and pharmacodynamics requires adequate modelling to be reliable [19–21].

The histamine-induced weal and flare test can be performed by administering histamine via an intradermal (ID) injection using a fine-gauge needle or epicutaneous puncture/skin prick, or by direct skin iontophoresis [22, 23]. The resulting weal is a sign of the direct vascular effects of histamine, namely increased vascular permeability and skin blood flow, while the flare reflects vasodilatation due to histamine-induced reflex neuropeptide release from local nerve terminals [22, 24, 25]. The weal reaction is generally assessed 10 min after the test and is measured as the mean diameter or by planimetry. Weal size measurement is reproducible with a co-efficient of variation of 8–22% depending on the device used [26]. In contrast, flare diameter may require more specialized

methods to reduce the variability of the measure such as thermography, telethermography, or laser Doppler flow, although the reproducibility of these methods remains to be determined [27–30]. Ideally, variability in histamine-induced weal and flare skin test reactivity should be minimized by the inclusion of a placebo arm; however, in practice, many comparative histamine-induced weal and flare trials between antihistamines do not.

A variety of factors that can influence the results of the histamine-induced weal and flare test need to be considered. The results can vary by skin-prick device [31] or injection site (e.g. the forearm is less sensitive than the back) [31, 32]. Studies have also shown that relevant circadian and seasonal variations in histamine-induced weal and flare response occur, while in females the histamine-induced weal and flare response is governed in part by hormonal changes across the menstrual cycle [33–35]. Such variations appear to affect the flare component to a greater extent than the weal component [22]. Studies also suggest that there are significant intra- and inter-subject variations in skin reactivity in both healthy volunteers and patients with allergies [36]. Finally, as noted above, the methods used to quantify the histamine-induced weal and flare response – particularly the flare – as well as the dosage and duration of the antihistamine treatment, introduce variability that could make comparisons among studies difficult [27–30, 32].

Another important area to be considered is the mechanistic differences between the introduction of exogenous histamine during a histamine-induced weal and flare test and the release of endogenous histamine following mast cell degranulation. Of critical significance is the concentration of histamine used in the histamine-induced weal and flare test. The baseline level of histamine in unprovoked skin is approximately 20 nM [25]. Separate ID injections of 50 µM histamine and 10 SQ IU/mL of grass pollen allergen provoked similar-sized weal responses; however, the peak tissue histamine concentration following ID histamine was almost four times that measured after an ID allergen injection [14]. Histamine concentrations in comparative histamine-induced weal and flare studies of antihistamines were from 2- to 200-fold higher than this level [37–48]. Such ID histamine injections resulted in tissue histamine levels at least one order of magnitude greater than that seen after allergen injections [37]. Therefore, it appears that to produce an equivalent weal size, exogenously administered histamine concentrations must be appreciably higher than those achieved following allergen activation of mast cells. Given that comparative histamine-induced weal and flare studies of antihistamines commonly assess onset of action, potency, and duration of action, it appears that future studies should be designed to measure antihistaminic effects at lower, more clinically relevant concentrations of administered histamine.

Most comparative studies of antihistamine have utilized the skin-prick method. A skin prick test (SPT) yielding a weal reaction comparable with an ID injection requires, on average, a 300-fold higher concentration of histamine [49, 50]. Based on this ratio, the threshold concentration of histamine by the SPT is about 9 mM (i.e. 1 mg/mL), which, by analogy with the above reasoning for histamine ID injection, would correspond to a three- to fourfold higher cutaneous exposure to histamine than after allergen challenge. This value is similar to the threshold concentrations reported by Frossard et al. [51], Purohit et al. [52], and Town et al. [53]. However, most of the skin-prick studies comparing the potencies of antihistamines used a 100-fold higher concentration of histamine (100 mg/mL) [54–62]. As noted previously, not only do such high concentrations of histamine limit the potential clinical significance of these studies, but they may also interfere with the accuracy of evaluations of the relative potencies of antihistamines.

The most accurate means to estimate the relative potencies of antihistamines is to determine histamine concentration–response curves for each agent, to calculate the log/log relationship between changes in weal responses and histamine concentrations, and to compare the linear log/log response curves if parallelism is statistically acceptable [49, 63]. Although this approach is considered the standard method for determining the relative potency of allergen preparations or drugs [63], it has been used in only one study using SPTs [51] and in none using ID injection. Histamine concentration–response curves provide a more meaningful comparison of the relative potencies of antihistamines than the ratio of threshold histamine concentrations required to produce a positive weal response of 10 mm² [51, 53], as up to 50% of subjects receiving an antihistamine do not reach the weal surface threshold when tested with a single predetermined concentration of histamine. In such cases, either the highest histamine concentration tested is used to calculate the threshold [51], or subjects in whom the weal threshold is not reached are excluded from the potency evaluation of the agent concerned [53], which may underestimate its relative potency.

Another approach to evaluating the relative potencies of antihistamines is to compare their inhibition of the flare reaction. In the great majority of studies (Table 1), such comparisons have found similar orders of potency for the antihistamines evaluated, regardless of the relative weal responses [37–48, 51, 52, 54–62, 64–83]. However, in the study by Frossard et al. [51], which used the concentration–response curve method, ebastine (10 and 20 mg) and cetirizine inhibited flare response to a similar degree but differed significantly in their inhibition of weal development. Thus, differences may occur in the relative potencies of agents as measured by their effects on weal vs. flare reactions; however, the clinical significance of such differences is doubtful.

In summary, the majority of comparative histamine-induced weal and flare studies have used very high histamine concentrations relative to the histamine levels produced after allergen challenge. More reliable methods of comparing antihistamine potencies using weal and flare response (e.g. the calculation of histamine concentration–response curves) have not been widely applied. These observations, combined with other methodological issues such as variations in skin sensitivity and intra-individual variability [36], can affect the applicability of the histamine-induced weal and flare to the clinical setting of AR and CIU.

Systematic review

A MEDLINE database search was undertaken in April 2006, using the basic terms 'histamine and [skin test or (wheal or weal) and flare]'. Nine hundred retrieved articles were reviewed, and articles that were not relevant to the methods or use of weal and flare skin tests in humans were discarded. One hundred thirty-seven studies were then analysed to identify relevant information. These studies included comparative trials among antihistamines, and incorporated studies that were placebo-controlled and non-placebo-controlled in order to obtain a comprehensive assessment of the comparative pharmacodynamics of antihistamines using this test. Of this number, a total of 44 were found to consist of comparisons among orally administered second-generation antihistamines. Supplemental MEDLINE searches were undertaken using the terms antihistamine, cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine, and mizolastine. A separate MEDLINE search was performed to identify comparative studies of orally administered second-generation antihistamines (astemizole, cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine, loratadine, mizolastine, terfenadine) in patients with AR or CIU, and 57 were deemed relevant for inclusion. The reference lists of articles and reviews were analysed for studies not identified initially in the two searches outlined above.

Comparative studies of histamine-induced weal and flare

Numerous studies have compared the effects of a single dose of different antihistamines on histamine-induced weal and flare, with the majority enrolling healthy volunteers (Table 1). Loratadine was included in 15 of the 28 studies of healthy volunteers [37, 38, 40, 41, 44, 45, 55–57, 65–70] and caused less suppression of weal and flare than other second-generation antihistamines in all but three of the studies, usually when antihistamines were studied within 24 h after drug intake [37, 69, 70]. On the other hand, cetirizine, included in 20 studies of healthy volunteers, suppressed weal and flare to a greater extent than loratadine (nine studies) [41, 44, 45, 55, 57, 67–70], terfenadine

Table 1. Histamine-induced weal and flare reactions in subjects treated with antihistamines

Reference	Pts (n)	Trial: duration and type	Measure (method)	Ranking (daily dose)
<i>Healthy volunteers – PC</i>				
Purohit et al. [60]	18	1 day DB, X, PC	Weal/flare (prick testing with histamine 100 mg/mL)	Weal and flare areas (AUC _{0–24 h}) Cetirizine (10 mg) > desloratadine (5 mg) > placebo
Takahashi et al. [64]	7	1 day DB, X, PC	Weal/flare [histamine (10 mg/mL) challenge by iontophoresis 0.1 mA]	Weal areas (0–24 h) Olopatadine (10 mg) = cetirizine (10 mg) > bepotastine (20 mg) > fexofenadine (120 mg) > placebo Flare areas (0–24 h) Olopatadine (10 mg) = cetirizine (10 mg) = bepotastine (20 mg) = fexofenadine (120 mg) > placebo
Wang and Zhang [65]	90	1 day DB, para, PC	Weal/flare (prick testing with histamine 54.3, 20.0, 7.3, and 2.7 mmol/L)	Weal and flare areas (AUC concentration–responses to histamine) Mizolastine (10 mg) > loratadine (10 mg) > placebo
Barbanoj et al. [43]	18	1–5 days DB, X, PC	Weal/flare (ID injection with 0.05 mL solution of 100 µg/mL histamine)	Weal and flare areas: (AUC _{0–24 h}) Ebastine (20 mg) > fexofenadine (120 mg)
Denham et al. [39]	12	1 day DB, X, PC	Weal/flare/itch (ID injection with histamine 20 µL, 100 µM)	Weal/flare (laser Doppler imaging) Levocetirizine (5 mg) > desloratadine (5 mg) > placebo
Kaliner et al. [66]	30	1 day DB, X, PC	Weal/flare (prick testing with histamine 1.8 mg/mL)	Flare (2–7 and 10–12 h) Fexofenadine (180 mg) > loratadine (10 mg) Weal (1–12 h) Fexofenadine (180 mg) > loratadine (10 mg)
Purohit et al. [59]	18	1 day DB, X, PC	Weal/flare (prick testing with histamine 100 mg/mL)	Weal and flare areas (AUC _{0–24 h}) Levocetirizine (5 mg) > desloratadine (5 mg) > placebo
Carey et al. [37]	15	6 days DB, X, PC	Weal (ID injection 0.1% histamine, 30 µL)	Weal Ebastine (10 mg) = cetirizine (10 mg) ≥ loratadine (10 mg) > fexofenadine (120 mg) > placebo
Gispert et al. [44]	20	1–7 days DB, X, PC	Weal (ID injection with 0.05 mL, histamine 100 µg/mL)	Weal and flare (4–8 h after first or last dose) Ebastine (20 mg) = cetirizine (10 mg) > loratadine (10 mg) > placebo
Grant et al. [56]	18	1 day DB, X, PC	Weal/flare (prick testing with histamine 100 mg/mL)	AUC _{0–24 h} of weal and flare areas Levocetirizine (5 mg) > ebastine (10 mg) = fexofenadine (180 mg) = mizolastine (10 mg) > loratadine (10 mg) > placebo
Purohit et al. [52]	36	1 day DB, X, PC	Weal/flare (prick testing with histamine 0, 5, 10, 20, 40, 80, and 160 mg/mL)	Weal and flare areas (AUC concentration – responses to histamine) Cetirizine (10 mg) > mizolastine (10 mg) > placebo
Purohit et al. [58]	26	1 day DB, X, PC	Weal/flare (prick testing with histamine 100 mg/mL)	Weal/flare area (0–24 h) Cetirizine (10 mg) > fexofenadine (180 mg) = fexofenadine (120 mg) > placebo
Hindmarch et al. [57]	20	1–4 days DB, X, PC	Weal/flare (prick testing with histamine 100 mg/mL)	AUC _{0–12 h} after first and last dose Levocetirizine (5 mg) = cetirizine (10 mg) > loratadine (10 mg) = promethazine (30 mg) > placebo
Frossard et al. [51]	24	6 days DB, X, PC	Weal/flare (prick testing with histamine 0, 0.5, 1, 2.5, 5, 10, 20, 50, 100, and 200 mg/mL)	Weal (24 h after last dose) Ebastine (20 mg) > ebastine (10 mg) = cetirizine (10 mg) > placebo Flare (24 h after last dose) Ebastine (20 mg) = ebastine (10 mg) = cetirizine (10 mg) > placebo
Grant et al. [55]	14	1 day DB, X, PC	Weal/flare (prick testing with histamine 100 mg/mL)	AUC _{0–24 h} of weal and flare areas Cetirizine (10 mg) > epinastine (20 mg) > terfenadine (60 mg) > ebastine (10 mg) > fexofenadine (60 mg) > loratadine (10 mg) > placebo
Rosenzweig et al. [41]	15	1 day DB, X, PC	Weal and flare (ID injection of histamine 2 µg in 100 µL)	Weal and flare areas (0–24 h) Mizolastine (10 mg) = terfenadine (120 mg) = cetirizine (10 mg) > loratadine (10 mg) > placebo
Lever et al. [45]	12	1 day DB, X, PC	Weal/flare (ID injection of histamine 20 µg in 100 µL)	Weal/flare area/weal thickness (0–24 h) Terfenadine (120 mg) = cetirizine (10 mg) > loratadine (10 mg) > placebo

Table 1. Continued

Reference	Pts (n)	Trial: duration and type	Measure (method)	Ranking (daily dose)
Shall et al. [67]	24	1 day SB, X, PC	Weal/flare (ID injection of 20 µg histamine in 0.05 mL)	Weal and flare areas (0–6 h) Cetirizine (10 mg) = terfenadine (120 mg) > loratadine (10 mg) > placebo
Van Neste et al. [68]	9	1 day DB, X, PC	Weal/flare (prick testing with histamine 8 mg/mL)	Weal/flare (6 h post-dose) Cetirizine (10 mg) > loratadine (10 mg) > placebo
Simons et al. [69]	20	1 day DB, X, PC	Weal/flare (prick testing with histamine 1 mg/mL)	Weal areas (0–24 h) Cetirizine (10 mg) > terfenadine (120 mg) > terfenadine (60 mg) > loratadine (10 mg) > astemizole (10 mg) > chlorpheniramine (4 mg) > placebo Flare areas (0–24 h) Cetirizine (10 mg) = terfenadine (120 mg) = terfenadine (60 mg) > loratadine (10 mg) > astemizole (10 mg) > chlorpheniramine (4 mg) = placebo
Roman et al. [40]	60	4 weeks DB, para, PC	Weal (ID with histamine solution of 20 µg/mL; 100 µL)	Weal areas (0–12 h) Loratadine (40 mg > 20 mg > 10 mg) = chlorpheniramine (12 mg) > placebo
<i>Healthy volunteers – non-PC</i>				
Purohit et al. [61]	42	1 day DB, X	Weal/flare (prick testing with histamine 100 mg/mL)	Weal and flare areas (time to, and frequency of, 95% inhibition) Fexofenadine (180 mg) = cetirizine (10 mg)
Clough et al. [38]	11	1 day DB, X	Weal/flare (ID injection with histamine 20 µL, 100 µM)	Weal/flare (laser Doppler imaging)/itch Levocetirizine (5 mg) > loratadine (10 mg) = placebo
Devalia et al. [54]	18	1 day DB, X	Weal/flare (prick testing with histamine 100 mg/mL)	Weal and flare (AUC _{0–32 h}) Levocetirizine (2.5 mg) = cetirizine (5 mg) > ucb 28557 (S-enantiomer of cetirizine, 2.5 mg)
Bayramgürler et al. [70]	60	1 day SB	Weal/flare (prick testing with 1% histamine solution)	Weal (90 min, 4, 6, 24 h) Cetirizine (10 mg) > acrivastine (8 mg) and loratadine (10 mg) Flare At 30 min: acrivastine (8 mg) > cetirizine (10 mg) and loratadine (10 mg) At 90 min: acrivastine (8 mg) = cetirizine (10 mg) > loratadine (10 mg) At 4 h: cetirizine (10 mg) > acrivastine (8 mg) > loratadine (10 mg) At 6 h: cetirizine (10 mg) > acrivastine (8 mg) = loratadine (10 mg) At 24 h: cetirizine (10 mg) > loratadine (10 mg) > acrivastine (8 mg)
Leroy et al. [71]	18	1 day DB, X	Weal/flare (iontophoresis 30 s, 1.4 mA/cm ² of histamine 10%)	Weal/flare (2–7 h) Cetirizine (10 mg) > ebastine (10 mg)
Rihoux and Van Neste [47]	10	3 weeks DB, X	Weal/flare [ID with histamine solution (10 µL containing 1 µg) and Phazet [®] dry prick test with histamine powder]	Weal/flare areas on days 7, 14, and 21 of drug administration Cetirizine (10 mg) > terfenadine (120 mg)
Pechadre et al. [46]	9	1 day DB, X	Weal/flare (ID histamine 1 µg in 10 µL)	Weal/flare At 2 h: cetirizine (10 mg) > terfenadine (60 mg) = placebo At 6 h: cetirizine (10 mg) = terfenadine (60 mg) > placebo
<i>Patients with AR and/or asthma – PC</i>				
Roongapinun et al. [72]	31	1 day O, para, PC	Weal and flare (prick testing with histamine 1 mg/mL)	Weal areas (30–240 min) Cetirizine (10 mg) = fexofenadine (60 mg) > loratadine (10 mg) > placebo Flare areas (30–240 min) Cetirizine (10 mg) = fexofenadine (60 mg) = loratadine (10 mg) > placebo

Table 1. Continued

Reference	Pts (n)	Trial: duration and type	Measure (method)	Ranking (daily dose)
Wang and Zhang [65]	60	1 day DB, para, PC	Weal/flare (prick testing with histamine 54.3, 20.0, 7.3, and 2.7 mmol/L)	Weal and flare areas (AUC concentration-responses to histamine) Mizolastine (10 mg) > loratadine (10 mg) > placebo
Simons et al. [73]	15	1 day DB, X, PC	Weal/flare (prick testing with histamine 1 mg/mL)	Weal and flare areas (0–24 h) Cetirizine (10 mg) > fexofenadine (30 mg) > placebo
van Steekelenburg et al. [74]	12	1 day SB, X, PC	Weal (ID with histamine)	Weal diameters (4–8 h after drug intake) Cetirizine (10 mg) ≥ ebastine (10 mg) = fexofenadine (120 mg) = mizolastine (10 mg) = loratadine (10 mg) > placebo
Simons et al. [75]	15	1 day DB, X, PC	Weal/flare (prick testing with histamine 1 mg/mL)	Weal areas (0.25–1 h) Cetirizine (10 mg) > loratadine (10 mg) Weal areas (2–24 h) Cetirizine (10 mg) = loratadine (10 mg) Flare areas (0.5–24 h) Cetirizine (10 mg) > loratadine (10 mg)
Persi et al. [76]	24	1 week DB, X, PC	Weal/flare (prick testing with histamine 10 mg/mL)	Weal and flare areas (2 h after last dose) Cetirizine (10 mg) > loratadine (10 mg) > placebo
Bousquet et al. [77]	38	1 week DB, para, PC	Weal and flare (prick testing with histamine 10 mg/mL)	Weal diameters Astemizole (10 mg) > loratadine (10 mg)
Hamilton et al. [78]	15	1 week DB, X, PC	Weal and flare (prick testing: 1, 10, 50, and 100 mg/L)	Weal Olopatadine (5, 10, 20 mg) > terfenadine (120 mg) > placebo
Fadel et al. [62]	7	1 day DB, X, PC	Weal/flare (prick testing with histamine 100 mg/mL)	Weal/flare (4 h after drug intake) Cetirizine (10 mg) > loratadine (10 mg) = placebo
Kontou-Fili et al. [48]	10	1 day DB, X, PC	Weal/flare at 10 min (ID injection of histamine 100 µg/mL, 0.02 mL)	Weal (2–6 h) Cetirizine (10 mg) > loratadine (10 mg) = placebo Flare (2–6 h) Cetirizine (10 mg) > loratadine (10 mg) > placebo
<i>Patients with AR and/or asthma – non-PC</i>				
Passalacqua et al. [79]	23	1 day DB, X	Weal/flare (prick testing with histamine 0.1% solution)	Flare areas (2 and 24 h) Levocetirizine (5 mg) > desloratadine (5 mg) Weal areas (2 h) Levocetirizine (5 mg) > desloratadine (5 mg) Weal areas (24 h) Levocetirizine (5 mg) = desloratadine (5 mg)
Sienra-Monge et al. [80]	80	4 weeks DB, para	Weal (prick testing with histamine)	Weal areas Cetirizine > loratadine (both 0.2 mg/kg/day)
Berkowitz et al. [81]	39	2 weeks DB, para	Weal and flare (prick testing with histamine 0.1 and 1.8 mg/mL)	Weal and flare areas (day 14) Cetirizine (10 mg = 5 mg) > astemizole (10 mg)
Humphreys and Hunter [42]	10	1 week O, X	Weal/flare (ID histamine, 4 µg in 0.1 mL)	% inhibition of weal and flare areas Weal: cetirizine (10 mg) > astemizole (10 mg) ≥ loratadine (10 mg) Flare: cetirizine (10 mg) = astemizole (10 mg) > loratadine (10 mg)
<i>Patients with CIU</i>				
Leynadier et al. [82]	61	4 weeks DB, para	Weal/flare (prick testing with histamine 1.25, 2.5, 5, and 10 mg/mL on days 0, 14, and 28 of drug administration)	Flare area Mizolastine (10 mg) > loratadine (10 mg) (on day 14 with 2.5 mg/mL histamine, and on day 28 with 10 mg/mL histamine)
<i>Patients with acquired cold urticaria</i>				
Villas et al. [83]	7	2 weeks SB, X	Weal (prick testing with histamine 10 mg/mL)	Weal areas Cyproheptadine (12 mg) ≥ cetirizine (10 mg) ≥ ketotifen (20 mg) ≥ loratadine (10 mg)

Pts, patients; DB, double-blind; X, crossover; PC, placebo-controlled; AUC, area-under-the-curve; para, parallel; SB, single-blind; O, open-label; AR, allergic rhinitis; CIU, chronic idiopathic urticaria.

(four studies) [46, 47, 55, 69], and desloratadine (one study) [60]. Cetirizine was also found in four studies to suppress weal and flare to a greater extent than fexofenadine [37, 55, 58, 64]; however, similar levels of suppression were found in a further study [61]. In addition, cetirizine was found to suppress weal and flare responses to a similar extent as ebastine 20 or 10 mg in three studies [37, 44, 51], but better than ebastine (10 mg) in two other studies [55, 71]. Levocetirizine reduced weal and flare to a greater extent than loratadine (three studies) [38, 56, 57], and desloratadine (two studies) [39, 59], as well as ebastine, fexofenadine, and mizolastine (one study each) [56].

Sixteen studies have compared the effects of different antihistamines on histamine-induced weal and flare in patients with allergic diseases [42, 48, 62, 65, 72–83]. In nine studies, cetirizine caused a greater suppression of weal and flare than fexofenadine (two studies) [73, 74] and loratadine (seven studies) [42, 48, 62, 72, 75, 76, 80]. In addition, fexofenadine was found to induce greater suppressive effects than loratadine in one study [72], but similar suppressive effects to loratadine in another study [74]. In a study of patients with AR, levocetirizine suppressed histamine-induced weal and flare more effectively than desloratadine, although there was no significant difference in weal measurements 24 h after treatment [79].

The major differences between antihistamines were observed following ingestion of a single dose of medication and the greatest differences mainly within the 4 h following drug intake [58]. Most of these results were obtained when studying the suppressive effects of cetirizine or its active enantiomer, levocetirizine, on histamine-induced weal or flare. Indeed, in the 24 comparative studies of healthy volunteers incorporating cetirizine and/or levocetirizine, these two antihistamines have had the shortest onset of action when compared with loratadine (14 studies) [38, 41, 44, 48, 55–57, 67, 68, 70, 72, 74, 75], desloratadine (three studies) [39, 59, 60], fexofenadine (six studies) [55, 58, 64, 72–74], and acrivastine (one study) [70]. Two studies found a similar onset of action for cetirizine or levocetirizine when compared with mizolastine and fexofenadine [56, 61]. In one study, mizolastine had a shorter onset of action compared with cetirizine [41].

Relationship between histamine-induced weal and flare and clinical efficacy

Measurements of the response to histamine in the skin do not necessarily accurately reflect the effects of antihistamines in other tissues, such as that of the upper respiratory tract. Numerous factors may confound the relationship between the suppression of histamine-induced weal and flare and clinical efficacy in patients with allergic conditions. These include differences in drug distribution to the target organ and in the relative role of histamine and other allergic inflammatory mediators in

the clinical expression of allergic diseases in different organs [84]. For example, it has been shown that cetirizine blocks eosinophils in the skin [85–87] but not in the nose [88], which suggests that effects in the skin may not be adequate predictors of nasal effects. Therefore, it is of interest to assess whether a relationship exists between the inhibition of histamine-induced weal and flare and the control of symptoms of allergy in the clinical setting if this is to be used as a surrogate measure to compare and contrast antihistamines. To explore whether such a correlation exists, the results for clinical efficacy in comparative studies of second-generation antihistamines were examined systematically.

Allergic rhinitis

Since 1985, 48 studies have compared the effects of different second-generation antihistamines in controlling the nasal symptoms of patients with AR (Table 2) [77, 79, 80, 89–133]. The duration of treatment ranged from 2 days to 8 weeks, which reflects the length of study recommended by regulatory authorities for the assessment of symptom control in AR in the clinical setting. This duration of treatment and assessment, measured in weeks, is in contrast to the short duration of assessment utilized in histamine-induced weal and flare studies as outlined in Table 1. Overall, 33/48 studies (69%) in AR demonstrated that the antihistamines studied were equivalent to one another in terms of the control of symptoms over the duration of the study. There was no consistent pattern of one antihistamine showing superiority over other antihistamines [142]. Notably, the greater magnitude of effect of cetirizine/levocetirizine over other antihistamines in histamine-induced weal and flare studies did not translate into a measurable benefit in terms of symptom control in the clinical setting.

Chronic idiopathic urticaria

The search strategy highlighted a total of nine comparative studies involving second-generation antihistamines in the treatment of CIU. The duration of treatment in these trials ranged from 4 to 6 weeks, reflecting the fact that the natural duration of symptoms in CIU is prolonged. Overall, 5/9 studies (56%) demonstrated no statistically significant difference between the antihistamines studied in terms of the primary end-points.

Discussion

The histamine-induced weal and flare response after a single-dose administration of an antihistamine is frequently used in studies of the pharmacodynamics of antihistamines and provides a readily obtained measure

Table 2. Comparative tabulation of second-generation antihistamines in patients with AR or CIU

Reference	# of patients randomized	Trial: duration and type	Primary efficacy outcome
<i>AR - PC</i>			
Raphael et al. [89]	610	1 week DB, para, PC	Diphenhydramine (50 mg) > desloratadine (5 mg) > placebo
Ciprandi et al. [90]	30	4 weeks DB, para, PC	Desloratadine (5 mg) = levocetirizine (5 mg) > placebo
Hyo et al. [91]	113	2 days DB, PC	Cetirizine (10 mg) > fexofenadine (120 mg) > loratadine (10 mg) > placebo
Stübner et al. [92]	110	16 days DB, PC	Levocetirizine (5 mg) = loratadine (10 mg) > placebo
Hampel et al. [93]	749	4 weeks DB, para, PC	Ebastine (20 mg) > loratadine (10 mg) > placebo Ebastine (10 mg) = loratadine (10 mg) > placebo
Ratner et al. [94]	703	4 weeks DB, para, PC	Ebastine (20 mg) > loratadine (10 mg) = placebo
Crampton [95]	82	4 weeks DB, PC	Ketotifen fumarate solution (0.025%) + desloratadine (5 mg) = ketotifen fumarate solution (0.025%) > desloratadine (5 mg)
Wilson et al. [96]	49	2 weeks DB, X, PC	Fexofenadine (180 mg) = desloratadine (5 mg) > placebo
Frèche et al. [97]	428	4 weeks DB, para, PC	Mizolastine (10 mg) > loratadine (10 mg) Mizolastine (10 mg) > placebo Loratadine (10 mg) = placebo
Ratner et al. [98]	565	4 weeks DB, para, PC	Ebastine (20 mg) > loratadine (10 mg) > placebo Ebastine (10 mg) = loratadine (10 mg) > placebo
Nunes and Ladeira [99]	90	4 weeks DB, para, PC	Cetirizine (10 mg) = loratadine (10 mg) > placebo
van Cauwenberge and Juniper [100]	688	2 weeks DB, PC, para	Fexofenadine (120 mg) = loratadine (10 mg) > placebo
Howarth et al. [101]	821	2 weeks DB, para, PC	Fexofenadine (120 and 180 mg) = cetirizine (10 mg) > placebo
Sabbah et al. [102]	375	4 weeks DB, DD, para, PC	Cetirizine (10 mg) = mizolastine (10 mg) > placebo
Bousquet et al. [77]	38	1 week DB, para, PC	Loratadine (10 mg) = astemizole (10 mg) > placebo
Druce et al. [103]	338	1 week DB, para, PC	Brompheniramine (24 mg) > loratadine (10 mg) > placebo
Lockey et al. [104]	311	2 weeks DB, para, PC	Cetirizine (10 mg) > terfenadine (120 mg) Cetirizine > placebo; Terfenadine = placebo
Del Carpio et al. [105]	317	2 weeks DB, para, PC	Loratadine (10 mg) = terfenadine (120 mg) > placebo
Horak et al. [106]	256	2 weeks DB, para, PC	Loratadine (10 mg) = terfenadine (120 mg) > placebo
Skassia-Brociek et al. [107]	69	2 weeks DB, para, PC	Loratadine (10 mg) = mequitazine (10 mg) > placebo
Buckley et al. [108]	244	1 week DB, para, PC	Terfenadine (120 mg) = chlorpheniramine (12 mg) > placebo
Oei [109]	65	2 weeks DB, para, PC	Loratadine (10 mg) > astemizole (10 mg) Loratadine > placebo; Astemizole = placebo
Dockhorn et al. [110]	330	2 weeks DB, para, PC	Loratadine (10 mg) = clemastine (2 mg) > placebo
Kemp et al. [111]	313	2 weeks DB, para, PC	Loratadine (10 mg) = clemastine (2 mg) > placebo
Kemp et al. [112]	397	1 week DB, para, PC	Terfenadine (120 mg) = chlorpheniramine (12 mg) > placebo
<i>AR - non-PC</i>			
Corren et al. [113]	306	2 weeks DB, para	Azelastine nasal spray > cetirizine (10 mg)

Table 2. Continued

Reference	# of patients randomized	Trial: duration and type	Primary efficacy outcome
Martinez-Cócerca et al. [114]	249	2 weeks DB, para	Rupatadine (10 mg) = cetirizine (10 mg)
Horak et al. [115]	120	2 weeks DB, para	Emedastine (4 mg) = cetirizine (10 mg)
Passalacqua et al. [79]	23	1 day DB, X	Desloratadine (5 mg) = levocetirizine (5 mg)
Saint-Martin et al. [116]	339	2 weeks DB, para	Rupatadine (20 mg) > rupatadine (10 mg) > loratadine (10 mg)
Hampel et al. [117]	495	2 weeks DB, para	Cetirizine (10 mg) = fexofenadine (180 mg)
Prenner et al. [118]	659	2 weeks DB, DD, para	Loratadine (10 mg) > fexofenadine (120 mg)
Sienra-Monge et al. [80]	80	4 weeks DB, para, pediatric study (2–6 years)	Cetirizine (0.2 mg/kg) > loratadine (0.2 mg/kg)
Murris-Espin et al. [119]	214	4 weeks DB, para	Cetirizine (10 mg) = ebastine (10 mg)
Crawford et al. [120]	14	2 weeks open label, X	Terfenadine (10 mg) = loratadine (10 mg) = astemizole (10 mg)
Al-Muhaimeed [121]	84	1 week DB, para	Loratadine (10 mg) = azelastine (10 mg)
Bellioni et al. [122]	68	4 weeks DB, para	Loratadine 10 mg = mizolastine (10 mg)
Gehanno et al. [123]	343	2 weeks DB, para	Ebastine (20 mg) > ebastine (10 mg) > cetirizine (10 mg)
Harcup et al. [124]	158	4 weeks DB, DD, para	Cetirizine (10 mg) = astemizole (10 mg)
Lockey et al. [125]	160	1 week SB, para	Cetirizine (10 mg) = terfenadine (120 mg)
Olsen et al. [126]	105	3 weeks DB, para	Loratadine (10 mg) = terfenadine (120 mg)
Caiaffa et al. [127]	142	1 week DB, DD, para	Cetirizine (10 mg) = terfenadine (120 mg)
Davies [128]	487	16 days DB, para	Cetirizine (10 mg) = terfenadine (120 mg)
Katellaris [129]	28	2 weeks DB, para	Loratadine (10 mg) = azatadine (2 mg)
Backhouse et al. [130]	285	1 week DB, DD, para	Cetirizine (10 mg) = terfenadine (120 mg)
Rijntjes et al. [131]	105	2 weeks DB, para/X	Cetirizine (10 mg) > astemizole (10 mg)
Davies et al. [132]	487	8 weeks DB, DD, para	Cetirizine (10 mg) = terfenadine (120 mg)
Backhouse and Rosenberg [133]	121	6 weeks DB, DD, para	Terfenadine (120 mg) = chlorpheniramine (12 mg)
<i>CIU – PC</i>			
Morita et al. [134]	10	4 weeks DB, X, PC	Cetirizine (10 mg) = olopatadine (5 mg) > placebo
Dubertret et al. [135]	247	4 weeks DB, para, PC	Loratadine (10 mg) = mizolastine (10 mg) > placebo
Breneman [136]	188	4 weeks DB, DD, para, PC	Cetirizine (10 mg) = hydroxyzine (75 mg) > placebo
Belaich et al. [137]	180	4 weeks DB, para, PC	Loratadine (10 mg) = terfenadine (120 mg) > placebo

Table 2. Continued

Reference	# of patients randomized	Trial: duration and type	Primary efficacy outcome
Grant et al. [138]	136	6 weeks DB, para, PC	Terfenadine (120 mg) > chlorpheniramine (12 mg) Terfenadine > placebo Chlorpheniramine = placebo
<i>CIU – non-PC</i>			
Handa et al. [139]	116	4 weeks DB	Cetirizine (10 mg) > fexofenadine (180 mg)
La Rosa et al. [140]	62	4 weeks DB	Cetirizine (5 mg) $\geq$ oxatomide (25 mg)
Leynardier et al. [82]	61	4 weeks DB, para	Loratadine (10 mg) = mizolastine (10 mg)
Alomar et al. [141]	47	4 weeks DB, para	Cetirizine (10 mg) $\geq$ astemizole (10 mg)

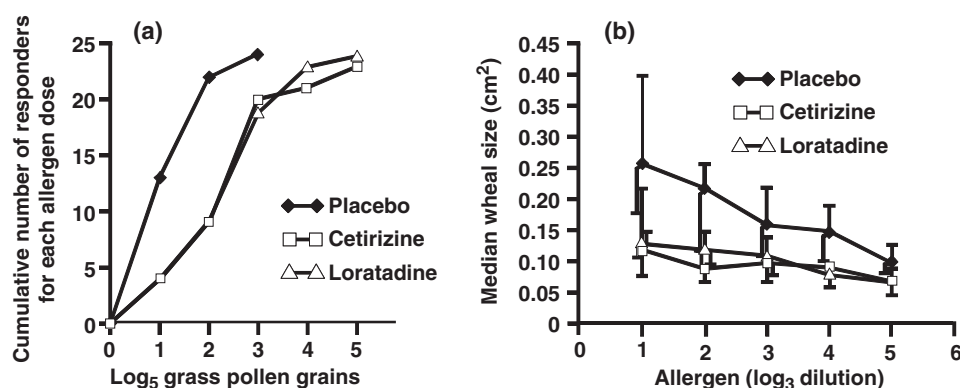


Fig. 1. Similarity of nasal (a) and skin (b) responses to allergen challenge in patients with allergic rhinitis receiving cetirizine or loratadine [76]. Copyright 1999, with permission from the American Academy of Allergy Asthma & Immunology.

of histamine H₁-receptor blockade. Histamine-induced skin reactions, as well as allergen-induced reactions, are also useful to assess the washout period required after cessation of antihistamine treatment for correct allergy skin testing [51]. In addition to these roles, however, histamine-induced weal and flare is often applied to the comparison of antihistamines for the purpose of attributing greater clinical efficacy to one compound over another. Pharmacological tests of antihistamine potency, such as the histamine-induced weal and flare, should be distinguished from tests of clinical efficacy as they do not mirror one another in terms of fundamental methodology. Differences in antihistaminic potency, whether measured as weal and flare inhibition or as *in vitro* H₁ receptor antagonism, do not directly translate into the clinical realm. In reality, multiple intervening factors including dose, metabolism, duration of treatment, and fundamental disease pathophysiology play vital roles in determining the true clinical efficacy of an antihistamine. The implication that an agent that provides greater suppression of skin reactivity to histamine would be expected to provide greater clinical efficacy is invalid. This systematic review indicates that a superior effect in terms of the histamine-

induced weal and flare pharmacodynamic response does not translate into similar efficacy in studies of patients with clinically active disease.

The results of this systematic review echo the findings of the very few studies that have been performed prospectively to assess both histamine-induced weal and flare and allergen-induced weal and flare suppression with various antihistamines and their subsequent clinical activity during the allergy season [76, 77]. For instance, Persi et al. [76] demonstrated that H₁-antihistamine effects differ according to whether the skin or nasal mucosa was challenged. In that placebo-controlled study, patients ($n = 22$) who received 7 days' treatment with either loratadine or cetirizine underwent nasal pollen challenge and pollen/histamine skin tests. Both drugs improved skin and nasal responses to pollen challenge as compared with placebo (Fig. 1). Only in terms of histamine-induced weal and flare was a difference noted that favoured cetirizine. In another double-blind, placebo-controlled, parallel-group study, Bousquet et al. [77] compared the effects of loratadine and astemizole treatment for 7 days on clinical symptoms of allergy in SAR patients during the pollen season. The responses of patients to skin testing with

pollen and the histamine-induced weal and flare response were also assessed. While both loratadine and astemizole significantly decreased allergic symptoms from baseline, the histamine-induced weal and flare and allergen-induced cutaneous responses were suppressed with a greater magnitude with astemizole. On the basis of these studies, it can be concluded that skin-test reactivity – in particular the histamine-induced weal and flare – may have an entirely different profile among second-generation antihistamines as compared with clinical control of symptoms following everyday exposure to allergens. It may be that regular administration of antihistamines in the clinical setting is sufficient to suppress histamine that is generated endogenously by activated mast cells and other sources, although experimental evidence to support this suggestion is lacking.

Furthermore, histamine-induced weal and flare skin studies appear to have no predictive value for determining the clinical superiority of one antihistamine over another in the field of CIU. The discrepancies between effects on histamine-induced weal and flare reactions and clinical efficacy could be due to several factors, including differences in the mechanisms of reactions caused by histamine or allergen, the use of supra-physiological histamine concentrations during skin testing, and the inability of histamine-induced weal and flare to model the effects of other allergic mediators, such as eicosanoids and inflammatory cytokines. Taken together, these results suggest that histamine-induced weal and flare testing should remain a standard pharmacodynamic tool for the study of antihistamines, but that the clinical superiority of one agent over another should be determined on the basis of more clinically relevant end-points.

References

- Salib RJ, Drake-Lee A, Howarth PH. Allergic rhinitis: past, present and the future. *Clin Otolaryngol* 2003; 28:291–303.
- Bousquet J, Neukirch F, Bousquet PJ *et al.* Severity and impairment of allergic rhinitis in patients consulting in primary care. *J Allergy Clin Immunol* 2006; 117:158–62.
- Dykewicz MS, Fineman S, Skoner DP *et al.* Diagnosis and management of rhinitis: complete guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. *Ann Allergy Asthma Immunol* 1998; 81:478–518.
- Leynaert B, Neukirch C, Liard R, Bousquet J, Neukirch F. Quality of life in allergic rhinitis and asthma: a population-based study of young adults. *Am J Respir Crit Care Med* 2000; 162:1391–6.
- European Academy of Allergology and Clinical Immunology. The impact of allergic rhinitis on quality of life and other airway diseases. Summary of a European conference. *Allergy* 1998; 53 (Suppl. 41):7–31.
- Reed SD, Lee TA, McCrory DC. The economic burden of allergic rhinitis: a critical evaluation of the literature. *Pharmacoeconomics* 2004; 22:345–61.
- Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001; 108 (Suppl.):S147–S334.
- Baiardini I, Pasquali M, Braidò F *et al.* A new tool to evaluate the impact of chronic urticaria on quality of life: chronic urticaria quality of life questionnaire (CU-Q2oL). *Allergy* 2005; 60:1073–8.
- O'Donnell BF, Lawlor F, Simpson J, Morgan M, Greaves MW. The impact of chronic urticaria on the quality of life. *Br J Dermatol* 1997; 136:197–201.
- Greaves M. Chronic urticaria. *J Allergy Clinical Immunol* 2000; 105:664–72.
- Baroody FM. Allergic rhinitis: broader disease effects and implications for management. *Otolaryngol Head Neck Surg* 2003; 128:616–31.
- Lee B-J, Naclerio RM, Bochner BS, Taylor RM, Lin MC, Baroody FM. Nasal challenge with allergen upregulates the local expression of vascular endothelial adhesion molecules. *J Allergy Clin Immunol* 1999; 94:1006–16.
- D'Andrea MR, Derian CK, Leturcq D *et al.* Characterization of protease-activated receptor-2 immunoreactivity in normal human tissues. *J Histochem Cytochem* 1998; 46:157–64.
- Bez C, Schubert R, Kopp M *et al.* Effect of anti-immunoglobulin E on nasal inflammation in patients with seasonal allergic rhinoconjunctivitis. *Clin Exp Allergy* 2004; 34:1079–85.
- Rauter I, Krauth M-T, Flicker S *et al.* Allergen cleavage by effector cell-derived protease regulates allergic inflammation. *FASEB J* 2006; 20:E61–9.
- Zuberbier T, Bindslev-Jensen C, Canonica W *et al.* EAACI/GA²LEN/EDF guidelines: management of urticaria. *Allergy* 2006; 61:321–31.
- Bousquet J, Bindslev-Jensen C, Canonica GW *et al.* The ARIA/EAACI criteria for antihistamines: an assessment of the efficacy, safety and pharmacology of desloratadine. *Allergy* 2004; 59 (Suppl. 77):4–16.
- Monroe EW, Daly AF, Shalhoub RF. Appraisal of the validity of histamine-induced wheal and flare to predict the clinical efficacy of antihistamines. *J Allergy Clin Immunol* 1997; 99:S798–806.
- Petersen LJ, Church MK, Rihoux JP, Skov PS. Measurement of interstitial cetirizine concentrations in human skin: correlation of drug levels with inhibition of histamine-induced skin responses. *Allergy* 1999; 54:607–11.
- Simons FER, Murray HE, Simons KJ. Quantitation of H₁-receptor antagonists in skin and serum. *J Allergy Clin Immunol* 1995; 95:759–64.
- Deschamps C, Dubruc C, Mentre F, Rosenzweig P. Pharmacokinetic and pharmacodynamic modeling of mizolastine in healthy volunteers with an indirect response model. *Clin Pharmacol Ther* 2000; 68:647–57.
- Howarth PH. Assessment of antihistamine efficacy and potency. *Clin Exp Allergy* 1999; 29 (Suppl. 3):87–97.
- Magerl W, Westerman RA, Mohner B, Handwerker HO. Properties of transdermal histamine iontophoresis: differential effects of season, gender, and body region. *J Invest Dermatol* 1990; 94:347–52.
- Schmelz M, Luz O, Averbach B, Bickel A. Plasma extravasation and neuropeptide release in human skin as measured by intradermal microdialysis. *Neurosci Lett* 1997; 230:117–20.

- 25 Petersen LJ, Church MK, Skov PS. Histamine is released in the wheal but not the flare following challenge of human skin in vivo: a microdialysis study. *Clin Exp Allergy* 1997; 27:284–95.
- 26 Demoly P, Bousquet J, Manderscheid J-C, Dreborg S, Dhivert H, Michel F-B. Precision of skin prick and puncture tests with nine methods. *J Allergy Clin Immunol* 1991; 88:758–62.
- 27 De Weck AL, Derer T, Bähre M. Investigation of the anti-allergic activity of azelastine on the immediate and late-phase reactions to allergens and histamine using telethermography. *Clin Exp Allergy* 2000; 30:283–7.
- 28 Hammarlund A, Olsson P, Pipkorn U. Blood flow in dermal allergen-induced immediate and late-phase reactions. *Clin Exp Allergy* 1989; 19:197–202.
- 29 Olsson P, Hammarlund A, Pipkorn U. Wheal-and-flare reactions induced by allergen and histamine: evaluation of blood flow with laser Doppler flowmetry. *J Allergy Clin Immunol* 1988; 82:291–6.
- 30 Hammarlund A, Olsson P, Pipkorn U. Blood flow in histamine- and allergen-induced wheal and flare responses, effects of an H1 antagonist, alpha-adrenoceptor agonist and a topical glucocorticoid. *Allergy* 1990; 45:64–70.
- 31 Carr WW, Martin B, Howard RS, Cox L, Borish Land the Immunotherapy Committee of the American Academy of Allergy, Asthma and Immunology. Comparison of test devices for skin prick testing. *J Allergy Clin Immunol* 2005; 116: 341–6.
- 32 Nelson HS, Knoetzer J, Bucher B. Effect of distance between sites and region of the body on results of skin prick tests. *J Allergy Clin Immunol* 1996; 97:596–601.
- 33 Kalogeromitros D, Katsarou A, Armenaka M, Rigopoulos D, Zapanti M, Stratigos I. Influence of the menstrual cycle on skin-prick test reactions to histamine, morphine and allergen. *Clin Exp Allergy* 1995; 25:461–6.
- 34 Lee RE, Smolensky MH, Leach CS, McGovern JP. Circadian rhythms in the cutaneous reactivity to histamine and selected antigens, including phase relationship to urinary cortisol excretion. *Ann Allergy* 1977; 38:231–6.
- 35 Haahtela T, Jokela H. Influence of the pollen season on immediate skin test reactivity to common allergens. *Allergy* 1980; 35:15–21.
- 36 Spiewak R. Inter-individual and intra-individual variability of skin reactivity to histamine at prick testing. *Dermatol Online J* 1995; 1:4.
- 37 Carey W, Warrington S, Boyce M, Luria X. Inhibition of the histamine wheal by ebastine compared with cetirizine, fexofenadine and loratadine at steady state. *Drugs Exp Clin Res* 2002; 28:243–7.
- 38 Clough GF, Boutsouki P, Church MK. Comparison of the effects of levocetirizine and loratadine on histamine-induced wheal, flare, and itch in human skin. *Allergy* 2001; 56:985–8.
- 39 Denham KJ, Boutsouki P, Clough GF, Church MK. Comparison of the effects of desloratadine and levocetirizine on histamine-induced wheal, flare and itch in human skin. *Inflamm Res* 2003; 52:424–7.
- 40 Roman IJ, Kassem N, Gural RP, Herron J. Suppression of histamine-induced wheal response by loratadine (SCH 29851) over 28 days in man. *Ann Allergy* 1986; 57:253–6.
- 41 Rosenzweig P, Caplain H, Chaufour S, Ulliac N, Cabanis MJ, Thebault JJ. Comparative wheal and flare study of mizolastine vs terfenadine, cetirizine, loratadine and placebo in healthy volunteers. *Br J Clin Pharmacol* 1995; 40:459–65.
- 42 Humphreys F, Hunter JA. The effects of astemizole, cetirizine and loratadine on the time course of wheal and flare reactions to histamine, codeine and antigen. *Br J Dermatol* 1991; 125:364–7.
- 43 Barbanj MJ, Antonijon RM, García-Gea C *et al.* A study comparing the inhibitory effects of single and repeated oral doses of ebastine and fexofenadine against histamine-induced skin reactivity. *Int Arch Allergy Immunol* 2003; 132:263–7.
- 44 Gispert J, Antonijon R, Barbanj M *et al.* Efficacy of ebastine, cetirizine, and loratadine in histamine cutaneous challenges. *Ann Allergy Asthma Immunol* 2002; 89:259–64.
- 45 Lever LR, Hill S, Marks R, Rosenberg R, Thompson D. Effects of cetirizine, loratadine and terfenadine on histamine wheal and flare reactions. *Skin Pharmacol* 1992; 5:29–33.
- 46 Pechadre JC, Vernay D, Trolese JF, Bloom M, Dupont P, Rihoux JP. Comparison of the central and peripheral effects of cetirizine and terfenadine. *Eur J Clin Pharmacol* 1988; 35:255–9.
- 47 Rihoux JP, Van Neste DJ. Quantitative time course study of the skin response to histamine and the effect of H1 blockers. A 3-week crossover double-blind comparative trial of cetirizine and terfenadine. *Dermatologica* 1989; 179:129–34.
- 48 Kontou-Fili K, Paleologos G, Herakleous M. Suppression of histamine-induced skin reactions by loratadine and cetirizine diHCl. *Eur J Clin Pharmacol* 1989; 36:617–9.
- 49 Turkeltaub PC, Rastogi SC, Baer H, Anderson MC, Norman PS. A standardized, quantitative skin-test assay of allergen potency and stability: studies on the allergen dose-response curve and effect of wheal, erythema, and patient selection on assay results. *J Allergy Clin Immunol* 1982; 70:343–52.
- 50 Squire JR. The relationship between horse dandruff and horse serum antigen in asthma. *Clin Sci* 1950; 9:127–50.
- 51 Frossard N, Benabdesselam O, Purohit A, Mounedji N, Pauli G. Activity of ebastine (10 and 20 mg) and cetirizine at 24 hours of a steady state treatment in the skin of healthy volunteers. *Fundam Clin Pharmacol* 2000; 14:409–13.
- 52 Purohit A, Mélac M, Pauli G, Frossard N. Comparative activity of cetirizine and mizolastine on histamine-induced skin wheal and flare responses at 24 h. *Br J Clin Pharmacol* 2002; 53:250–4.
- 53 Town GI, Holgate ST. Comparison of the effect of loratadine on the airway and skin responses to histamine, methacholine, and allergen in subjects with asthma. *J Allergy Clin Immunol* 1990; 86:886–93.
- 54 Devalia JL, Hanotte F, Baltes E, De Vos C. A randomized, double-blind, crossover comparison among cetirizine, levocetirizine, and ucb 28557 on histamine-induced cutaneous responses in healthy adult volunteers. *Allergy* 2001; 56:50–57.
- 55 Grant JA, Danielson L, Rihoux J-P, DeVos C. A double-blind, single-dose, crossover comparison of cetirizine, ebastine, epinastine, fexofenadine, terfenadine, and loratadine versus placebo: suppression of histamine-induced wheal and flare response for 24 h in healthy male subjects. *Allergy* 1999; 54:700–7.
- 56 Grant JA, Riethuisen J-M, Moulart B, DeVos C. A double-blind, randomized, single-dose, crossover comparison of levocetirizine with ebastine, fexofenadine, loratadine, mizolastine, and placebo: suppression of histamine-induced wheal-and-flare

- response during 24 hours in healthy male subjects. *Ann Allergy Asthma Immunol* 2002; **88**:190–7.
- 57 Hindmarch I, Johnson S, Meadows R, Kirkpatrick T, Shamsi Z. The acute and sub-chronic effects of levocetirizine, cetirizine, loratadine, promethazine and placebo on cognitive function, psychomotor performance, and weal and flare. *Curr Med Res Opin* 2001; **17**:241–55.
 - 58 Purohit A, Duvernelle C, M  lac M, Pauli G, Frossard N. Twenty-four hours of activity of cetirizine and fexofenadine in the skin. *Ann Allergy Asthma Immunol* 2001; **86**:387–92.
 - 59 Purohit A, M  lac M, Pauli G, Frossard N. Twenty-four-hour activity and consistency of activity of levocetirizine and desloratadine in the skin. *Br J Clin Pharmacol* 2003; **56**:388–94.
 - 60 Purohit A, M  lac M, Pauli G, Frossard N. Comparative activity of cetirizine and desloratadine on histamine-induced wheal-and-flare responses during 24 hours. *Ann Allergy Asthma Immunol* 2004; **92**:635–40.
 - 61 Purohit A, N'Gom AS, Deslandes B, Pauli G, Frossard N. Similar rapid onset of action and magnitude of effect of fexofenadine and cetirizine as assessed by inhibition of histamine-induced wheal-and-flare reaction. *Ann Allergy Asthma Immunol* 2004; **93**:562–7.
 - 62 Fadel R, Herpin-Richard N, Dufresne F, Rihoux JP. Pharmacological modulation by cetirizine and loratadine of antigen and histamine-induced skin weals and flares, and late accumulation of eosinophils. *J Int Med Res* 1990; **18**:366–71.
 - 63 Basomba A. Evaluation of changes in skin sensitivity by means of skin tests. EACCI '93 subcommittee on skin tests. *Allergy* 1993; **48**:71–75.
 - 64 Takahashi H, Ishida-Yamamoto A, Iizuka H. Effects of bepotastine, cetirizine, fexofenadine, and olopatadine on histamine-induced wheal-and flare-response, sedation, and psychomotor performance. *Clin Exp Dermatol* 2004; **29**:526–32.
 - 65 Wang RQ, Zhang HY. Comparative activity of antihistamines on area under dose-response curve from histamine-induced wheal and flare responses in human skin. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao* 2004; **26**:634–8.
 - 66 Kaliner MA, White MV, Economides A *et al.* Relative potency of fexofenadine HCl 180 mg, loratadine 10 mg, and placebo using a skin test model of wheal-and-flare suppression. *Ann Allergy Asthma Immunol* 2003; **90**:629–34.
 - 67 Shall L, Thompson DA, Barkley AS, Millard LG. Comparative inhibition profiles of three non-sedating antihistamines assessed by an extended Lewis model. *Clin Exp Allergy* 1992; **22**:711–6.
 - 68 Van Neste D, Coussement C, Ghys L, Rihoux JP. Agonist-antagonist interactions in the skin: comparison of effects of loratadine and cetirizine on skin vascular responses to prick tests with histamine and substance P. *J Dermatol Sci* 1992; **4**:172–9.
 - 69 Simons FE, McMillan JL, Simons KJ. A double-blind, single-dose, crossover comparison of cetirizine, terfenadine, loratadine, astemizole, and chlorpheniramine versus placebo: suppressive effects on histamine-induced wheals and flares during 24 hours in normal subjects. *J Allergy Clin Immunol* 1990; **86**:540–7.
 - 70 Bayramg  rl  r D, Bilen N, Apayd  n R *et al.* Effects of acrivastine, loratadine and cetirizine on histamine-induced wheal and flare responses. *Clin Exp Dermatol* 1999; **24**:407–11.
 - 71 Leroy T, Tasset C, Valentin B, Van Neste D. Comparison of the effects of cetirizine and ebastine on the skin response to histamine iontophoresis monitored with laser Doppler flowmetry. *Dermatology* 1998; **197**:146–51.
 - 72 Roongapinun S, Wajajamrean S, Fooanant S. Comparative efficacy of wheal-and-flare suppression among various non-sedating antihistamines and the pharmacologic insights to their efficacy. *J Med Assoc Thailand* 2004; **87**:551–6.
 - 73 Simons FER, Semus MJ, Goritz SS, Simons KJ. H₁-antihistaminic activity of cetirizine and fexofenadine in allergic children. *Pediatr Allergy Immunol* 2003; **14**:207–11.
 - 74 van Steekelenburg J, Clement PAR, Beel MHL. Comparison of five new antihistamines (H₁-receptor antagonists) in patients with allergic rhinitis using nasal provocation studies and skin tests. *Allergy* 2002; **57**:346–50.
 - 75 Simons FER, Johnston L, Simons KJ. Clinical pharmacology of the H₁-receptor antagonists cetirizine and loratadine in children. *Pediatr Allergy Immunol* 2000; **11**:116–9.
 - 76 Persi L, Demoly P, Harris AG, Tisserand B, Michel F-B, Bousquet J. Comparison between nasal provocation tests and skin tests in patients treated with loratadine and cetirizine. *J Allergy Clin Immunol* 1999; **103**:591–4.
 - 77 Bousquet J, Czarlewski W, Cougnard J, Danzig M, Michel FB. Changes in skin-test reactivity do not correlate with clinical efficacy of H₁-blockers in seasonal allergic rhinitis. *Allergy* 1998; **53**:579–85.
 - 78 Hamilton SA, Duddle J, Herdman MJ, Trigg CJ, Davies RJ. Comparison of a new antihistaminic and antiallergic compound KW 4679 with terfenadine and placebo on skin and nasal provocation in atopic individuals. *Clin Exp Allergy* 1994; **24**:955–9.
 - 79 Passalacqua G, Guerra L, Compalati E *et al.* Comparison of the effects in the nose and skin of a single dose of desloratadine and levocetirizine over 24 hours. *Int Arch Allergy Immunol* 2004; **135**:143–7.
 - 80 Sienna-Monge JJ, Gazca-Aguilar A, Del Rio-Navarro B. Double-blind comparison of cetirizine and loratadine in children ages 2 to 6 years with perennial allergic rhinitis. *Am J Ther* 1999; **6**:149–55.
 - 81 Berkowitz RB, Dockhorn R, Lockey R *et al.* Comparison of efficacy, safety, and skin test inhibition of cetirizine and astemizole. *Ann Allergy Asthma Immunol* 1996; **76**:363–8.
 - 82 Leynadier F, Duarte-Risselin C, Murrieta M, for the URTILOR Study Group. Comparative therapeutic effect and safety of mizolastine and loratadine in chronic idiopathic urticaria. *Eur J Dermatol* 2000; **10**:205–11.
 - 83 Villas Martinez F, Contreras FJ, Lopez Cazana JM, Lopez Serrano MC, Martinez Alzamora F. A comparison of new non-sedating and classical antihistamines in the treatment of primary acquired cold urticaria (ACU). *J Invest Allergol Clin Immunol* 1992; **2**:258–62.
 - 84 Howarth PH, Salagean M, Dokic D. Allergic rhinitis: not purely a histamine-related disease. *Allergy* 2000; **55** (Suppl. 64):7–16.
 - 85 Charlesworth EN, Kagey-Sobotka A, Norman PS, Lichtenstein LM. Effect of cetirizine on mast cell-mediator release and cellular traffic during the cutaneous late-phase reaction. *J Allergy Clin Immunol* 1989; **83**:905–12.
 - 86 De Vos C. H₁ antagonists and inhibitors of eosinophil accumulation. *Clin Exp Allergy* 1991; **21** (Suppl. 1):277–81.

- 87 Walsh GM, Moqbel R, Hartnell A, Kay AB. Effects of cetirizine on human eosinophil and neutrophil activation in vitro. *Int Arch Allergy Appl Immunol* 1991; 95:158–62.
- 88 Klementsson H, Andersson M, Pipkorn U. Allergen-induced increase in nonspecific nasal reactivity is blocked by antihistamines without a clear-cut relationship to eosinophil influx. *J Allergy Clin Immunol* 1990; 86:466–72.
- 89 Raphael GD, Angello JT, Wu M-M, Druce HM. Efficacy of diphenhydramine vs desloratadine and placebo in patients with moderate-to-severe seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 2006; 96:606–14.
- 90 Ciprandi G, Cirillo I, Vizzaccaro A *et al.* Desloratadine and levocetirizine improve nasal symptoms, airflow, and allergic inflammation in patients with perennial allergic rhinitis: a pilot study. *Int Immunopharmacol* 2005; 5:1800–8.
- 91 Hyo S, Fujieda S, Kawada R, Kitazawa S, Takenaka H. The efficacy of short-term administration of 3 antihistamines vs placebo under natural exposure to Japanese cedar pollen. *Ann Allergy Asthma Immunol* 2005; 94:457–64.
- 92 Stübner P, Ziegelmayer R, Horak F. A direct comparison of the efficacy of antihistamines in SAR and PAR: randomised, placebo-controlled studies with levocetirizine and loratadine using an environmental exposure unit – the Vienna Challenge Chamber (VCC). *Curr Med Res Opin* 2004; 20:891–902.
- 93 Hampel F Jr, Howland W III, Van Bavel J, Ratner P. A randomized, double-blind, placebo-controlled study comparing the efficacy and safety of ebastine (20 mg and 10 mg) to loratadine 10 mg once daily in the treatment of seasonal allergic rhinitis. *J Invest Allergol Clin Immunol* 2004; 14:56–63.
- 94 Ratner P, Hampel F Jr, Van Bavel J, Howland W III. Efficacy and safety of ebastine 20 mg compared to loratadine 10 mg once daily in the treatment of seasonal allergic rhinitis: a randomized, double-blind, placebo-controlled study. *Int Arch Allergy Immunol* 2004; 133:371–9.
- 95 Crampton HJ. Comparison of ketotifen fumarate ophthalmic solution alone, desloratadine alone, and their combination for inhibition of the signs and symptoms of seasonal allergic rhinoconjunctivitis in the conjunctival allergen challenge model: a double-masked, placebo- and active-controlled trial. *Clin Ther* 2003; 25:1975–87.
- 96 Wilson AM, Haggart K, Sims EJ, Lipworth BJ. Effects of fexofenadine and desloratadine on subjective and objective measures of nasal congestion in seasonal allergic rhinitis. *Clin Exp Allergy* 2002; 32:1504–9.
- 97 Frèche C, Leynadier F, Horak F *et al.* Mizolastine provides effective symptom relief in patients suffering from perennial allergic rhinitis: a double-blind, placebo-controlled study versus loratadine. *Ann Allergy Asthma Immunol* 2002; 89:304–10.
- 98 Ratner PH, Lim JC, Georges GC, and the Ebastine Study Group. Comparison of once-daily ebastine 20 mg, ebastine 10 mg, loratadine 10 mg, and placebo in the treatment of seasonal allergic rhinitis. *J Allergy Clin Immunol* 2000; 105:1101–7.
- 99 Nunes C, Ladeira S. Double-blind study of cetirizine and loratadine versus placebo in patients with allergic rhinitis. *Invest Allergol Clin Immunol* 2000; 10:20–23.
- 100 van Cauwenberge P, Juniper EF, and the STAR Study Investigating Group. Comparison of the efficacy, safety and quality of life provided by fexofenadine hydrochloride 120 mg, loratadine 10 mg and placebo administered once daily for the treatment of seasonal allergic rhinitis. *Clin Exp Allergy* 2000; 30:891–9.
- 101 Howarth PH, Stern MA, Roi L, Reynolds R, Bousquet J. Double-blind, placebo-controlled study comparing the efficacy and safety of fexofenadine hydrochloride (120 and 180 mg once daily) and cetirizine in seasonal allergic rhinitis. *J Allergy Clin Immunol* 1999; 104:927–33.
- 102 Sabbah A, Daele J, Wade AG, Ben-Soussen P, Attali P, and the MIZOCET Study Group. Comparison of the efficacy, safety, and onset of action of mizolastine, cetirizine, and placebo in the management of seasonal allergic rhinoconjunctivitis. *Ann Allergy Asthma Immunol* 1999; 83:319–25.
- 103 Druce HM, Thoden WR, Mure P *et al.* Brompheniramine, loratadine, and placebo in allergic rhinitis: a placebo-controlled comparative clinical trial. *J Clin Pharmacol* 1998; 38:382–9.
- 104 Lockey RF, Widlitz MD, Mitchell DQ *et al.* Comparative study of cetirizine and terfenadine versus placebo in the symptomatic management of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 1996; 76:448–54.
- 105 Del Carpio J, Kabbash L, Turenne Y *et al.* Efficacy and safety of loratadine (10 mg once daily), terfenadine (60 mg twice daily), and placebo in the treatment of seasonal allergic rhinitis. *J Allergy Clin Immunol* 1989; 84:741–6.
- 106 Horak F, Bruttman G, Pedrali P *et al.* A multicentric study of loratadine, terfenadine and placebo in patients with seasonal allergic rhinitis. *Arzneimittelforschung* 1988; 38:124–8.
- 107 Skassia-Brociek W, Bousquet J, Montes F *et al.* Double-blind placebo-controlled study of loratadine, mequitazine, and placebo on the symptomatic treatment of seasonal allergic rhinitis. *J Allergy Clin Immunol* 1988; 81:725–30.
- 108 Buckley CE, Buchman E, Falliers CJ *et al.* Terfenadine treatment of fall hay fever. *Ann Allergy* 1988; 60:123–8.
- 109 Oei HD. Double-blind comparison of loratadine (SCH 29851), astemizole, and placebo in hay fever with special regard to onset of action. *Ann Allergy* 1988; 61:436–9.
- 110 Dockhorn RJ, Bergner A, Connell JT *et al.* Safety and efficacy of loratadine (Sch-29851): a new non-sedating antihistamine in seasonal allergic rhinitis. *Ann Allergy* 1987; 58:407–11.
- 111 Kemp JP, Bahna SL, Chervinsky P *et al.* A comparison of loratadine, a new nonsedating antihistamine, with clemastine and placebo in patients with fall seasonal allergic rhinitis. *Am J Rhinol* 1987; 1:151–4.
- 112 Kemp JP, Buckley CE, Gershwin ME *et al.* Multicenter, double-blind, placebo-controlled trial of terfenadine in seasonal allergic rhinitis and conjunctivitis. *Ann Allergy* 1985; 54:502–9.
- 113 Corren J, Storms W, for the Azelastine Cetirizine Trial No. 1 (ACT 1) Study Group. *et al.* Effectiveness of azelastine nasal spray compared with oral cetirizine in patients with seasonal allergic rhinitis. *Clin Ther* 2005; 27:543–53.
- 114 Martinez-Cócerca C, De Molina M, on behalf of the Spanish Rupatadine Rhinitis Study Group. *et al.* Rupatadine 10 mg and cetirizine 10 mg in seasonal allergic rhinitis: a randomised, double-blind parallel study. *J Invest Allergol Clin Immunol* 2005; 15:22–29.
- 115 Horak F, Stübner P, Ziegelmayer R *et al.* Clinical study of the therapeutic efficacy of emedastine difumarate versus cetirizine in the treatment of seasonal allergic rhinitis. *Arzneimittelforschung* 2004; 54:666–72.

- 116 Saint-Martin F, Dumer JP, Pérez I, Izquierdo I. A randomized, double-blind, parallel-group study, comparing the efficacy and safety of rupatadine (20 and 10 mg), a new PAF and H₁ receptor-specific histamine antagonist, to loratadine 10 mg in the treatment of seasonal allergic rhinitis. *J Invest Allergol Clin Immunol* 2004; **14**:34–40.
- 117 Hampel F, Ratner P, Mansfield L, Meeves S, Liao Y, Georges G. Fexofenadine hydrochloride, 180 mg, exhibits equivalent efficacy to cetirizine, 10 mg, with less drowsiness in patients with moderate-to-severe seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 2003; **91**:354–61.
- 118 Prenner BM, Capano D, Harris AG. Efficacy and tolerability of loratadine versus fexofenadine in the treatment of seasonal allergic rhinitis: a double-blind comparison with crossover treatment of nonresponders. *Clin Ther* 2000; **22**:760–9.
- 119 Murris-Espin M, Melac M, Charpentier J-C, Didier A. Comparison of efficacy and safety of cetirizine and ebastine in patients with perennial allergic rhinitis. *Ann Allergy Asthma Immunol* 1998; **80**:399–403.
- 120 Crawford WW, Klaustermeyer WB, Lee PH, Placik IM. Comparative efficacy of terfenadine, loratadine, and astemizole in perennial allergic rhinitis. *Otolaryngol Head Neck Surg* 1998; **118**:668–73.
- 121 Al-Muhaimeed H. A parallel-group comparison of astemizole and loratadine for the treatment of perennial allergic rhinitis. *J Int Med Res* 1997; **25**:175–81.
- 122 Bellioni P, Catalano B, Cervellera G, Filiaci F, Mira E, Carraro A. Comparison of mizolastine with loratadine in the treatment of perennial allergic rhinitis. *Rhinology* 1996; **34**:101–4.
- 123 Gehanno P, Bremard-Oury C, Zeisser P. Comparison of ebastine to cetirizine in seasonal allergic rhinitis in adults. *Ann Allergy Asthma Immunol* 1996; **76**:507–12.
- 124 Harcup JW, Hawkes G, Saul PA. The efficacy and sedative profile of astemizole and cetirizine in the treatment of grass pollen hay fever in general practice. *Br J Clin Pract* 1993; **47**:131–5.
- 125 Lockey RF, Findley S, Mitchell DQ, Woehler T, Lieberman P, Nicodemus CF. Effects of cetirizine versus terfenadine in seasonal allergic rhinitis. *Ann Allergy* 1993; **70**:311–5.
- 126 Olsen OT, Nüchel Petersen L, Høi L, Lorentzen KA, Hindberg Rasmussen W, Svendsen UG. Comparison of loratadine and terfenadine in allergic seasonal rhinoconjunctivitis with emphasis on nasal stuffiness and peak flow. *Arzneimittelforschung* 1992; **42**:1227–31.
- 127 Caiaffa MF, Iudice A, Macchia L *et al.* Multicenter double-blind comparative study of terfenadine and cetirizine in hay fever. *J Invest Allergol Clin Immunol* 1992; **2**:162–6.
- 128 Davies BH. Prophylactic treatment of seasonal allergic rhinitis. *Clin Ther* 1991; **13**:87–91.
- 129 Katelaris C. Comparative effects of loratadine and azatadine in the treatment of seasonal allergic rhinitis. *Asian Pacific J Allergy Immunol* 1990; **8**:103–7.
- 130 Backhouse CI, Renton R, Fidler C, Rosenberg RM. Multicentre double-blind comparison of terfenadine and cetirizine in patients with seasonal allergic rhinitis. *Br J Clin Pract* 1990; **44**:88–91.
- 131 Rijntjes E, Ghys L, Rihoux J-P. Astemizole and cetirizine in the treatment of seasonal allergic rhinitis: a comparative double-blind, multicentre study. *J Int Med Res* 1990; **18**:219–24.
- 132 Davies BH, Mullins J, Couch HA. Prophylactic treatment of seasonal allergic rhinitis. A comparison of cetirizine (Zirtek) and terfenadine (Triludan). *Clin Trials J* 1989; **26**:100–7.
- 133 Backhouse CI, Rosenberg R. Prophylaxis of whole season hay fever symptomatology: a comparison of terfenadine with chlorpheniramine. *Br J Clin Pract* 1987; **41**:995–9.
- 134 Morita E, Matsuo H, Zhang Y. Double-blind, crossover comparison of olopatadine and cetirizine *versus* placebo: suppressive effects on skin response to histamine iontophoresis. *J Dermatol* 2005; **32**:58–61.
- 135 Dubertret L, Murrieta Aguttes M, Tonet J, and the MILOR Study Group. Efficacy and safety of mizolastine 10 mg in a placebo-controlled comparison with loratadine in chronic idiopathic urticaria: results of the MILOR study. *J Eur Acad Dermatol Venerol* 1999; **12**:16–24.
- 136 Breneman DL. Cetirizine versus hydroxyzine and placebo in chronic idiopathic urticaria. *Ann Pharmacother* 1996; **30**:1075–9.
- 137 Belaich S, Bruttman G, DeGreef H *et al.* Comparative effects of loratadine and terfenadine in the treatment of chronic idiopathic urticaria. *Ann Allergy* 1990; **64**:191–4.
- 138 Grant JA, Bernstein DI, Buckley CE *et al.* Double blind comparison of terfenadine, chlorpheniramine, and placebo in the treatment of chronic idiopathic urticaria. *J Allergy Clin Immunol* 1988; **81**:574–9.
- 139 Handa S, Dogra S, Kumar B. Comparative efficacy of cetirizine and fexofenadine in the treatment of chronic idiopathic urticaria. *J Dermatol Treat* 2004; **15**:55–57.
- 140 La Rosa M, Leonardi S, Marchese G *et al.* Double-blind multicenter study on the efficacy and tolerability of cetirizine compared with oxatomide in chronic idiopathic urticaria in preschool children. *Ann Allergy Asthma Immunol* 2001; **87**:48–53.
- 141 Alomar A, De La Cuarda J, Fernandez J. Cetirizine vs astemizole in the treatment of chronic idiopathic urticaria. *J Int Med Res* 1990; **18**:358–65.
- 142 Plaut M, Valentine MD. Clinical practice. Allergic rhinitis. *N Engl J Med* 2005; **353**:1934–44.