

Duration of the inhibitory activity on histamine-induced skin weals of sedative and non-sedative antihistamines

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The inhibitory effect of orally administered dexchlorfeniramine (4 mg/day), cyproheptadine (8 mg/day), astemizole (20 mg/day), loratadine (40 mg/day) and terfenadine (120 mg/day) on the size of histamine-induced weals was tested by skin prick test with histamine in an open study including 23 healthy individuals. The antihistamines were administered for 2 days in the nationally recommended therapeutic doses. For all drugs the maximal weal suppression with the dosage chosen was recorded the day after the last dosage, being 29% (for dexchlorfeniramine), 72% (for cyproheptadine), 50% (for astemizole), 62% (for loratadine), and 56% (for terfenadine) of the baseline value. For the drugs in the same order the duration of the inhibitory effect of the drugs after the last dose administered was between 3-4, 7-11, 17-28, 4-7, and 4-7 days, respectively.

Key words: antihistamines; histamine-induced skin weals, inhibition of.

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Skin testing is used in the routine for diagnosing atopic diseases. A common clinical problem is that the patients have been ingesting antihistamines before having skin tests performed. The suppressive effect on the histamine-induced weal- and flare-response is well-known, and for traditional antihistamines it is generally believed to last for up to 1 week (2, 3). As this aspect is unexamined in several new, non-sedating antihistamines, the purpose of this study was to examine the duration of the suppressive effect of five antihistamines on the histamine-induced weal response, including three new, non-sedating histamine antagonists, all orally administered for 2 days.

MATERIAL AND METHODS

Twenty-three healthy subjects (18 women and 5 men) entered and completed the study. All had a well-known measurable skin reaction to histamine by prick test (SPT), and no reaction to the diluent alone (negative control).

Histamine dihydrochloride dissolved in glycerol diluent (glycerol 50%, sterile water 50%) was used in the concentrations 3, 10, 30 and 100 mg/ml.

Medication

The following five drugs and daily dosages were used: dexchlorfeniramine (Polaramin®, Schering Corp.) 2 mg × 2, cyproheptadine (Periac-tin®, Merck, Sharp & Dome) 4 mg × 2, astemizole (Hismanal®, Janssen Pharmaceutica Inc.) 10 mg × 2, loratadine (Essex, Schering Corp.) 10 mg × 4, and terfenadine (Tel-danex®, Draco AB, Sweden) 60 mg × 2. The daily dosages are those recommended in Denmark.

Skin prick test (SPT)

SPT was performed four-fold on the volar site of both forearms, approximately 5 cm below the

elbow flexure to about 5 cm above the wrist. Drops for histamine were placed in straight lines and the same sites for SPT were never used 2 days in succession. One mm precision needles ("The allergy pricker", Dome/Hollister-Stier (10, 12)) were jabbed through the drops at a 90° angle to the skin, and the drops wiped off. Weals were recorded after 10 min, outlined with a ballpen, and transferred to transparent tape as permanent records. The weal area was measured in mm², using electronic planimetry (Hewlett Packard 9111 A, graphic tablet interfaced to Hewlett-Packard 85).

Study design

Each drug was tested in 10 subjects, implying that each of the 23 subjects was tested with 2-3 drugs. In each test the total daily dosage was taken in the evening on 2 consecutive days (days 0 and 1). SPT were performed in the morning before the first dosage on day 0 (baseline), and on each of the following 4 days (days 1, 2, 3, and 4), on days 7, 11, 17, and 28. To exclude the possibility of a carry-over effect, at least 2 weeks were allowed to pass after skin reactions had returned to baseline before the subjects were tested with another drug. The weal area after SPT with both 3, 10, 30 and 100 mg of histamine dihydrochloride/ml glycerol diluent was measured on the above-mentioned days. The reactions were not regarded as normal until *all* the four skin reactions at each time (means of the values observed in the whole group) had returned to normal size (i.e. baseline ± 2 SD).

Statistics

Weal areas were stated in percentages of baseline, which implies a proportional model (i.e. weal areas compared by proportion (A/B) rather than by absolute differences (A-B)). Proportional models imply log transformation of data, and to eliminate problems with negative skin reactions (weal area of null) 1 mm² was added to all weal areas. In keeping with the proportional model, data from all subjects were

pooled at each time and with each drug by geometric means. A 5% significance level was considered significant.

RESULTS

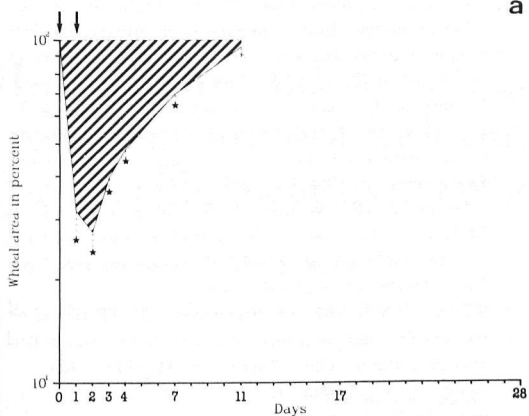
The results are summarized in Figs. 1 a-e showing the suppressions in per cent and standard error of the mean (SEM). For all five antihistamines the most pronounced inhibition was recorded on day 2, i.e. the day after cessation of antihistamine ingestion. With the administered doses, the maximal inhibitory effects of cyproheptadine on that day was 72% of the baseline value, loratadine 62%, terfenadine 56%, astemizole 50%, and dexchlorfeniramine 29%. No significant decrease in skin sensitivity to the histamine concentrations could be recorded on day 4 in the group receiving dexchlorfeniramine, on day 7 in the groups ingesting terfenadine and loratadine, on day 11 in those taking cyproheptadine, and on day 28 in the group taking astemizole.

DISCUSSION

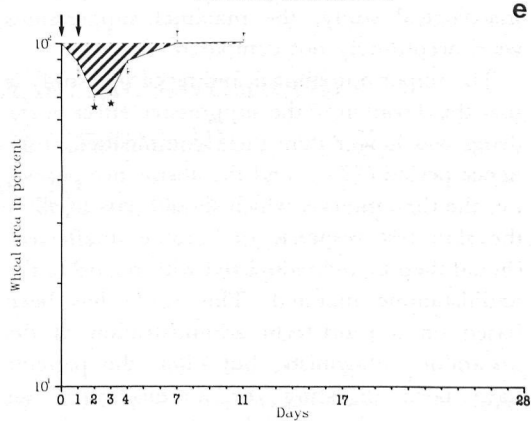
Five H₁-receptor antagonists astemizole, terfenadine, loratadine, dexchlorfeniramine, and cyproheptadine were tested. Others have studied the degree and duration of some of these antihistamines, and have presented comparable and similar results but only with some of the drugs (1, 3-9, 11). The present study is the first to investigate all the new non-sedating antihistamines.

The maximal suppression is evidently dependent on the dosage and the period of time allowed to pass before skin testing after ingestion. In the present study we wanted to investigate solely a clinical problem, viz. the length of time before skin reactivity returned to normal with four commonly used antihistamines, and a new one (loratadine), administered in the dose recommended. Accordingly, the maximal suppressions assessed in this study may not be the largest to be observed after 12 or 18 h. The present findings might illustrate a simple additive effect of the 2 days' treatment (maximal suppressive effect of *all* drugs the day after the

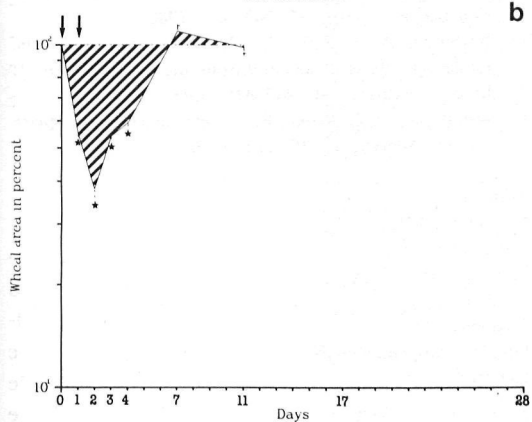
Cyproheptadine



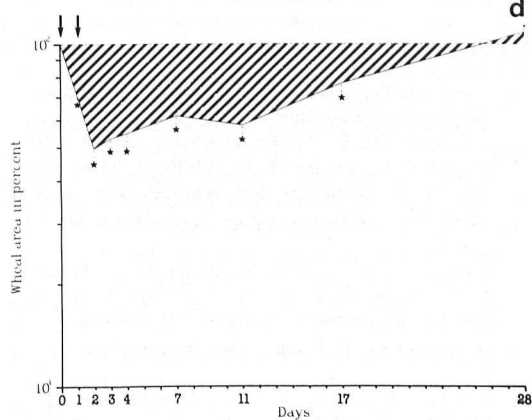
Dexchlorfeniramine



Loratadine



Astemizole



Terfenadine

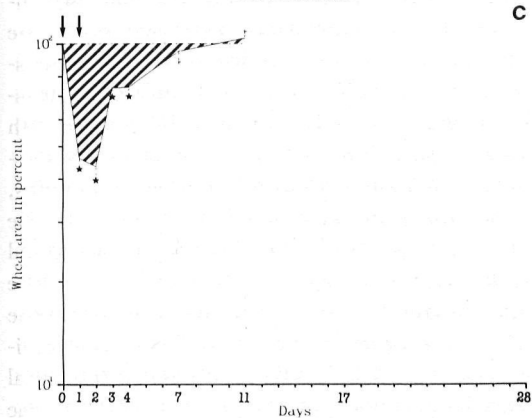


Fig. 1 a-e. Wheal size suppressions and standard error in the days following 2 days' ingestion of:

- a: Cyproheptadine (4 mg $\times$ 2 daily)
- b: Loratadine (10 mg $\times$ 4 daily)
- c: Terfenadine (60 mg $\times$ 2 daily)
- d: Astemizole (10 mg $\times$ 2 daily)
- e: Dexchlorfeniramine (2 mg $\times$ 2 daily).

second dosage). And, since this was not a pharmacological study, the maximal suppressions were accordingly not compared.

The important clinical finding of this study is that the duration of the suppressive effect of the drugs was longer than the recommended abstinence period (72 h), and the abstinence period, i.e. the time interval which should pass to allow the skin test response to become unaffected, should then be individualized with regard to the antihistamine ingested. This study has been based on a short-term administration of the histamine antagonists, but often the patients have been ingesting the antihistamines for weeks to months rather than days, and a future study of the cumulative drug effect on duration and degree of suppression therefore appears appropriate.

REFERENCES

1. Chapman, P. D. & Rawlins, M. D.: A randomized - blind study of astemizole and chlorpheniramine in normal volunteers. *Br. J. Clin. Pharmacol.* 13, 593, 1982.
2. Chipps, B. E., Talamo, R. C., Mellits, E. D. & Valentine, M. D.: Immediate (IgE-mediated) skin testing in the diagnosis of allergic disease. *Ann. Allergy* 41, 211-215, 1978.
3. Cook, T. J., MacQueen, M., Wittig, H. J., Thornby, J. I., Lantos, R. L. & Virtue, C. M.: Degree and duration of skin test suppression and side effects with antihistamines. *J. Allergy Clin. Immunol.* 51, 71-77, 1973.
4. Galant, S. P., Bullock, J., Wong, D. & Maibach, H. I.: The inhibitory effect of antiallergy drugs on allergen- and histamine-induced weal-and-flare response. *J. Allergy Clin. Immunol.* 51, 11-21, 1973.

5. Howarth, P. H., Emanuel, M. B. & Holgate, T.: Astemizole, a potent histamine H₁-receptor antagonist: effect in allergic rhinoconjunctivitis on antigen and histamine induced skin weal response and relationship to serum levels. *Br. J. Clin. Pharmacol.* 18, 1-8, 1984.
6. Hüther, K. J., Renftle, G., Barraud, N., Burke, J. T. & Koch-Weser, J.: Inhibitory activity of terfenadine on histamine-induced skin weals in man. *Eur. J. Clin. Pharmacol.* 12, 195-199, 1977.
7. Johnson, C. E., Weiner, J. S., Wagner, D. S. & McLean, J. A.: Effect on H₁- and H₂-receptor blockade on the inhibition of immediate cutaneous reactions. *Clin. Pharmacol* 3, 60-64, 1984.
8. Kjelman, N.-I. M. & Andersson, B.: Terfenadine reduces skin and conjunctival reactivity in grass pollen allergic children. *Clin. Allergy* 16, 441-449, 1986.
9. Long, W. F., Taylor, R. J., Wagner, C. J., Leavengood, D. C. & Nelson, H. S.: Skin test suppression by antihistamines and the development of subsensitivity. *J. Allergy Clin. Immunol.* 76, 113-117, 1984.
10. Malling, H.-J., Andersen, C. E., Boas, M.-B., Holgersen, F., Munch, E. P. & Weeke, B.: The Allergy prickler. Qualitative aspects of skin testing using a precision needle. *Allergy* 37, 563-567, 1982.
11. Reinberg, A. & Sidi, E.: Circadian changes in the inhibitory effects of an antihistaminic drug in man. *J. Invest. Dermatol.* 46, 415-419, 1966.
12. Østerballe, O. & Weeke, B.: A new lancet for skin prick testing. *Allergy* 34, 209-212, 1979.

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