

Effect in Man of Oral Terbutaline on Cutaneous Reactions Induced by Allergen and Cold Stimulation

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In eight atopic subjects wheal and flare responses to intradermally injected horse dander and histamine were determined after pretreatment with 5 mg oral terbutaline or placebo in a double-blind cross-over study. In each individual a dose of allergen was used that produced a flare reaction approximately the size of the ED₅₀ for histamine. Pretreatment with terbutaline was found to attenuate both the wheal and the flare reactions to allergen throughout the observation period of 150 min but only the effect on the wheal response reached statistical significance ($P < 0.01$). The responses to histamine were not influenced. In five subjects with cold urticaria, treatment with 2.5 mg terbutaline t.i.d. for a week had no effect on the time period of cold provocation needed to evoke an urticarial lesion.

It is concluded that oral treatment with terbutaline may produce an inhibitory action on allergen induced reactions but that this effect is not strong enough to interfere with clinical skin testing and hence the drug need not to be withdrawn prior to such testing.

Key words: β -adrenergic stimulant; allergen; cold stimulation; histamine; histamine release

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In a previous investigation it was shown that skin reactions induced by intradermally injected allergen were suppressed by pretreating the skin sites with terbutaline, a β_2 -adrenoceptor stimulating agent (2). In contrast, the responses elicited by histamine, the histamine liberator compound 48/80 and the proteolytic and histamine releasing enzyme trypsin were not influenced (flares) or only inconsistently (wheals) by terbutaline. It was suggested that pretreatment of the skin with terbutaline interferes with the ability of the cutaneous mast cells to respond to challenge with allergen.

The aim of the present study was to investigate whether the selective inhibitory action of terbutaline on the allergen induced response could be demonstrated following the

administration of a single oral dose of terbutaline. A few subjects with cold urticaria were included in the study to allow a preliminary evaluation of the effect of maintenance treatment with terbutaline on the cutaneous response to cold provocation.

PATIENTS AND METHODS

Cutaneous responses to allergen and histamine were studied in eight atopic subjects, aged 18-32 years, with a history of allergic rhinitis and/or bronchial asthma and with a positive skin test to horse dander. The majority of the patients also had a positive RAST test to horse dander. No participant exhibited dermographism or suffered from atopic dermatitis. A single oral dose of 5 mg terbutaline (Bricanyl®,

Draco, Lund, Sweden) and a placebo tablet, respectively, were administered to the atopic subjects on two occasions. No medication was allowed during the week preceding the study. Half of the subjects received terbutaline and the other half placebo as the first tablet. There was at least 1 week between the two tests.

Allergen (horse dander, Vitrum, Stockholm, Sweden) was given in a dose approximately corresponding to the ED_{50} for a histamine elicited flare reaction as previously determined. Allergen and histamine were injected using a micrometer syringe in a random fashion on the back before (control injections) and 30, 60, 90, 120 and 150 min after administration of terbutaline or placebo. The technique used for the injections and the measurements of the resulting flare and wheal responses have been described in detail elsewhere (2).

In order to minimize differences in day-to-day skin reactivity the two series of experiments were performed at approximately the same time of the day. Furthermore, neither terbutaline nor placebo were administered to atopic subjects until steady-state in heart rate, as measured every 10 min, was reached. The testing was performed with the subjects in the supine position.

The areas of the flare and wheal responses (mm^2) were outlined on transparent paper and later measured by planimetry 5 and 15 min after injection of allergen and histamine. The areas obtained before administration of tablets (control injections) were compared with the corresponding areas obtained after administration of tablets (expressed as per cent of control values). The effects of terbutaline and placebo were then compared for each individual and the differences were evaluated by four-way analysis of variance.

Five patients, aged 21–48 years, with cold urticaria since 1.5–40 years, were included in the study. Except for cold urticaria they were healthy and on no medication during the study. The cold sensitivity in each individual was assessed by gently pressing a number of wide test tubes (diameter 30 mm) containing

ice water against different sites of the abdominal skin and removing one tube every 30 s, as described by Illig (3). The shortest application time required to evoke a wheal reaction was found to vary from 1 to 20 min in the different subjects. The wheals appeared 2–6 min after removal of the tubes.

The patients were then given 2.5 mg terbutaline or placebo three times daily for 7 days according to a double-blind cross-over scheme with a drug-free period of at least 1 week between the two cross-over administrations. After each treatment period the shortest time required to produce an urticarial reaction was again determined by application of the tubes with ice water. In patient No. 3 with long provocation times, the application times were 15, 20, 25 and 30 min, see Table 1. The last tablet of terbutaline or placebo was taken about 2 h before the testing procedure.

RESULTS

Allergen induced reactions

The concentrations of allergen needed to produce flare reactions of a size similar to that produced by the ED_{50} for histamine varied between 10^{-11} and 10^{-6} w/v due to the differences in reactivity of the allergic subjects. When the test subjects were injected with allergen, pretreatment with a single oral dose of 5 mg terbutaline was found to produce a slight, but statistically significant, inhibition of the wheal response ($P < 0.01$). The flare response was also reduced but this effect did not reach statistical significance (Figs. 1 and 2). The inhibitory effect of terbutaline was demonstrable 30 min after administration of the drug and lasted throughout the observation period of 150 min. After placebo there was no inhibition of the skin response to allergen. In the placebo series the mean coefficient of variance for the allergen induced reactions (15 min values) was 12.8% (flare) and 20.9% (wheal), respectively, which may be considered an acceptable reproducibility.

The histamine induced responses were

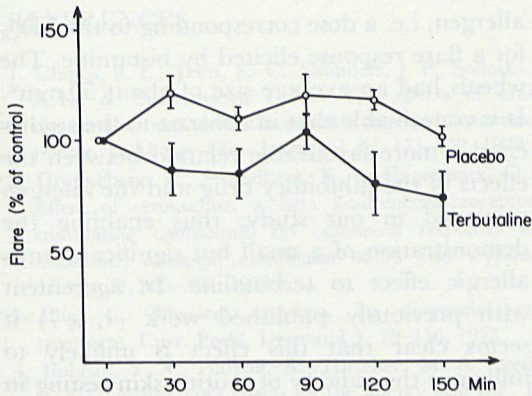


Fig. 1. Flare responses induced by allergen after oral terbutaline, 5 mg, or placebo. Allergen was injected 30, 60, 90, 120 and 150 min after administration of tablets (mean $\pm$ s.e.: $n = 8$). The flare areas were measured 15 min after injection of allergen.

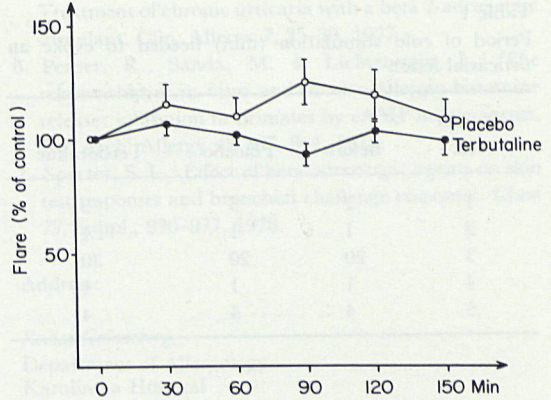


Fig. 3. Flare responses induced by histamine after oral terbutaline, 5 mg, or placebo. Histamine was injected 30, 60, 90, 120 and 150 min after administration of tablets (mean $\pm$ s.e.: $n = 8$). The flare areas were measured 15 min after injection of histamine.

influenced neither by terbutaline nor by placebo (Figs. 3 and 4). The mean coefficient of variance for the histamine induced responses (15-min values) was 13.2% and 32.1%, respectively. The lower reproducibility of the histamine induced wheal reaction in comparison with the allergen induced wheal is due to the 90-min response to histamine, which was inexplicably large.

The heart rate did not significantly differ between the two experimental series and no participant experienced tremor after terbutaline administration.

Cold urticaria

An oral regimen with 2.5 mg terbutaline three times daily for 7 days had no effect on the time

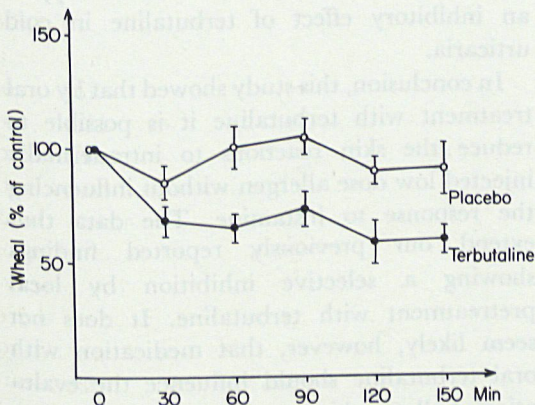


Fig. 2. Wheal responses induced by allergen after oral terbutaline, 5 mg, or placebo. Allergen was injected 30, 60, 90, 120 and 150 min after administration of tablets (mean $\pm$ s.e.: $n = 8$). The wheal areas were measured 15 min after injection of allergen.

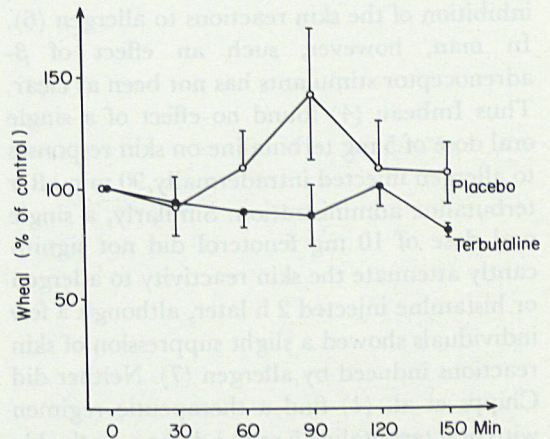


Fig. 4. Wheal responses induced by histamine after oral terbutaline, 5 mg, or placebo. Histamine was injected 30, 60, 90, 120 and 150 min after administration of tablets (mean $\pm$ s.e.: $n = 8$). The wheal areas were measured 15 min after injection of histamine.

Table 1

Period of cold stimulation (min) needed to evoke an urticarial lesion

Patient No.	Before	Placebo	Terbutaline
1	2	3	3
2	1	1	1
3	20	20	30
4	1	1	1
5	4	4	4

period of cold stimulation needed to evoke an urticarial lesion in the five patients with cold urticaria (Table 1). One of the patients (No. 4) was also given 5 mg terbutaline three times daily for 7 days without any influence on the test.

DISCUSSION

In the present investigation a therapeutically effective oral dose of terbutaline caused a slight reduction of the wheal response induced by allergen, whereas the suppression of the flare response was not statistically significant. Skin reactions to histamine were not influenced. In rhesus monkeys oral salbutamol (0.5 mg/kg) has been reported to produce a selective inhibition of the skin reactions to allergen (6). In man, however, such an effect of β -adrenoceptor stimulants has not been as clear. Thus Imbeau (4) found no effect of a single oral dose of 5 mg terbutaline on skin responses to allergen injected intradermally 90 min after terbutaline administration. Similarly, a single oral dose of 10 mg fenoterol did not significantly attenuate the skin reactivity to allergen or histamine injected 2 h later, although a few individuals showed a slight suppression of skin reactions induced by allergen (7). Neither did Chipps et al. (1) find a therapeutic regimen with oral terbutaline 5 mg t.i.d. for a week able to interfere with the skin response to allergen or histamine.

In this investigation we used a low dose of

allergen, i.e. a dose corresponding to the ED_{50} for a flare response elicited by histamine. The wheals had an average size of about 50 mm². It is conceivable that in contrast to the studies cited a more favourable relation between the effects of the inhibitory drug and the allergen prevailed in our study, thus enabling the demonstration of a small but significant anti-allergic effect to terbutaline. In agreement with previously published work (1, 4, 7) it seems clear that this effect is unlikely to influence the validity of routine skin testing in clinical allergology. More interestingly, however, our data indicate that systemic treatment with β -adrenoceptor stimulants carries the potential of a clinically important effect.

In a preliminary attempt to evaluate the effect of terbutaline on cold provocation in patients with cold urticaria five patients were given 2.5 mg terbutaline or placebo t.i.d. for a week prior to the test. The dose of terbutaline used was chosen for two reasons. Firstly, a 2.5-mg dosage was not expected to give rise to tremor or tachycardia with potential risk for loss of the controlled design of the study. Secondly, this dosage is comparable to a regimen of 1.25/mg t.i.d. which was reported to be successful in the treatment of patients with chronic urticaria (5). Although we are aware of the limited number of individuals included in our study the results do not support an inhibitory effect of terbutaline in cold urticaria.

In conclusion, this study showed that by oral treatment with terbutaline it is possible to reduce the skin reactions to intradermally injected low dose allergen without influencing the response to histamine. The data thus extend our previously reported findings showing a selective inhibition by local pretreatment with terbutaline. It does not seem likely, however, that medication with oral terbutaline should influence the evaluation of allergy skin tests in routine work when rather high allergen doses are used and accordingly the drug need not be withdrawn before skin testing.

REFERENCES

1. Chipps, B. E., Teets, K. C., Saunders, J. P., Sobotka, A. K. & Lichtenstein, L. M.: The effects of oral theophylline and terbutaline on skin tests and histamine release. *J. Allergy Clin. Immunol.* 61, 171-172, 1978.
2. Grönneberg, R., Strandberg, K. & Hägermark, Ö.: Effect of terbutaline, a beta 2-adrenergic receptor stimulating compound, on cutaneous responses to histamine, allergen, compound 48/80 and trypsin. *Allergy* 34, 303-309, 1979.
3. Illig, L.: Physical urticaria. Its diagnosis and treatment. *Curr. Probl. Dermatol* 5: 79-116, 1973.
4. Imbeau, S. A., Harruff, R., Hirscher, M. & Reed, C. E.: Terbutaline's effects on the allergy skin test. *J. Allergy Clin. Immunol.* 62, 193-196, 1978.
5. Kennes, B., de Maubeuge, J. & Delespesse, G.: Treatment of chronic urticaria with a beta 2-adrenergic stimulant. *Clin. Allergy* 7, 35-39, 1977.
6. Perper, R., Sanda, M. & Lichtenstein, L.: The relationship of in vitro and in vivo allergic histamine release: inhibition in primates by cAMP active agents. *Int. Arch. Allergy* 43, 837-844, 1972.
7. Spector, S. L.: Effect of beta-adrenergic agents on skin test responses and bronchial challenge responses. *Chest* 73, Suppl., 976-977, 1978.

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