

# The effect of astemizole on bronchial hyperresponsiveness and exercise-induced asthma in children

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The ability of the new generation H<sub>1</sub>-receptor antagonist, astemizole, to prevent histamine-induced airway obstruction and exercise-induced asthma (EIA) was studied in 20 children with asthma. The study was a randomised clinically controlled trial of oral astemizole versus placebo in a cross-over study. In each of the two treatment periods the children were tested at days 0, 6, 15 and 22 of therapy. The two treatment periods were separated by a washout period of 50 days, and at each visit a bronchial challenge with increasing concentrations of histamine followed by an exercise test was performed, and peak flow and asthmatic symptom score were recorded daily. The children tolerated significantly higher mean concentrations of histamine when treated with astemizole compared with placebo ( $P < 0.001$ ). Astemizole postponed the response to exercise, but no change in the maximal response was found. No differences between the treatment periods were found regarding frequency of asthmatic symptoms or the daily recording of peak flow.

*Key words:* antihistamine; asthma; children

*Accepted for publication 7 November 1988*

## CLINICAL ASPECTS

Decreased lung symptoms in patients treated with antihistamine for allergic rhinitis have previously been demonstrated. Therefore, antihistamines have been suggested as treatment for bronchial asthma. The results of this double-blind, placebo-controlled cross-over study of the effect of astemizole in children with bronchial asthma indicate that astemizole inhibits histamine-induced bronchoconstriction, but not exercise-induced asthma, and no changes in peak flow or subjective asthma symptoms were observed.

Histamine reduces the vital capacity after intravenous administration or inhalation in patients with asthma (8), and presumably acts directly on H<sub>1</sub>-receptors of the bronchial smooth muscle (13). Antihistamines acting on H<sub>1</sub>-receptors are effective against allergic disorders, particularly urticaria and rhinoconjunctivitis (11, 12). The inadequate blockade of bronchial H<sub>1</sub>-receptors seen in asthma with use of antihistamines could be due to insufficient doses, but the new generation of anti-

histamines can be administered in larger doses as their sedative effect is reduced.

In some cases, antihistamines offer useful protection against seasonal asthma (9) and are more potent in antagonizing histamine-induced airway obstruction than sodium cromoglycate (16). Clemastine (7), terfenadine (14) and astemizole 10 mg daily (2) have a protective effect on exercise-induced asthma in adults when given orally. This randomised cross-over study was performed in order to investigate the

effect of astemizole in chronically asthmatic children.

## MATERIAL AND METHODS

### *Material*

Twenty children (11 boys and 9 girls) aged 6 to 15 years (median 13 years) from the Pediatric Allergy Unit participated in the study. All had perennial asthmatic bronchoconstriction relieved by bronchodilator, and 85 % had known exogenous allergy. The children had, at the start of the study, exercise-induced decrease in FEV<sub>1</sub> of at least 20 % (median 30.3 %) from baseline FEV<sub>1</sub> after a 6-min treadmill exercise screening test, and had a moderate degree of bronchial hyperresponsiveness (PC<sub>20</sub> median 0.54 mg/ml, defined as the provocative concentration of histamine required to produce a 20 % fall in FEV<sub>1</sub>).

### *Methods*

The children were seen at the same time in the afternoon at each visit. The study was conducted as a randomised double-blind clinically controlled cross-over trial with two test periods of 22 days duration. Between these two periods a washout period of 50 days was interposed. For the first 6 days of the test period, medication consisted of astemizole tablets 30 mg daily or placebo, and for the last 16 days astemizole tablets 20 mg daily or placebo. The plasma level of astemizole was estimated to reach the steady state level of an oral dose of astemizole of 10 mg daily on day 6 of the test period and the 20 mg daily steady state level on day 15. The order of administration of astemizole and placebo was chosen randomly for each child.

During the test period four control visits were performed (days 0, 6, 15 and 22). At each visit the following procedures were performed: A bronchial provocation with histamine, using a Wright® nebulizer, was done according to the procedure suggested by Cockcroft (3), with successive inhalation of histamine solutions of increasing concentrations

(0.075, 0.15, 0.3, 0.6, 1.2, 2.4, 4.8, and 8.0 mg/ml) until either the maximum concentration of 8.0 mg/ml had been reached or the FEV<sub>1</sub> decreased to 80 % (PC<sub>20</sub>) of the initial FEV<sub>1</sub> obtained before the start of the test. The exercise test consisted of steady state running for 6 min on an inclined treadmill (10°) at the same speed at each test performed. The speed chosen was the one resulting (at the first visit) in a pulse rate of at least 180/min and a fall of 20 % or more in FEV<sub>1</sub>. FEV<sub>1</sub> was measured before, at the end, and 1, 3, 5, 10 and 15 min after exercise. The room temperature (21°C) and relative humidity (40–50 %) were kept constant. At each visit a blood sample was drawn from an antecubital vein for analysis of plasma astemizole concentrations. Between the two challenges the children rested, as recommended, for 45 min (5, 6).

A diary-card of morning and evening peak flow (Mini-Wright peak flow meter®) and asthmatic symptoms were recorded each day as described by Petersen et al. (15). The children kept their basal prophylactic medication unchanged throughout the study.

The children and their parents gave their informed consent according to the Helsinki-II declaration, and the trial was approved by the local ethics committee.

### *Statistical analysis*

The matched paired signed rank test using Wilcoxon rank sums was used to compare data from astemizole and placebo periods. Friedman's test supplemented by the Page test was used in the analysis of repetitive measurements in the same patients. McNemar test was used when analysing differences in changes of bronchial response to histamine and exercise between astemizole and placebo groups. Further, the Mann-Whitney two-sample rank test using the sums and differences of results in the astemizole and placebo periods and non-parametric two-way analysis of variance was used to analyse whether there were any carry-over or period effects. The significance level of the type 1 error was fixed at 0.05.

RESULTS

Of the 160 visits (8 visits per child) 155 were performed as planned. One child was excluded from the study because of change in the daily medication. There were no significant differences in the bronchial reactivity (PC<sub>20</sub>) on the first day of the astemizole period (median 0.85 mg/ml) and the first day of the placebo period (median 0.99 mg/ml), and no significant differences were observed in the reduction of FEV<sub>1</sub> after exercise on the first day of astemizole and placebo periods.

There were no significant fluctuations in bronchial reactivity during the placebo period either after histamine challenge or exercise (*P* values > 0.25, Friedman and Page test). During the astemizole period a significant reduction in bronchial reactivity after histamine challenge was observed (*P* < 0.05, Friedman and Page test), while no change was found in response to exercise (*P* < 0.30, Friedman and Page test). At days 6 and 15 of the astemizole period 12 of 17 children and at day 22, 13 of 18 had PC<sub>20</sub> > 8 mg/ml (Table 1). In the placebo period, two children had PC<sub>20</sub> > 8 mg/ml at days 15 and 22 respectively (Table 1). These differences were statistically significant. There was a significant difference between PC<sub>20</sub> in placebo and astemizole periods at each visit (*P* < 0.001, matched paired signed rank test), but at no point were significant differences between the two treatment periods observed regarding reduction of FEV<sub>1</sub> after exercise (data not shown). However, treatment with astemizole postponed the response to exercise after 22 days of treatment, as the maximal reduction in FEV<sub>1</sub> was observed significantly later in the astemi-

zole period than in the placebo period (Table 2). No difference was observed between treatments regarding time to maximal exercise-induced reduction of FEV<sub>1</sub> at entry (Table 2).

The basal FEV<sub>1</sub> level did not change throughout the study, and in the analyses of variance the fluctuations between children of PC<sub>20</sub> after histamine challenge and reduction in FEV<sub>1</sub> after exercise in the two treatment periods were independent of whether placebo or astemizole was given first. No carry-over or period effects were observed.

There were no changes in peak flow recordings between the two periods (Table 3) and no differences in frequency and degree of asthmatic symptoms (Table 4).

In all children the plasma concentration of astemizole increased during the astemizole period and decreased to zero during the wash-out period. At day 6 plasma concentration was median 11.9 ng/ml (interquartile range 7.1–17.6 ng/ml), at day 15 median 15.5 ng/ml (interquartile range 11.4–29.5 ng/ml) and at day 22 median 12.7 ng/ml (interquartile range 9.4–19.9 ng/ml). We found a significant positive correlation between plasma concentrations of astemizole and PC<sub>20</sub> in the astemizole period (Spearman rank correlation *P* < 0.05).

Table 1

Number of children in astemizole and placebo periods with PC<sub>20</sub> > 8 mg/ml

|                             | Day 0 | Day 6            | Day 15          | Day 22          |
|-----------------------------|-------|------------------|-----------------|-----------------|
| Astemizole ( <i>n</i> = 19) | 2     | 12               | 12              | 13              |
| Placebo ( <i>n</i> = 19)    | 0     | 0                | 2               | 2               |
| Significance                | NS    | <i>P</i> = 0.002 | <i>P</i> = 0.02 | <i>P</i> = 0.05 |

NS = not significant (*P* > 0.05) McNemar test

Table 2

Number of children in astemizole and placebo periods at entry and after 22 days of treatment with maximal exercise-induced reduction of FEV<sub>1</sub> occurring after > 5 min

| Day 0      |         | Placebo |         |
|------------|---------|---------|---------|
|            |         | < 5 min | > 5 min |
| Astemizole | < 5min  | 12      | 2       |
|            | > 5 min | 2       | 2       |

Not significant; McNemar test

| Day 22     |         | Placebo |         |
|------------|---------|---------|---------|
|            |         | < 5 min | > 5 min |
| Astemizole | < 5min  | 4       | 1       |
|            | > 5 min | 8       | 5       |

Chi-square = 5.44; *P* < 0.05; McNemar test

DISCUSSION

Antihistamines acting on H<sub>1</sub>-receptors are effective in the treatment of allergic disorders, particularly urticaria and rhinoconjunctivitis (11, 12). However, antihistamines also have protective properties in seasonal symptoms of asthma (9), but the clinical experience is ambiguous (10). Most of the old antihistamines have sedative side effects, and high doses are not acceptable, but the new generation of drugs with high affinity to lung tissue (1) can be administered in larger doses. Many authors have administered antihistamines with relatively weak potency in small doses because of side effects (4, 17).

Many children with asthma have exercise-induced asthma (EIA) (6). The children in this

study had a history of almost daily asthma, and were under the same basic conditions in the two treatment periods. We found no significant changes in FEV<sub>1</sub>, peak flow or frequency of asthmatic symptoms during the study. We were not able to demonstrate any significant protection against EIA among these children as others have done in adult studies (7, 13, 14).

The children tolerated significantly higher median concentration of histamine on days 6, 15 and 22, when treated with astemizole compared with placebo, and this reduced sensitivity to histamine correlated significantly to plasma concentrations of astemizole. The shift of the histamine dose response curve suggests that the protection is due to competitive antagonism. Astemizole produced no change in histamine-

Table 3  
Peak flow recordings in astemizole and placebo periods at entry, days 6, 15 and 22. Figures are medians and (interquartile ranges)

| Peak flow (l/min) | Day              |                  |                  |                  |
|-------------------|------------------|------------------|------------------|------------------|
|                   | 0                | 6                | 15               | 22               |
| Astemizole*       | 350<br>(280-450) | 375<br>(250-455) | 380<br>(270-480) | 385<br>(298-470) |
| Placebo*          | 350<br>(250-400) | 348<br>(273-392) | 350<br>(270-470) | 350<br>(260-495) |
| Significance      | NS               | NS               | NS               | NS               |

NS = not significant ( $P > 0.05$ ); Matched pair signed rank test using Wilcoxon rank sums.  
\*No significant change during each period ( $P > 0.05$ ; Friedman test).

Table 4  
Lung symptom score from diary cards in astemizole and placebo periods at entry, days 6, 15 and 22. Figures are medians and (interquartile ranges)

| Lung symptom score | Day              |                  |                  |                  |
|--------------------|------------------|------------------|------------------|------------------|
|                    | 0                | 6                | 15               | 22               |
| Astemizole*        | 1.7<br>(0.8-2.6) | 0.5<br>(0-2.8)   | 0.8<br>(0.1-2.1) | 0.7<br>(0.1-1.6) |
| Placebo*           | 0.8<br>(0.1-3.0) | 0.3<br>(0.3-1.3) | 0.2<br>(0-1.3)   | 0.4<br>(0-4.0)   |
| Significance       | NS               | NS               | NS               | NS               |

NS = not significant ( $P > 0.05$ ); Matched pair signed rank test using Wilcoxon rank sums.  
\*No significant change during each period ( $P > 0.05$ ; Friedman test).

induced airway obstruction in four of the 20 children. A possible explanation might be differences in types of asthma.

The suggested mechanism of action of antihistamines is a blockade of bronchial  $H_1$ -receptors (3). Previous studies have suggested that inhaled antihistamine in adults with severe bronchoconstriction may cause bronchodilation (13), but others have been unable to confirm this in adults with stable asthma (14, 16). In our study no significant degree of bronchodilation or bronchoconstriction resulted from antihistamine taken orally for 6, 15, or 22 days.

In each patient the two challenges were performed 45 min apart, with the bronchial histamine challenge first because of the lack of refractory period (3, 6). Thus mediator depletion was not the reason for our findings.

We found a high variation in astemizole concentrations, presumably reflecting a high variation in the children's volumes of distribution, as the astemizole concentration correlated significantly with age.

In conclusion we have shown that astemizole taken orally (10 mg daily) can inhibit histamine-induced airway obstruction in children with proven asthma. However, we found no protective effect of the drug against exercise-induced decrease in  $FEV_{10}$ , asthma symptoms, or change in daily peak flow recordings.

## ACKNOWLEDGEMENTS

We wish to thank the children and their parents who willingly participated in the study, and we are grateful for the support of Janssen Pharma, who supplied the astemizole and placebo tablets.

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