

Letter to the Editor

Effect of ingested H₁ antihistamines on methacholine challenge*To the Editor:*

Current guidelines recommend withholding H₁ antihistamines before methacholine challenge.¹ There does not appear to be much evidence to support this recommendation. We performed a double-blind random-order study comparing single-dose diphenhydramine, desloratadine, and cetirizine to placebo on the airway response to methacholine.

Twelve mild well-controlled atopic asthmatic subjects completed the study. The subjects (7 women) were 29 ± 3.8 years old and 66.3 ± 1.4 inches tall. All had an FEV₁ value of greater than 70% predicted ($89\% \pm 3.1\%$) and a screening 2-minute tidal breathing¹ provocation concentration (of methacholine) causing a 20% FEV₁ fall (PC₂₀) of less than 16 mg/mL (geometric mean, 2.9 mg/mL). Pregnant and lactating women were excluded. Subjects had no other chronic diseases. Two of the 12 were using low-dose budesonide in stable dose; the remainder used only infrequent as needed albuterol. No subject had any allergen exposure, respiratory infection, or exacerbation for more than 4 weeks. The study was approved by the University of Saskatchewan Biomedical Research Ethics Committee and was registered at clinicaltrials.gov (no. NCT01985789); signed informed consent was obtained. Following screening, subjects attended the laboratory on 4 occasions at the same time of day 7 or more days apart. At each visit, after a 30-minute rest, methacholine PC₂₀ was measured; airflow obstruction was not reversed. Blinded medication was administered (placebo, diphenhydramine 50 mg, desloratadine 5 mg, or cetirizine 10 mg). Two hours later, the methacholine PC₂₀ was measured again. At that point, single prick skin tests were done with diluent, histamine, and a relevant allergen: The wheal and flare diameter of the allergen and histamine skin test (greater than any diluent response) was measured in 2 perpendicular directions at 15 minutes and the mean value was recorded. Subjects were queried regarding sleepiness at the completion of the day. The primary end point, change in log PC₂₀, as well as mean wheal and flare diameters were analyzed with a 2-way ANOVA (subject, treatment). Drowsiness (yes, no) was assessed using the χ^2 test applied to a 4×2 table.

All 12 subjects completed the study without any adverse event. There was no significant difference in FEV₁ pretreatment, 2-hour posttreatment, or for the change in FEV₁ between pre- and posttreatment. The mean changes in FEV₁ were small and ranged from -0.05 to 0.07 L (-1.5% to 2%). Methacholine PC₂₀ ($n = 96$) values are shown pre- and posttreatments in Fig 1. There was no significant treatment effect (ANOVA; $P = .29$). The mean changes in log PC₂₀ were 0.19 ± 0.07 , 0.14 ± 0.11 , 0.11 ± 0.07 , and -0.006 ± 0.08 for placebo, diphenhydramine, cetirizine, and desloratadine, respectively. The histamine wheal diameters were 4.2 ± 0.32 , 3.0 ± 0.39 , 2.7 ± 0.35 , and 3.3 ± 0.18 mm ($P = .018$), respectively, for the 4 treatments; wheal diameters for diphenhydramine and cetirizine were significantly smaller than that for placebo. The histamine flare diameters were 20.9 ± 2.0 , 8.66 ± 2.15 , 8.05 ± 2.33 , and 12.9 ± 1.87 mm, respectively ($P = .0007$); flare diameters for all active treatments were significantly smaller than that for placebo. The allergen wheal ($P = .0006$) diameter was significantly reduced only by cetirizine and the flare diameter ($P = .0025$) by diphenhydramine and cetirizine. Eight of the 12 subjects reported drowsiness, 5 markedly so, after diphenhydramine compared with 2 after placebo, 2 after desloratadine, and 1 after cetirizine, all mild ($\chi^2 = 12.9$; $P = .005$).

These data demonstrate that pharmacologically active single doses of 3 H₁ antihistamines fail to have any effect on the methacholine inhalation test. The largest mean change in PC₂₀, about one-half doubling concentration, occurred after the administration of placebo. Although not significant, this is possibly attributable to the known tendency to develop tolerance to inhaled methacholine, a feature limited to subjects with normal² and possibly very mild asthma. The inclusion screening PC₂₀ value was 16 mg/mL or less (1 subject had a screening PC₂₀ value of 16.8); however, a few of the subjects had substantially higher PC₂₀ values during the study. Data from our laboratory and from the literature show that with 12 subjects there is greater than 95% power to detect a one-half doubling concentration and a 99% power to detect a minimal clinically significant difference of one doubling concentration in methacholine PC₂₀.

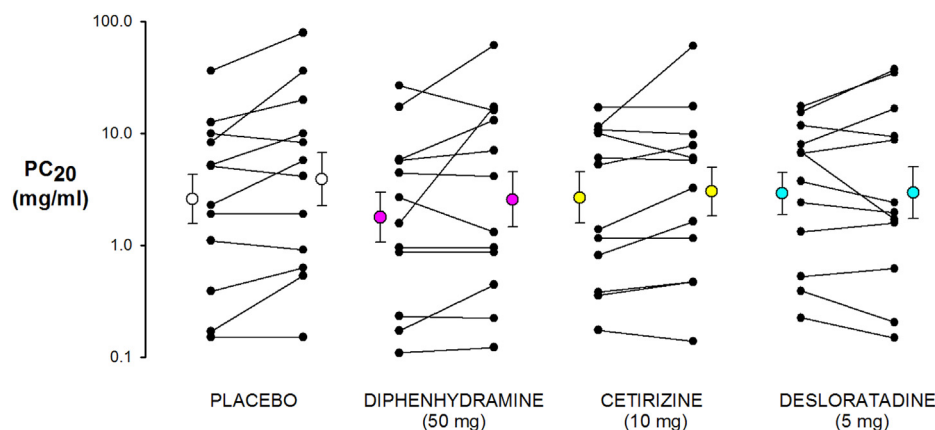


FIG 1. Methacholine PC₂₀ before (left) and after (right) each treatment. The methacholine PC₂₀ (mg/mL) is on the vertical axis (log scale) and the time points on the horizontal axis.

H₁ antihistamines inhibit airway response to inhaled histamine (as expected) as well as airway response to indirect stimuli³ which is due to histamine and other mediators released from inflammatory cells. The intrinsic H₁-blocking effect should not affect methacholine; the concerns regarding H₁ blockers and methacholine testing likely relate to their recognized antimuscarinic effects.⁴ We chose a relatively high dose (double the standard dose) of the first-generation H₁-blocker diphenhydramine as a potential positive control. Although this induced both significant drowsiness and significant antihistaminic effect in subjects who underwent the skin tests, there was no effect on airway response to methacholine.

We were able to identify only a few previous studies addressing this issue. A relatively high single dose of inhaled chlorpheniramine, a first-generation H₁ blocker, produced a small (less than one doubling dose) increase in methacholine PC₂₀.⁵ The clinical significance of these findings is uncertain. In contrast, inhaled clemastine,⁶ oral terfenadine,⁷ oral ketotifen,⁸ and oral cetirizine⁹ have been shown to have no effect on the methacholine challenge.

Antihistamines are frequently used in subjects with atopic disease including those in whom asthma is a potential diagnosis. These data along with other published reports suggest that it is not necessary to withhold these H₁ blockers before performing a methacholine challenge.

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REFERENCES

1. Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, et al. Guidelines for methacholine and exercise challenge testing-1989. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. *Am J Respir Crit Care Med* 2000; 161:309-29.
2. Stevens WH, Manning PJ, Watson RM, O'Byrne PM. Tachyphylaxis to inhaled methacholine in normal but not asthmatic subjects. *J Appl Physiol* (1985) 1990; 69:875-9.
3. Holgate ST, Finnerty JP. Antihistamines in asthma. *J Allergy Clin Immunol* 1989; 83:537-47.
4. Orzechowski RF, Currie DS, Valancius CA. Comparative anticholinergic activities of 10 histamine H₁ receptor antagonists in two functional models. *Eur J Pharmacol* 2005;506:257-64.
5. O'Byrne PM, Thomson NC, Morris M, Roberts RS, Daniel EE, Hargreave FE. The protective effect of inhaled chlorpheniramine and atropine on bronchoconstriction stimulated by airway cooling. *Am Rev Respir Dis* 1983;128:611-7.
6. Nogrady SG, Bevan C. Inhaled antihistamines—bronchodilatation and effects on histamine- and methacholine-induced bronchoconstriction. *Thorax* 1978;33: 700-4.
7. Ruffin RE, Latimer KM. Lack of effect of 4 weeks of oral H₁ antagonist on bronchial responsiveness. *Eur Respir J* 1991;4:575-9.
8. Graff-Lonnevig V, Hedlin G. The effect of ketotifen on bronchial hyperactivity in childhood asthma. *J Allergy Clin Immunol* 1985;76:59-63.
9. Aubier M, Neukirch C, Peiffer C, Melac M. Effect of cetirizine on bronchial hyperresponsiveness in patients with seasonal allergic rhinitis and asthma. *Allergy* 2001; 56:35-42.

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