THE EFFECT OF BROMPHENIRAMINE ON COUGH SENSITIVITY IN HEALTHY VOLUNTEERS

Haytham M. El-Khushman MD*

ABSTRACT

Objective: To evaluate the anti-tussive effect of brompheniramine maleate a non-selective, sedative antihistamine using capsaicin challenge.

Methods: Twelve subjects, five females and seven females, mean age 32 years with a range of (23-39) years, were studied on two occasions. On the two visits a baseline capsaicin dose-response was performed to determine C5 (the lowest concentration causing 5 coughs). After 30 minutes two C5 doses of capsaicin were given and the total cough over one minute was counted. On the first visit Brompheniramine 8mg or a matched placebo was given orally, and 120, 240 minutes after administration, two C5 doses of capsaicin were given and the total coughs over one minute period were counted. This was repeated exactly in the second visit except subjects received either a placebo or active treatment; either which they had not received on their first visit. Subjects were also asked to quantify their drowsiness using a 100 mm visual analogue scale.

Results: Baseline mean cough number (confidence interval) was similar on the two study occasions 9.9 (8.2-11.7) before Brompheniramine and 9.2 (7.3-11.1) before placebo. Cough number did not differ on the two study days at 120 and 240 min after Brompheniramine treatment: 7.7 (5.5-9.8), 7.4 (5.1-9.6) compared to 8.7 (6.4-11.0), 8.3 (6.8-9.8) after placebo. Mean visual analogue scale (confidence interval) after Brompheniramine was 31 (14-48) and 40 (21-60) compared to 7 (2-12) and 7 (2-12) after Placebo at 120 and 240 min respectively ($p<0.008$).

Conclusion: The sedative anti histamine Brompheniramine did not affect capsaicin induced cough though it produced significant drowsiness.

Key words: Brompheniramine, Capsaicin, Cough.

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Introduction

Cough is the most common respiratory symptom, however there is no specific anti tussive agent of proven efficacy[1-4]. Opioids are effective anti tussive agents but at their effective doses they also cause physical dependence, respiratory depression, and gastrointestinal symptoms. The non-narcotic opiate isomer Dextromethorphan is used as anti tussive agent but it has a sedative effect. Persistent non-productive cough can be a major clinical problem. A selective, non-sedating anti histamine (terfenadine) has been shown to have an effect on cough in seasonal rhinitis without sinusitis or post nasal drip, but it had no effect on induced cough suggesting an indirect mechanism of action on cough reflex[5]. Non-selective antihistamines are common constituents of over the counter cough and cold remedies and they are claimed to have an anti-tussive effect[2,3,6]. The mechanism of action of these non-selective antihistamines is not very well understood; it was thought to be due to their sedative effect, which can suppress most respiratory reflexes[1]. Brompheniramine maleate is a histamine H1-receptor antagonist given by mouth for the symptomatic relief of hypersensitivity reactions and in pruritic skin disorders. It is common ingredient of cough and cold preparations. It may cause some adverse effects such as sedation and antimuscarinic effects. In this study the anti-tussive effect of brompheniramine maleate was examined using the capsaicin challenge.

*From the Department of Internal Medicine, Respiratory Medicine Division, King Hussein Medical Center, (KHMC), Amman-Jordan
Correspondence should be addressed to Dr. H. El-Khushman, P. O. Box 2399 Amman 11953 Jordan. E-mail: helkhushman@hotmail.com
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Methods

The study had the approval of the Royal Postgraduate Medical School (RPMS) and Hammersmith Hospital Research Ethical Committee. All the subjects gave their written informed consent. Verbal consent was obtained from Healthy employed volunteers recruited from the RPMS and Hammersmith hospital. Subjects were excluded if they were smokers, had bronchial asthma, chronic obstructive pulmonary disease, chronic sinusitis or allergic rhinitis, persistent cough, a clinically significant history of other drug intake, drug or alcohol abuse, or a respiratory tract infection within the previous eight weeks. Subjects were asked if they had taken an investigational drug in the previous three months and they were asked not to drive on the study days.

The study was randomized, double blind, placebo-controlled, cross over design. 12 healthy volunteers (5 females and seven males), mean age 32 years with a range of (23-39) years attended on two separate days with a minimum interval of two days between the visits and a maximum interval of four weeks from the last visit. On the first visit the study was explained and informed consents were obtained. After history taking and physical examination baseline data (height, weight and lung functions) were collected. Capsaicin cough challenge was then carried out using doubling concentrations starting at 0.500 μM at one minute interval according to a standard protocol[7]. Subjects inhaled (starting from just below functional residual capacity) a single breath of capsaicin from a nebulizer attached to a breath-activated dosimeter (PK Morgan Ltd, UK). The output and the mass median diameter of the aerosol were 5-7 μl and 3.5-4μ respectively[7]. The number of coughs in response to each concentration (over the one minute period immediately after each breath of capsaicin) was recorded by an experienced observer. The challenge was stopped when the lowest concentration required to elicit at least 5 coughs (C5) was reached. After a 30 minute delay, two C5 doses of capsaicin were then administered within 30 seconds apart and the total coughs in the first minute following the first C5 dose (expected to equal 10) were recorded. After further 5 minutes either Brompheniramine 8 mg or exactly matched placebo (which was prepared at Hammersmith Hospital pharmacy) were given orally. Two doses (C5) of capsaicin were then administered with cough counting, as at baseline, at 12o and 240 minutes. At these time points subjects were asked to quantify the degree of drowsiness they were experiencing using a 10 cm visual analogue scale (VAS), this was marked “fully alert” at one end and “extremely sleepy” at the other. In the second visit the procedure was repeated exactly as the first, except that subjects were crossed over to receive either placebo or active treatment, either which they had not received on their first visit.

Results

The procedures were well tolerated by all subjects. Capsaicin produced a reproducible cough response though individual sensitivity varied. Cough number was expressed as mean ± confidence interval (CI). Analysis of variance was used to compare the differences in the two visits. Wilcoxon rank test used to compare the number of cough and the level of alertness VAS between treatments. Results were expressed as treatment (active-placebo) differences (Table I). There was no significant difference between baseline cough number on the two study days; 9.9 before Brompheniramine and 9.2 before placebo (p=0.34). Mean total cough in response to capsaicin after placebo pretreatment were similar at 120 and 240 minutes; (8.7, 8.3 respectively). Though there was a slight trend to a decrease of mean total cough after placebo treatment, there was no significant difference between mean total cough at 240 minutes 8.3 (6.8-9.8) and baseline 9.2 (7.3-11.1) (p=0.43). Mean total cough (CI) at 120 min on the active day of treatment was 7.7 (5.5-9.8) compared to 9.9 (8.2-11.7) at baseline (p=0.49). Mean total cough at 240 min after Brompheniramine treatment was 7.4 (5.1-9.6) compared to 9.9 (8.2-11.7) at baseline (p=0.42).

The comparison between the two treatment days did not show any statistically significant results at both time points (Fig. 1). Oral Brompheniramine did not induce a significant inhibitory effect on capsaicin-induced cough compared to placebo. Oral Brompheniramine induced significant level of drowsiness at 120 min and 240 min following intake; mean VAS (confidence interval) was 31 (14-48) and 40 (21-60) compared to 7 (2-12) and 7 (2-12) after placebo at 120 and 240 min respectively (p<0.008), (Fig. 2).

Discussion

This study demonstrated for the first time, that oral Brompheniramine has no statistically significant effect on capsaicin-induced cough in normal subjects.

Rafferty *et al*[5] reported that the selective, non-sedative antihistamine, terfenadine, was effective at reducing cough in seasonal rhinitis patients without sinusitis and post-nasal drip suggesting terfenadine may have a direct action on the sensory limb of the cough reflex.

Studham and Fuller[8] demonstrated that terfenadine does not reduce the cough response to inhaled capsaicin in normal volunteers suggesting the effect of the non-selective antihistamines used over the counter remedies and that of the terfenadine in rhinitis is probably indirect. The effect in rhinitis is likely to be either

through prevention of post-nasal drip, although the patients did not report symptom or through inhibition of histamine release in the airways in amounts that did not lead to brnchospasm. It had been postulated that the anti-tussive effect of the non-selective antihistamine could be through inhibition of post-nasal drip in patients with viral infections or through inhibitions of other receptors, such as acetylcholine or 5-hydroxytryptamin receptors[5]. The most likely effect of these drugs was thought to be through sedation, which will suppress most respiratory reflexes. The hypothesis in this study was that brompheniramine possibly by its central sedative activity might have an inhibitory effect on the sensory afferent arm of the cough reflex[8]. Capsaicin by inhalation caused cough and is used as a clinical measure of the sensitivity of the cough reflex. Patients with dry cough are hypersensitive to capsaicin. In this study Brompheniramine had a significant drowsiness effect at both time points of the study in comparison to the baseline as was measured by VAS. Brompheniramine did not show a statistically significant effect on capsaicin-induced cough in comparison to the baseline at both time points (120 and 240 min). The measured effect of Brompheniramine on alertness did not reflect on cough response measured by capsaicin challenge. The effect of Brompheniramine on capsaicin cough challenge is comparable to that of the non-sedative antihistamine terfendine[8]. Cough is inhibited by morphine and local anesthetics but the selective, non-sedative antihistamine terfendine was shown to have no effect in a placebo-controlled study in normal volunteers[8].

This study showed that the purported anti-tussive action of the non-selective antihistamines might not be related to there sedative effect.

Further research is needed in order to provide a better understanding of cough reflex using the same capsaicin cough reflex which stimulates the C-fibers or the identification of several new mechanisms which may lead to new drugs that target the increased sensitivity of sensory fibers resulting in exaggerated cough.

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Table I. Cough number and alertness visual analogue scale (VAS) in mm. at different time points

Time points	Baseline		120 min		240 min	
	Cough	VAS	Cough	VAS	Cough	VAS
Brompheniramine	9.9	8.0	7.7	31	7.4	40
Placebo	9.2	6.7	8.7	7.0	8.3	7.0

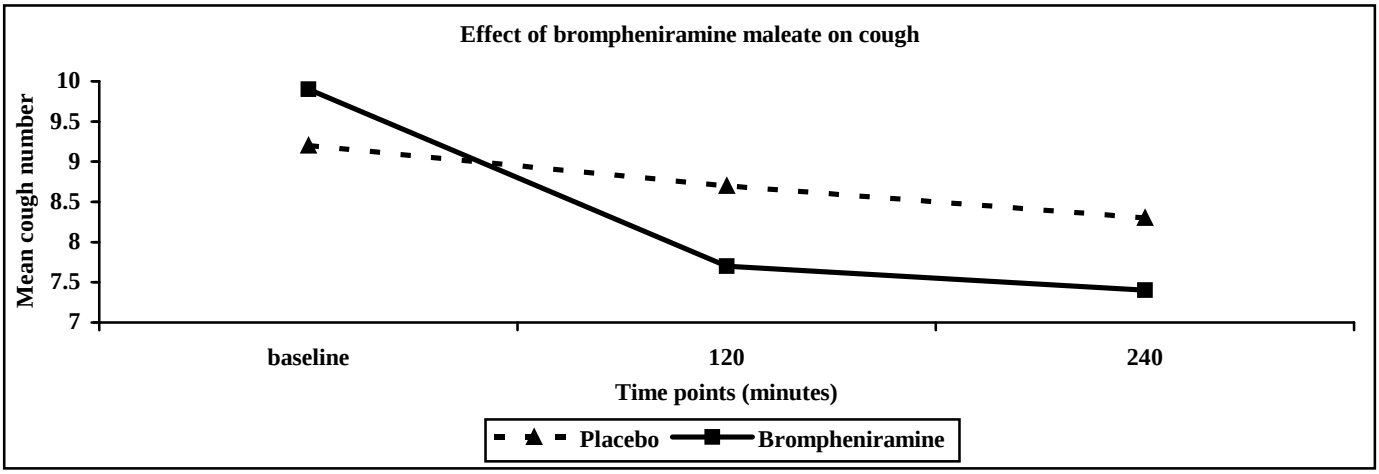

Fig. 1. Effect of brompheniramine maleate on cough.

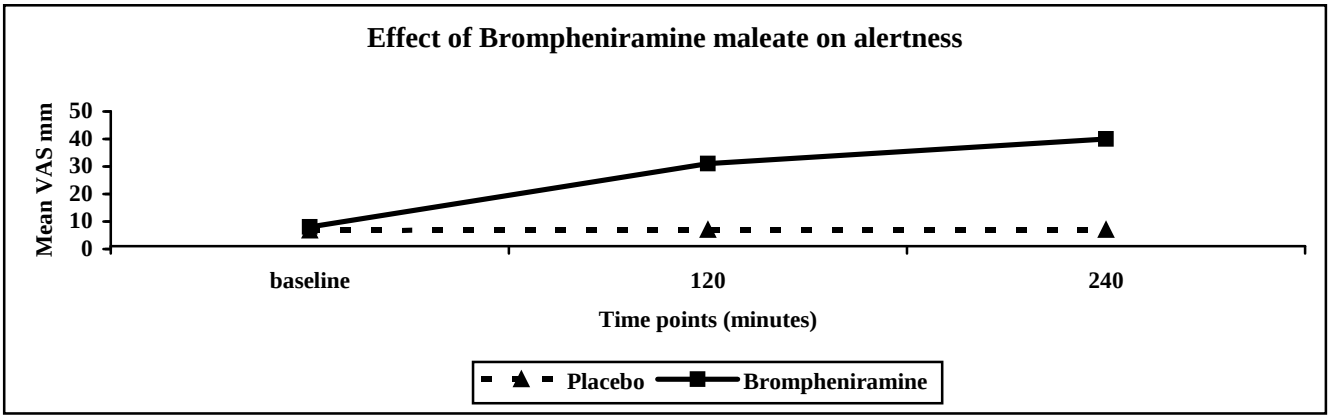

Fig. 2. Effect of brompheniramine maleate on alertness

References

1. **Fuller RW, Jackson DM.** Physiology and treatment of cough. *Thorax* 1990; 45(6): 425-430. Review.
2. **Curley FJ, Irwin RS, Pratter MR, *et al.*** Cough and the common cold. *Am Rev Respir Dis.* 1988; 138(2): 305-311.
3. **Belvisi MG, Geppetti P.** Cough. 7: Current and future drugs for the treatment of chronic cough. *Thorax.* 2004; 59(5): 438-440.
4. **Chung KF, Lalloo UG.** Diagnosis and management of chronic persistent dry cough. *Postgrad Med J* 1996; 72(852): 594-598.
5. **Rafferty P, Jackson L, Smith R, Holgate ST.** Terfenadine, a potent histamine H1-receptor antagonist in the treatment of grass pollen sensitive asthma. *Br J Clin Pharmacol* 1990; 30(2): 229-235.
6. **Morice AH, Fontana GA, Sovijarvi AR, *et al.*** The diagnosis and management of chronic cough. *Ur Respir J* 2004; 24(3): 481-492.
7. **O'Connell F, Thomas VE, Pride NB, Fuller RW.** Capcaisin cough sensitivity decreases with successful treatment of chronic cough. *Am J Respir Crit Care Med* 1994; 150: 347-380.
8. **Studham J, Fuller W.** The effect of oral terfenadine on the sensitivity of the cough reflex in normal volunteers. *Pulm Pharm* 1992; 5: 51-52.