

## Short Report

# Effect of menthol vapour on airway hyperresponsiveness in patients with mild asthma

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## Introduction

Menthol (2-isopropyl-5-methyl-cyclohexanol), a cyclic alcohol widely appreciated for its ability to produce a cooling sensation, has been used as a constituent of food and drink, tobacco and cosmetics. This compound can reduce flatulence and colic pain in patients with irritable bowel syndrome probably through blockade of  $\text{Ca}^{2+}$  channels on intestinal smooth muscle (1). A recent report indicates that menthol vapour possesses an anti-tussive action (2). The objective of the present study was to investigate the effect of menthol on airway hyperresponsiveness in asthma.

## Patients and Methods

Twenty-three non-smoking subjects with chronic mild asthma (twelve males, eleven females; aged 19–46 years) (3) were enrolled into the trial after obtaining written informed consent. None of the patients had had either exacerbation of wheezing or respiratory infection in the preceding 4 weeks. Each subject had only occasional symptoms, which were controlled by  $\beta_2$ -adrenoceptor agonists from metered dose inhalers on demand.

The study had a randomized, placebo-controlled design, which was approved by Tokyo Women's Medical College Ethics Committee. After a 2-week run-in period, subjects were randomized to receive nebulized menthol (10 mg, twice a day, Hohei Co., Tokyo, Japan) or matching placebo for 4 weeks. This dose of menthol was chosen based on the report by Laude *et al.* (2). Each subject was given a mini-Wright peak flow meter to record peak expiratory flow rate (PEFR) twice a day (at

awakening and on going to bed) before inhalation of menthol, placebo or  $\beta_2$ -agonists. Patients were asked to record three values, and the better two reproducible ( $\pm 20 \text{ l min}^{-1}$ ) values on each occasion were kept for analysis. The amplitude of changes in daily PEFR ( $\Delta\text{PEFR}$ ) was calculated from the following formula: (highest value – lowest value)  $\times 100$  / (highest value). Vital capacity (VC) and forced expiratory volume in one second ( $\text{FEV}_1$ ) were measured by spirometry before and at the end of the treatment period. In addition, methacholine inhalation tests were performed with the Wright's nebulizer at tidal volume breathing for 2 min according to a standardized procedure (4), and a provocative concentration that caused a 20% decrease in  $\text{FEV}_1$  ( $\text{PC}_{20}$ ) was determined.

Patients attended the clinic on a weekly basis. Asthma symptoms, possible adverse effects and changes in concomitant medication were evaluated from asthma diaries, and full blood count, serum biochemistry and urinalysis were performed.

All data were expressed as mean  $\pm$  SE. Statistical analysis was performed using a paired Student's *t*-test, and a *P* value of less than 0.05 was considered significant.

## Results

Two patients in the menthol group were withdrawn because of an uncomfortable sensation in the upper airway, thus 21 patients completed the full protocol. As shown in Table 1, there were no significant differences in VC,  $\text{FEV}_1$ ,  $\Delta\text{PEFR}$  and  $\text{PC}_{20}$  between the menthol group and the placebo group. In the placebo group, these values were unchanged throughout the trial. In contrast, menthol therapy did not significantly alter VC or  $\text{FEV}_1$ , but produced a decrease in  $\Delta\text{PEFR}$  from  $17.4 \pm 3.3$  to  $11.2 \pm 3.3\%$  and an increase in  $\text{PC}_{20}$  from  $5.1 \pm 1.2$  to  $10.7 \pm 2.8 \text{ mg ml}^{-1}$  ( $P < 0.05$ ,  $n = 11$  in each case).

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Table 1 Clinical data before and after treatment with menthol or placebo

|   | Menthol group |            |            | Placebo group |            |            |
|---|---------------|------------|------------|---------------|------------|------------|
|   | Before        | After      | Difference | Before        | After      | Difference |
| <b>Lung function</b>                      |               |            |            |               |            |            |
| VC (% predicted)                          | 94.4 ± 1.2    | 95.3 ± 0.9 | n.s.       | 93.8 ± 1.0    | 95.0 ± 1.1 | n.s.       |
| FEV <sub>1</sub> (% predicted)            | 81.6 ± 2.1    | 84.2 ± 3.0 | n.s.       | 85.5 ± 1.8    | 84.4 ± 2.6 | n.s.       |
| ΔPEFR (%)                                 | 17.4 ± 3.3    | 11.2 ± 3.3 | P<0.05     | 16.8 ± 2.7    | 17.0 ± 3.6 | n.s.       |
| PC <sub>20</sub> (mg ml <sup>-1</sup> )   | 5.1 ± 1.2     | 10.7 ± 2.8 | P<0.05     | 5.8 ± 1.1     | 6.5 ± 2.5  | n.s.       |
| Wheezing episodes (week <sup>-1</sup> )   | 3.3 ± 0.3     | 1.8 ± 0.7  | P<0.05     | 2.9 ± 0.3     | 2.7 ± 0.5  | n.s.       |
| MDI inhalation (puff week <sup>-1</sup> ) | 5.2 ± 0.4     | 2.1 ± 0.3  | P<0.01     | 4.8 ± 0.5     | 4.4 ± 0.3  | n.s.       |

VC, vital capacity; FEV<sub>1</sub>, forced expiratory volume in one second; ΔPEFR, diurnal variation in peak expiratory flow rate; PC<sub>20</sub>, provocative concentration of methacholine required to cause a 20% fall in FEV<sub>1</sub>; MDI, metered-dose inhaler; n.s., not significant. Values are expressed as mean ± SE; n=11 for menthol group and n=10 for placebo group.

None of the patients showed apparent adverse effects in either group. In the menthol group, patients had fewer wheezing episodes and less consumption of bronchodilators after the treatment.

## Discussion

Our study indicates that menthol might be beneficial in the treatment of mild asthma. As our preliminary experiment showed that menthol vapour did not produce acute bronchodilatory effects, we examined a long-term effect of this compound on airway hyperresponsiveness in asthmatic patients. We found that 4-week inhalation of menthol vapour decreased diurnal variation in PEFr, a value that reflects airway excitability (5), but had no significant effect on FEV<sub>1</sub>. Thus, menthol may lead to an improvement of airway hyperresponsiveness without altering the magnitude of airflow limitation. This notion is also supported by the finding that the PC<sub>20</sub> values for methacholine were increased after treatment with menthol.

Although the mechanism of efficacy of menthol on airway hyperresponsiveness is uncertain, menthol and other aromatic vapours have been used in the symptomatic treatment of upper respiratory infections because of its ability to stimulate laryngeal cold receptors (5). Recent evidence suggests that menthol inhibits the cough reflex (2). In addition, menthol can decrease intracellular free Ca<sup>2+</sup> concentration through an inhibition of voltage-dependent Ca<sup>2+</sup>

channels, thereby producing hyperpolarization of various types of cells (7,8). Therefore, these mechanisms could be operating in the observed effect of menthol in the present study.

## References

- Hills JM, Aaronson PI. The mechanism of action of peppermint oil on gastrointestinal smooth muscle. *Gastroenterology* 1991; **101**: 55–65.
- Laude EA, Grattan TJ, Morice AH. The anti-tussive action of menthol and other aromatic vapours in conscious guinea-pigs. *Am J Respir Crit Care Med* 1994; **149**: (suppl): A187.
- International Consensus Report on the Diagnosis and Management of Asthma. *Clin Exp Allergy* 1991; **22** (suppl 1): 1–72.
- Cockcroft DW. Bronchial inhalation test. I. Measurement of nonallergic bronchial responsiveness. *Ann Allergy* 1985; **55**: 527–534.
- Ryan G, Latimer KM, Dolovich J, Haargreave FE. Bronchial responsiveness to histamine: relationship to diurnal variation of peak flow rate, improvement after bronchodilator, and airway caliber. *Thorax* 1982; **37**: 423–429.
- Schäfer K, Braun HA, Isenberg C. Effect of menthol on cold receptor activity. *J Gen Physiol* 1986; **88**: 757–776.
- Howthorne M, Ferrante J, Luchowski E, Rutledge A, Wei X, Triggle DJ. Menthol and peppermint oil actions on calcium channel dependent processes in cardiac, intestinal and neuronal preparations. *Aliment Pharmacol Therapy* 1988; **2**: 101–118.
- Swandulla D, Schäfer K, Lux HD. Calcium channel current inactivation is selectively modulated by menthol. *Neurosci Lett* 1986; **68**: 23–28.