

## SHORT COMMUNICATION

# Effect of oxolamine on cough sensitivity in COPD patients

B. B. CEYHAN AND S. KARAKURT

Department of Pulmonary Medicine, Marmara University School of Medicine, Istanbul, Turkey

Cough is the most common symptom of chronic obstructive pulmonary disease (COPD) (1). Mucolytic expectorant and anti-tussive therapy had been largely overlooked because of the difficulty in demonstrating effectiveness by objective criteria, the lack of definitive clinical data and uncertainty about the type of patients who are likely to benefit from this therapeutic modality. Oxolamine is one of the synthetic derivatives of 3,5-disubstituted 1,2,4-oxodiazole, used particularly for its anti-tussive activity (2). Although the anti-inflammatory action of oxolamine in the airway was observed in animal experiments, little is known about the effect of oxolamine on the cough symptoms of COPD patients (3).

The provocation studies would be useful in studies of cough. Capsaicin is the pungent component of hot pepper that specifically stimulates afferent nerve fibres, non-myelinated C-fibre endings in the lungs (4). It is well tolerated as a cough provocator in COPD patients (5–7). The primary objective of this study was to assess the safety and efficacy of orally administered oxolamine syrup vs. placebo as an adjunctive therapy and to evaluate objectively the use of cough sensitivity test in determining the efficacy of anti-tussive therapy in patients with COPD.

This study was carried out on 19 COPD patients with the symptom of cough as defined by ATS criteria (1). Patients completed a cough and other symptoms diary during an initial 1 week run-in period. Symptom parameters included assessments of the following: cough frequency, sputum production, chest discomfort, dyspnoea and frequency of as-required  $\beta_2$  agonist use. The patients' global assessment was defined as the sum of symptom scores which contained a definition of each rating scale (1–5) (8). At the end of the run-in period, cough sensitivity to

inhaled capsaicin and lung function test indices were measured. The patients were then randomized to either oral oxolamine phosphate syrup (PEREBRON® 50 mg 5 ml<sup>-1</sup>, Santa Pharma, Istanbul, Turkey) or placebo (prepared by drug company). Four weeks later they had repeated cough challenge with capsaicin, lung function test and 1 week symptom scoring. The same procedure was then repeated with the other choice. Each patient received 100 mg oxolamine twice daily. The assigned regimen was entered to each patient for 4 weeks in a single-blind, placebo-controlled, cross-over, randomized design. Measurement of cough threshold to inhaled capsaicin was carried out using the method reported previously (9). The capsaicin cough threshold was defined as the lowest concentration of capsaicin causing five or more coughs ( $D_5$ ). Capsaicin cough threshold values were log-transformed and expressed as geometric mean  $\pm$  SEM. Friedman variance analysis, Wilcoxon-signed rank test and Spearman Rank correlation tests were used as statistical tests.

The clinical characteristics of patients are given in Table I. Regarding pulmonary function tests no significant changes were observed in each study period (Table I). Ten of 19 (53%) of patients reported improvement and relief of cough symptoms after oxolamine but symptom scores did not result in any statistical significance. The geometric mean of cough threshold was  $-0.23 \pm 0.03 \mu\text{M}$  (95% CI:  $-0.30$  to  $-0.17$ ) in run-in period and  $-0.10 \pm 0.07 \mu\text{M}$  (95% CI:  $-0.26$ – $0.05$ ) after placebo, and  $0.16 \pm 0.09 \mu\text{M}$  (95% CI:  $-0.040$ – $0.36$ ) after oxolamine ( $P < 0.01$ , Table I). The capsaicin cough threshold increased significantly after oxolamine compared with the run-in period ( $P < 0.0007$ ); there was no significant difference between placebo and run-in period cough thresholds (Table I). The cough threshold for capsaicin increased in 6/19 (32%) of patients after placebo and in 12/19 (63%) of patients after oxolamine. There were no correlations between cough threshold and lung function test parameters and symptom scores.

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Correspondence should be addressed to: Dr Berrin Bağcı Ceyhan, Marmara University Hospital, Department of Pulmonary Medicine, Altunizade, Istanbul, Turkey. Fax: 90-216-3027107; E-mail: [bbcey@superonline.com](mailto:bbcey@superonline.com)

**TABLE I.** Clinical characteristics of patients

Male	15		
Female	4		
Age (yr)	65 ± 12		
Duration of disease (yr)	9.6 ± 9.0		
	Run-in period	Placebo	Oxolamine
FEV <sub>1</sub> (l)	1.46 ± 0.79	1.55 ± 0.86	1.53 ± 0.88
FEV <sub>1</sub> pred (%)	52.8 ± 21.9	54.6 ± 24.2	55.5 ± 24.8
FEV <sub>1</sub> /FVC (%)	60.6 ± 13.2	62.0 ± 14.3	60.0 ± 15.8
Symptoms cores	2.02 ± 0.69	1.91 ± 0.74	1.92 ± 0.76
Cough score	2.14 ± 0.98	2.01 ± 0.99	1.96 ± 1.08
Cough sensitivity (D5 log) μM	-0.23 ± 0.03	-0.10 ± 0.07	0.16 ± 0.09*
CI95%	-0.30-0.17	-0.26-0.05	-0.040-0.36

\**P* < 0.01.

The reasons for the difference between perception and cough sensitivity are unclear. It is known that the patients with more severe fixed airway obstruction perceive acute changes in dyspnoea less well and dyspnoea is poorly correlated with lung function test indices (10). Furthermore, the perception of symptoms for COPD patients is known to be blunted in comparison with normal controls and asthmatics (11). Hence, they may not register improvements in symptoms following oxolamine therapy.

Ours is the first study to our knowledge to assess the anti-tussive effect of oxolamine in patients with COPD using capsaicin test. A few studies with capsaicin were applied in patients with COPD previously (5,7). Capsaicin was used to investigate the efficacy of several antitussive drugs. Gamma-aminobutyric acid (GABA) is a central inhibitory neurotransmitter that also exists in lung, has been shown to inhibit cough response to inhaled capsaicin (12). Furthermore, Fuller *et al.* used capsaicin to investigate the sensitivity of cough response against to inhaled and systemic opiates (13).

We could not find any difference in lung function test parameters after oxolamine and any correlation between forced expiratory volume in 1 sec (FEV<sub>1</sub>) and cough symptom scores in our study. The findings of this study were in agreement with previous reports in that no significant changes in lung function parameters were detected after adjunctive anti-tussive or mucolytic therapy (14). It has also been shown that cough sensitivity did not correlate with FEV<sub>1</sub> in asthmatics (15).

In conclusion, this randomized single-blind, placebo-controlled study demonstrated that oxolamine reduced cough sensitivity and statistically insignificant symptom improvement in patients with COPD. These results can be interpreted as a pilot observation rather than a definitive investigation because of small numbers of patients and single-blind study protocol. Further studies

are needed to test clinical effectiveness and safety of oxolamine given as adjunctive therapy in COPD patients.

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