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Effect of Clarithromycin on Sputum Production and Its Rheological Properties in Chronic Respiratory Tract Infections

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Macrolide antibiotics possess a variety of actions other than antimicrobial activities. To determine the effects of long-term administration of clarithromycin (CAM) on the amount and physical properties of sputum in patients with clinical conditions associated with excessive airway secretions, we conducted the present study in a parallel, double-blind, placebo-controlled fashion. Patients were divided into two groups: the first group ($n = 16$) received CAM (100 mg, twice a day) for 8 weeks, and the second group ($n = 15$) received placebo. In evaluating airway secretion, the daily amount of expectorated sputum, solid composition, viscoelastic properties (including elastic modulus and dynamic viscosity), and sputum microbiology were assessed. CAM decreased sputum production from 51 ± 6 to 24 ± 3 g/day after treatment, whereas placebo had no effect. The bacterial density and sputum flora were unaltered. In the group receiving CAM, the percent solid composition and elastic modulus increased from 2.44% ± 0.29% to 3.01% ± 0.20% and 66 ± 7 to 87 ± 8 dyne/cm^2 ($P < 0.05$), respectively, but the dynamic viscosity remained unchanged. These results suggest that long-term treatment with CAM reduces the amount of sputum production, probably by inhibiting airway secretions, and increases sputum elasticity.

There is increasing evidence that long-term administration of the macrolide antibiotic erythromycin is effective in the treatment of chronic respiratory infections, probably through actions other than its antimicrobial properties (6). Although the mechanism of the efficacy is uncertain, several hypotheses have been proposed, such as immunomodulatory action on inflammatory cells (1, 8), inhibition of glycoconjugate secretion from submucosal glands (3), and inhibition of airway epithelial chloride transport and the concomitant secretion of water (12). However, the effects of newly developed macrolides on airway secretion are unknown. Therefore, to investigate whether long-term treatment with oral clarithromycin (CAM) alters sputum production and its rheological properties, we conducted a placebo-controlled trial with a group of patients with chronic bronchitis, bronchiectasis, or diffuse panbronchiolitis. Diffuse panbronchiolitis is a recently described clinicopathologic condition which is found in Japanese, Chinese, and Korean populations and which is characterized by severe, chronic airflow limitation and excessive sputum production accompanied by persistent sinopulmonary infection, respiratory bronchiolitis, and peribronchiolitis (4).

MATERIALS AND METHODS

Patients. Thirty-one patients, 33 to 77 years of age, who had chronic bronchitis, bronchiectasis, or diffuse panbronchiolitis and who had been continuously expectorating more than 30 g of sputum per day for at least 2 weeks prior to the study were selected after their consent was obtained. All cases of chronic bronchitis conformed to the World Health Organization's definition of the disease (15), and all patients with chronic bronchitis were or had been heavy smokers. Bronchiectasis was confirmed by computer tomography of the chest. The diagnosis of diffuse panbronchiolitis was established by transbronchial lung biopsy (4). None of the patients had received treatment with antibiotics, mucolytic agents, corticosteroids, or anticholinergic agents during the previous 14 days. For eight patients (two with bronchiectasis and six with diffuse panbronchiolitis) the expectorated secretions contained *Pseudomonas aeruginosa*, for two patients the secretions contained *Haemophilus influenzae*, and for one patient the secretion contained *Staphylococcus aureus*, but there was no evidence of pneumonic consolidation on any chest radiograph.

Study design. The study was conducted in a parallel, double-blind, placebo-controlled fashion with a 2-week run-in period. A doctor not involved in the disease follow-up or data analysis was assigned the task of dividing the patients into two groups matched for clinical diagnosis (Table 1). Patients continued their usual therapies, including oral and inhaled β_2-adrenergic agonists and oral theophylline preparations. In the first group (CAM group; $n = 16$), patients received oral CAM (100 mg, twice a day; Taisho Pharmaceutical Co. Ltd., Tokyo, Japan) for 8 weeks. In the second group (placebo group; $n = 15$), patients received identical placebos by the same route and on the same schedule. Patient compliance with the medication schedule was assessed from an individual record supplied by each patient at the end of the trial.

Analysis of sputum. All patients were hospitalized for 2 days prior to the beginning of the run-in period, during which time they were instructed to collect and weigh their sputum samples accurately. The patients were then given preweighed, covered plastic cups and were asked to collect and weigh all sputum expectorated during every 24 h of the run-in period and the following trial period at home. They were also asked to swallow saliva immediately before the expectoration of sputum to minimize mixing with saliva. At the beginning and after 4 and 8 weeks of the trial, sputum samples collected in the morning (0700 to 1000 h) were transported to the laboratory, and after the determination of the wet weight, they were dried in a microwave oven (500 W for 30 min) and reweighed. The percent solid composition (%SC) was then calculated from the ratio of wet to dry weight (9).

To determine alterations in rheological properties of the sputum, parameters of viscoelasticity, i.e., the elastic modulus (G') and dynamic viscosity (η'), were measured by a microrheometric method of Lutz and associates (7). To perform these measurements, a magnetically oscillated steel microsphere suspended in a drop of mucus was used as a mechanical probe, and the oscillation amplitude of a 100- to 200-μm-diameter iron sphere driven by sinusoidal magnetic forces was recorded. The measurements were made at a frequency of 10 Hz, because this frequency approximates the human tracheal ciliary beat frequency (5). Two or three specimens from each sputum sample produced between 0700 and 1000 h were tested, and the results were expressed as the means.

To assess the change in bacterial density of the sputum, 500-mg aliquots of the sputum were diluted 1:1 in sterile distilled water, vortexed to achieve a uniform suspension, and subsequently diluted in serial 10-fold increments. These samples were spread on sheep blood agar, MacConkey agar, colistin-nalidixic acid-sheep blood agar, and *Haemophilus* isolation agar, and colony counts on the plates were made to calculate $\log_{10}$ CFU per gram of sputum. *P. aeruginosa* was identified as gram-negative, non-lactose-fermenting colonies, and other organisms were identified by conventional techniques.

Statistics. All data are expressed as means ± standard errors. Statistical analyses were performed by the Kruskal-Wallis one-way analysis of variance, and a P value of less than 0.05 was considered significant.

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TABLE 1. Demographic characteristics of patients

Characteristic	Value for group	
	CAM (n = 16)	Placebo (n = 15)
Age (yr)		
Mean ± SE	58 ± 6	61 ± 5
Range	33–72	44–77
No. of males	11	9
No. of females	5	6
No. with diagnosis[a]		
CB	9	7
BE	3	4
DPB	4	4
No. with other therapy		
Inhaled β_2 agonists	3	4
Oral β_2 agonists	2	2
Oral theophylline	5	3

[a] CB, chronic bronchitis; BE, bronchiectasis; DPB, diffuse panbronchiolitis.

RESULTS

All patients completed the study protocol, with medication schedule compliance being 96% ± 2% (n = 16) for the CAM group and 95% ± 2% (n = 15) for the placebo group over the 8-week treatment period. No apparent adverse effects were seen in either the CAM group or the placebo group during the trial, but two patients in the former group complained of dryness of the mouth at 4 weeks.

As shown in Table 2, the amount of daily sputum production for the placebo group did not change during the 8-week trial period. In contrast, the administration of CAM gradually decreased sputum production after 4 weeks, and this decrease became significant after 6 weeks and remained so. The amount of sputum decreased from the baseline value of 51 ± 6 to 24 ± 3 g/day after 8 weeks ($P < 0.001$, n = 16). Patients with diffuse panbronchiolitis produced greater quantities of sputum than did those with chronic bronchitis or bronchiectasis, but the efficacies of CAM were similar in the three diseases. Administration of placebo did not significantly alter the %SC, G′, or η′ of the sputum during the trial, and CAM likewise did not affect these parameters until 4 weeks of treatment. However, administration of CAM for 8 weeks increased the %SC and G′ from 2.44% ± 0.29% to 3.01% ± 0.20% and from 66 ± 7 to 87 ± 8 dyne/cm^2 ($P < 0.05$; n = 16 in each case), respectively, whereas it did not significantly alter the η′.

TABLE 2. Sputum analysis results before and after 8 weeks of treatment

Sputum characteristic	Value[a] for group			
	CAM (n = 16)[b]		Placebo (n = 15)[c]	
	Before treatment	After treatment	Before treatment	After treatment
Wet wt (g/day)	51 ± 6	24 ± 3	45 ± 4	42 ± 5
%SC	2.44 ± 0.29	3.01 ± 0.20	2.35 ± 0.50	2.53 ± 0.38
G′ (dyne/cm^2)	66 ± 7	87 ± 8	64 ± 4	66 ± 4
η′ (P)	36 ± 3	41 ± 4	38 ± 3	40 ± 4
Log_{10} CFU bacteria/g	3.8 ± 0.7	3.2 ± 0.6	3.3 ± 1.1	2.9 ± 0.8

[a] Values are expressed as means ± standard errors.
[b] Statistically significant differences between values before and after treatment were observed only for wet weight ($P < 0.001$), %SC ($P < 0.05$), and G′ ($P < 0.05$).
[c] No differences between values before and after treatment for the placebo group were statistically significant.

For both groups, neither changes in the total bacterial CFU per gram of sputum nor differences in bacterial flora in the sputum samples were observed during the trial, and there was no correlation between colony counts and the effectiveness of CAM in reducing sputum production.

DISCUSSION

Our double-blind, placebo-controlled study demonstrates that long-term treatment with the newly developed macrolide CAM decreased the amount of sputum expectorated by patients with either chronic bronchitis, bronchiectasis, or diffuse panbronchiolitis. Increased production of sputum is one of the most common symptoms of chronic bronchitis, bronchiectasis, and diffuse panbronchiolitis (4, 15). Large quantities of airway secretions interfere with mucociliary clearance of inhaled particles, bacteria, and cellular debris from conducting airways (14) and cause airway obstruction (13). Moreover, a 22-year mortality survey of more than 1,000 patients with chorionic bronchitis showed that mortality was related not only to the severity of airway obstruction but also to chronic sputum production (2). Because all patients who entered into the present study had complained of continuous expectoration of excessive sputum, the reduction of sputum production by CAM may benefit their clinical course.

Although the mechanisms underlying airway hypersecretion in chronic respiratory diseases are uncertain, infectious or inflammatory events and the generation of putative mediators may play important roles. In the present study, treatment with CAM had no influence on sputum microbiology, suggesting that the CAM-induced decrease in sputum production may not be attributable to the antibacterial activity of the drug itself. However, expectorated sputum is not representative of lower airway secretion in terms of bacterial flora. Thus, the possibilities that CAM acted as an antibiotic and that the decrease in sputum production resulted from better control of lower airway infection cannot be excluded. It is also possible that the observed effect of CAM could show only that less sputum was removed from the respiratory tract because of the impairment of ciliary activity of airway epithelial cells to propel the sputum toward the oropharynx. However, this possibility seems unlikely, because the macrolide instead stimulates ciliary motility without affecting the coordinated beating pattern of cilia (11). Therefore, we speculate that the effect of CAM on sputum production might be derived from its inhibitory action on airway secretory cells.

It has recently been shown that long-term therapy with low doses of erythromycin is effective in the treatment of diffuse panbronchiolitis (6), probably through actions other than its antibacterial activity. Regarding the effects on airway secretory responses, Goswami and coworkers (3) have reported that erythromycin directly inhibits glycoprotein secretion from submucosal glands, and we have shown that erythromycin inhibits chloride secretion of airway epithelial cells and the concomitant secretion of water across the mucosa toward the respiratory lumen (12). These findings support our speculation that CAM might have exerted its effect through the inhibition of airway secretion.

During the 8-week treatment with CAM, the SC and G′ of the sputum increased, whereas the η′ did not. The increases in SC and G′ suggest decreased hydration of the sputum and/or increased mucus glycoprotein secretion, but the latter possibility is unlikely, because the calculated values of total solids (sputum wet weight × %SC) decreased from 1.24 g/day on day 0 to 0.72 g/day after treatment. These results suggest that CAM reduced secretion of both mucus and water in the airway. In

the present study, CAM increased the G′ but had no effect on the η′ of the sputum. A previous in vitro study with reconstituted lyophilized mucus showed that the transport rate of mucus in bullfrogs increased with increasing G′ up to 10 dyne/cm^2 and then gradually decreased with increasing elasticity (10). However, this finding may not be true for human airways in vivo, and the clinical significance of the altered sputum elasticity is uncertain.

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