Chemical Properties of Bronchorrhea
Sputum in Bronchial Asthma*

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Bronchorrhea, defined as watery sputum of 100 ml or more per day, was seen in 18 of 207 patients (8.7 percent) with bronchial asthma during attack. Fifteen bronchorrhea sputum samples were chemically examined using ten parameters: dry weight, albumin, IgA, pH, Na+, Cl−, K+, prostaglandins E and F and histamine, and compared with eight saliva samples and 17 mucoid sputum samples. Bronchorrhea sputum differed from saliva in its chemical parameters. Bronchorrhea sputum exhibited parameter values intermediate between those of saliva and mucoid sputum, except for the two following parameters. The pH of bronchorrhea sputum was significantly lower than that of mucoid sputum and histamine concentration, expressed as weight per dry weight of sample, was significantly higher in bronchorrhea than in mucoid sputum. Administration of corticosteroid or an histamine H1-blocker to five to nine asthmatic patients with associated bronchorrhea sputum during asthmatic attacks, significantly reduced the volume of bronchorrhea sputum, whereas anticholinergics and H2-blocker did not alter the sputum volume. (Chest 1988; 94:1211-15)

METHODS

Subjects

From 1973 to 1984, 207 patients with bronchial asthma (excluding repeated admission) were hospitalized in the First Department of Internal Medicine, Tohoku University Hospital, because of an asthma attack with no significant respiratory infection. On admission, sputum specimens were cultured quantitatively by tenfold serial dilution and attempts to detect the bacteria causing the airway infection failed. Patients with fever (37.5°C or higher) were also excluded from the present study since it was possible that they had viral airway infection, as well as bacterial infections. The group of patients studied consisted of 118 male and 89 female subjects aged 43.7 ± 17.1 years. During the asthma attack, 44.4 percent (92 patients) experienced significant sputum production of 64.5 ± 15.1 ml per day declining to 14.3 ± 27.2 ml per day during clinical remission (p<0.01, paired Student's t-test), and they contained 8.7 percent (18 patients; 11 men and seven women) who had "bronchorrhea," defined as production of over 100 ml per day of watery sputum. These patients produced 186.5 ± 81.3 ml per day during asthmatic attack which declined to 31.4 ± 36.6 ml per day during clinical remission. In the case of repeated admission, sputum volume on the first admission or in the admission closest to the date when the following chemical analysis, methacholine challenge and effect of drugs were examined, was chosen for data analysis. Fifteen bronchorrhea samples were subjected to the following chemical analysis. The diagnosis of bronchial asthma was made in accordance with the following criteria: (1) a history of asthma attack; and (2) acute reversibility of airway obstruction after inhalation of isoproterenol, defined by an improvement in FEV1, of greater than 15 percent. Patients in this group may or may not have had the following: (1) a personal history of allergic disease (allergic rhinitis or allergic dermatopathy); (2) a family history of asthma or allergic disease; (3) blood eosinophilia (total eosinophil count greater than 400); (4) sputum eosinophil population greater than 10 percent; or (5) a clinical history of inhaled or orally administered corticosteroids or cromolyn sodium. For comparative purposes, eight saliva samples were obtained from eight patients with bronchorrhea and 17 mucoid sputum samples were obtained from 15 patients with bronchial asthma (11 men and four women, 49.2 ± 18.2 years). Care was taken not to permit the patients to swallow any sputum during collection and not to include saliva in the sputum by rinsing out the mouth prior to sputum collection. All patients were receiving maintenance medication with beta-stimulants or theophylline derivatives or both, but none of them was given any medication 12 hours before or during the test.

Chemical Analysis

Saliva and sputum samples were collected over a maximum period of three hours in the morning on a day of the height of the attack and stored at −20°C until used. The samples were thawed at room temperature and were then homogenized by ultrasonification at 20

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RESULTS

Chemical C

K Hz and 100 W for 30 s before measurements. The pH was measured with a pH meter, albumin by the Brom Cresol Green method, Na+ and K+ by flame emission spectrophotometry, Cl− by Hamilton's method, IgA by laser nephrometry using anti-IgA serum, prostaglandins E and F using a prostaglandin E, Fα RI kit, dry weight by evaporation to dryness on heating at 105°C for four hours, and histamine by a fluorometric method using an autoanalyzer.

Methacholine Challenge

Within three months before or after the collection of sputum, methacholine provocation tests were performed during clinical remission using a technique reported previously. From the dose-response curves, three parameters, baseline respiratory resistance (Rbs), minimum dose of methacholine (Dmin: bronchial sensitivity) and linear slope of the Grs decreased (SGr: bronchial reactivity), were obtained and compared among the following three groups: group A consisted of 30 subjects without sputum production during asthmatic attack (15 women and 15 men, 47.8 ± 15.5 years); group B of 31 subjects with significant sputum production during attack other than bronchorrhea (15 women and 17 men, 41.9 ± 17.1 years); and group C of ten subjects with bronchorrhea during attack (four women, six men, 45.3 ± 18.9 years).

Effects of Drugs on Sputum Volume

Effects of four drugs on sputum volume were examined in five to nine subjects with associated bronchorrhea during asthmatic attacks. These were: an inhaled or intravenous anticholinergic agent (inhaled ipratropium bromide, 40 μg × 4/day, four women and three men, 55.7 ± 13.9 years, or intravenous atropine sulfate, 0.5 mg/day, one man 61 years and one woman 30 years), an orally administrated histamine H1-blocker (di-chlorpheniramine maleate, 18 mg/day, five men and one woman, 45.5 ± 21.9 years), an orally administrated histamine H2-blocker (cimetidine, 300 mg/day, two women and three men, 45 ± 15.2 years), and orally or intravenously by administrated corticosteroids (dexamethasone, 2 to 5 mg/day, or beclomethasone, 2 to 4 mg/day, two women and seven men, 49.0 ± 15.0 years). The average sputum volume (milliliters) per day for three days as duration of administration of each drug was compared with that three days before administration. When a drug was administrated and judged to be effective on sputum volume, an interval of two weeks or more was allowed between administration of the next drug to the same patient. Although some patients on repeated admission received the same drugs more than once, data regarding the effect on sputum volume were obtained from the administration which showed the most representative response.

Statistical Analysis

Statistical comparisons of means were made using two-tailed paired or unpaired Student's t-tests. Data are expressed as mean ± SD.

RESULTS

Chemical Analysis

Chemical data from saliva, bronchorrhea sputum, and mucoid sputum are shown in Table 1. Bronchorrhea sputum was significantly different from saliva in five of nine parameters and from mucoid sputum in six of ten parameters. Bronchorrhea samples showed values intermediate between saliva and mucoid sputum, except for two parameters; pH and histamine concentration. The pH values of bronchorrhea sputum were significantly lower than those of mucoid sputum (p<0.02, unpaired Student's t-test). Histamine concen-
trations in bronchrorhrea sputum, expressed as weight per dry weight of sample, were significantly higher than those of mucoid sputum (p<0.02, unpaired Student's t-test). However, when histamine concentrations were expressed as weight per deciliter of sample, no significant difference between bronchorrhea and mucoid sputum samples was found. The Na+/Cl− ratio calculated for each sample was significantly lower in bronchorrhea samples than in mucoid samples (p<0.01, unpaired Student’s t-test).

**Methacholine Challenge**

Although groups B and C tended to have somewhat lower values of Dmin and higher values of baseline Rs and SGRs than group A, no significant differences among the three groups were found with respect to the three parameters, methacholine challenge, Rs, Dmin and SGRs (Table 2).

**Effect of Drugs on Sputum Volume**

The H1-blocker or corticosteroids reduced sputum volume significantly (p<0.05 each, paired Student’s t-test), whereas anticholinergic agents or H2-blocker did not alter sputum volume significantly (Table 3). A representative example of corticosteroid-induced reduction of sputum volume is shown in Figure 1. The reduction in sputum volume was associated with relief of bronchoconstriction and clinical improvement in general. Furthermore, although the data are not shown, we had the impression that the responses to drugs were reproducible in a given patient. Although the other patients did not complain of symptoms due to the administrations of these drugs, one patient experienced difficulty in expectoration after intravenous administration of atropine. Atropine has been demonstrated to depress ciliary beat frequency and to slow airway mucociliary clearance, whereas ipratropium, in the doses used for the present study, would not have such an effect.

**DISCUSSION**

Our present study shows that 44 percent of asthmatics have mucus hypersecretion during attack, and 8.7 percent have 100 ml or more watery sputum per day during attack, ie, bronchorrhea, as defined by Keal et al. To our knowledge, there have been no studies characterizing bronchorrhea in bronchial asthma.

The present study shows that bronchorrhea sputum differs chemically from saliva, indicating that it does not result from hypersalivation. Examination of viscoelastic properties of bronchorrhea sputum has also shown a difference between saliva; bronchorrhea sputum increased in viscoelasticity over a period of some hours, whereas saliva never increased.

It is possible that bronchorrhea has its origin in the following: (1) fluid movement into the lumen by active ion transport in the epithelium; (2) increased permeability in the epithelium; (3) fluid transfer by high negative pressures within the airways, not involving increased permeability; or (4) increased submucosal gland secretion involving mainly serous cells. Among these possibilities, increased permeability seems unlikely because albumin concentration in bronchorrhea, which is known to be an indicator of permeability, is much lower, compared to mucoid sputum. Although there is no direct evidence to suggest which, among the remaining three possibilities, is the main mechanism of bronchorrhea sputum production, one can speculate on the role of “active ion transport in the epithelium” in the formation of bronchorrhea sputum. Histamine concentration, expressed as weight per dry weight of sample, in bronchorrhea sputum is significantly higher than that in mucoid sputum which is compatible with Bryant and Pui's report.

### Table 2—Methacholine Challenge Data

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline Rs (cmH2O/L/s)</th>
<th>Dmin (unit)</th>
<th>Grs (L/cmH2O/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>5.64 ± 2.39</td>
<td>0.78 ± 0.91</td>
<td>0.25 ± 0.27</td>
</tr>
<tr>
<td></td>
<td>(n=30)</td>
<td>(n=28)</td>
<td>(n=23)</td>
</tr>
<tr>
<td>B</td>
<td>5.88 ± 3.86</td>
<td>0.69 ± 0.78</td>
<td>0.34 ± 0.47</td>
</tr>
<tr>
<td></td>
<td>(n=31)</td>
<td>(n=27)</td>
<td>(n=24)</td>
</tr>
<tr>
<td>C</td>
<td>5.78 ± 3.55</td>
<td>0.71 ± 0.66</td>
<td>0.28 ± 0.17</td>
</tr>
<tr>
<td></td>
<td>(n=10)</td>
<td>(n=6)</td>
<td>(n=6)</td>
</tr>
</tbody>
</table>

**Group A**, no significant sputum during asthmatic attack; group B, sputum other than bronchorrhea during asthmatic attack; and group C, bronchorrhea during asthmatic attack.

### Table 3—Effect of Histamine H1-Blocker, Corticosteroids, Histamine H2-Blocker and Anticholinergic Agent on Sputum Volume (ml) per Day

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Before Administration, ml/day</th>
<th>After Administration, ml/day</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1-blocker (dl-chlorpheniramine malate, orally)</td>
<td>121.3 ± 46.9</td>
<td>85.1 ± 25.0 (n = 7)</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Corticosteroids (dexamethazone or beclomethazone, orally)</td>
<td>115.0 ± 120.2</td>
<td>42.3 ± 57.2 (n = 6)</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>H2-blocker (cimetidine, orally)</td>
<td>97.8 ± 56.6</td>
<td>98.5 ± 59.7 (n = 5)</td>
<td>NS</td>
</tr>
<tr>
<td>Anticholinergic agent (ipratropium bromide, inhaled)</td>
<td>162.1 ± 96.3</td>
<td>168.4 ± 110.8 (n = 9)</td>
<td>NS</td>
</tr>
</tbody>
</table>
the bronchorrhea sputum had a histamine concentration similar to mucoid sputum when expressed as weight per volume of sample, the total histamine in the secretion must be considerably greater in bronchorrhea since patients with bronchorrhea expectorated three times as much as those with mucoid sputum did. In the present study, histamine H1-blocker reduced significantly the amount of bronchorrhea sputum and H2-blocker did not alter sputum volume. Exogenous histamine added to human airways increased secretion of mucus glycoprotein which is the solid component of mucus, and this effect was inhibited by H2-antagonist but not by H1-antagonist. Thus, histamine, acting through stimulation of H2-receptors, increases airway mucus glycoprotein secretion in humans. On the other hand, histamine is known to increase secretion of the fluid component of mucus. Marin et al. have shown that histamine significantly increases the net flux of chloride and sodium toward the lumen in canine trachea (Cl- secretion) and that H2-type receptors mediate the increase of ion flux toward the lumen, which is associated with water or fluid movement. The present study revealed a significant decrease in Na+/Cl- ratio of bronchorrhea sputum, compared to that of mucoid sputum. Further, administration of corticosteroids also reduced bronchorrhea, and corticosteroids are known to inhibit the release of chemical mediators including histamine and to directly reduce submucosal gland secretion. These facts suggested that histamine released during an asthma attack may play a role in the formation of bronchorrhea sputum in the airways via the increased water movement across airway mucosa into the airway lumen. Meanwhile, there were fewer prostaglandins in bronchorrhea sputum than in mucoid sputum. Prostaglandins, especially F2α, are known to increase mucus secretion from human bronchi in vitro. It has been reported that in human airways, sputum produced after inhalation of histamine contains relatively more tissue transudate than sputum produced after inhalation of prostaglandin F2α. These facts do not conflict with the present observation that prostaglandins seem not to play a major role in the formation of bronchorrhea sputum. Further, we speculate that bronchorrhea during the asthmatic attack is not under cholinergic nervous control since the volume did not alter with either inhaled or injected anticholinergic agents. Lopez-Vidriero et al. studied the effect of atropine and found no significant change in bronchorrhea sputum volume except for one of five patients with bronchial asthma, and in no case was there any change in the sputum dry weight, neuraminic acid, or fucose content.

Compared with mucoid sputum, bronchorrhea sputum had significantly lower pH. The pH of mucus in the normal rat trachea is reported to range from 7.42 to 7.57 and average 7.52 ± 0.05 (mean ± SD) which is similar to that from mucoid sputum samples in the present study. Holma et al. have reported that ciliary inhibition is seen in bovine trachea at low pH, especially near 6.5. Thus, both low pH in bronchorrhea and much lower viscoelasticity apart from the optimal range for mucociliary velocity during the asthma attack, may indicate a lower mucociliary transport rate in the airways than in the case of mucoid sputum, probably leading to the formation of mucus plugs. Duliano and Luk have found a ciliary inhibitory factor in watery sputum obtained from bronchial asthma during attacks. It remains to be determined how the chemical and viscoelastic properties peculiar to bronchorrhea found in our study are related to the ciliary inhibitory factor.

Although patients with mucus hypersecretion showed somewhat lower Dmin than patients without sputum during attack, the differences were not statistically significant. Recent studies have shown that bronchial sensitivity to inhaled aerosol is underestimated when mucus hypersecretion occurs. This

![Figure 1. A typical example of bronchorrhea from a patient during asthmatic attack (30-year-old woman). She expectorated 200 to 500 mL per day of watery sputum with asthmatic dyspnea on admission. Inhaled or intramuscular anticholinergic agents (ipratropium bromide or atropine sulphate) did not alter the volume but intravenously or orally administered corticosteroid (dexamethasone) abolished expectoration.](image-url)
may be one possible explanation for the lack of a significant difference in bronchial sensitivity among the three groups in the present study, since half of the patients with hypersecretion still had significant sputum even during remission, in spite of the significant reduction in volume.

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