A Trial of Aerosolized Theophylline in Relieving Bronchospasm*

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Theophylline was administered as an aerosol to nine patients with known bronchospastic disease. No significant improvement in the forced expiratory volume in one second was observed after administration of aerosolized theophylline, although improvement did occur following administration of aerosolized isoproterenol. The theoretic mechanisms of bronchodilator aerosols are discussed, as well as the possible reasons for not obtaining a response with administration of theophylline.

Aminophylline (theophylline ethylenediamine) has been established as an effective treatment for bronchospasm since its introduction in 1937 by Hermann and Aynesworth.† The drug has been used widely in oral, rectal, and parenteral forms. Although there is good correlation between therapeutic effects or toxic manifestations and serum concentration, erratic and unpredictable absorption of oral and rectal agents has been a problem. Furthermore, studies have also shown that half-lives are variable even with parenteral administration. Theophylline given as an aerosol has theoretic advantages in avoiding these problems. This route of therapy has been reported to be successful by several investigators, however, these studies were not controlled and had several problems in experimental design. In 1949, Segal et al stated that administration of aerosolized aminophylline was not beneficial; however, in this study, his only objective measurement was the forced vital capacity. Because of the lack of agreement on the value of aerosol therapy, we decided to study the problem. If a low-dosage form of theophylline was effective as an aerosol without producing therapeutic levels of the drug in the serum, this would suggest that local receptors existed in the tracheobronchial tree.

Our initial intention was to design a double-blind study comparing theophylline to isoproterenol and saline aerosolized by a micronebulizer (Bird). We planned to use spirometric measurements (forced expiratory volume in one second [FEV1]; mean forced expiratory flow during the middle half of the forced vital capacity [FEF25-75%]) and body plethysmographic studies (total airway resistance) at frequent intervals over several hours to measure the response to the administered drug. Serum levels of theophylline would be measured to exclude the possibility of a systemic effect; however, before embarking on such a study, we needed to determine in a pilot study what dose of theophylline to administer. Since the micronebulizer can nebulize at a rate of approximately 5 ml every 15 to 20 minutes, the maximum dose for that period of time would be 5 ml of undiluted theophylline solution (62.5 mg). There was no attempt to make this pilot study double-blind or to monitor serum levels of theophylline after administration of the drug, since our purpose was to determine if any significant reversal of bronchospasm occurred with the maximum dose. The present paper is the report of that pilot study, which confirms the negative findings of Segal et al. The lack of improvement in the FEV1 in a group of subjects who responded to isoproterenol administration suggests that theophylline is not clinically efficacious by the aerosol route.

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parabens per milliliter at pH 8.9 (Microphyllin*).

The patients discontinued the use of all theophylline-containing drugs for at least 24 hours and all sympathetic amines for at least 12 hours prior to the experiment. Five milliliters (69.5 mg) of the theophylline solution was administered by the micronebulizer connected to a motor-driven pump. The time for nebulization usually required 10 to 15 minutes. Spirometric studies were performed with a bellows spirometer (Med Science Electronics) immediately prior to the administration of theophylline and 20, 40, and 60 minutes later. At the conclusion of the experiment, 250 µg of isoproterenol was given by a propellant-driven hand-held nebulizer, and the spirometric studies were repeated.

Blood was drawn immediately prior to starting the experiment, and later the serum was analyzed for theophylline. The technique employed was essentially that of Schack and Waxler, but as modified by Jenne et al. This was done to ensure that any lack of response was not secondary to an already existing therapeutic serum level of the drug.

RESULTS

Patients found to have baseline serum levels of theophylline greater than 3 mg/ml prior to receiving aerosolized theophylline were excluded from the analysis. There were nine remaining patients, seven men and two women, with mean age of 50 years (range, 33 to 57 years). The mean serum level of theophylline for this group prior to receiving theophylline was 0.81 µg/ml (range, 0 to 2.12 µg/ml). These low values might, in part, be related to interfering substances found in coffee, tea, cola, and cocoa but are not considered clinically effective. Among individual patients, there was no relationship between the degree of response to aerosol administration of theophylline or isoproterenol and the low baseline serum level of theophylline.

Table 1 shows the cumulative data on FEV1, with each time period analyzed for significance by the paired Students’ t-test for dependent variables.

<table>
<thead>
<tr>
<th>Patient</th>
<th>After Theophylline</th>
<th>After Isoproterenol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 min</td>
<td>20 min</td>
</tr>
<tr>
<td>1</td>
<td>1.05</td>
<td>1.20</td>
</tr>
<tr>
<td>2</td>
<td>2.45</td>
<td>2.45</td>
</tr>
<tr>
<td>3</td>
<td>1.77</td>
<td>1.65</td>
</tr>
<tr>
<td>4</td>
<td>0.90</td>
<td>0.75</td>
</tr>
<tr>
<td>5</td>
<td>1.55</td>
<td>1.40</td>
</tr>
<tr>
<td>6</td>
<td>1.90</td>
<td>1.85</td>
</tr>
<tr>
<td>7</td>
<td>1.65</td>
<td>1.97</td>
</tr>
<tr>
<td>8</td>
<td>0.80</td>
<td>0.85</td>
</tr>
<tr>
<td>9</td>
<td>0.75</td>
<td>0.75</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>1.42 ± 0.58</td>
<td>1.43 ± 0.60</td>
</tr>
<tr>
<td>P</td>
<td>. . .</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Significance was tested by comparing this group at 40 minutes with the same group (patients 2 to 9) at 0 minutes.

There was no significant response in the FEV1 to administration of theophylline for any period within 60 minutes. Nevertheless, each patient obtained a significant improvement in the FEV1 within five minutes after administration of isoproterenol (P < 0.01).

DISCUSSION

Both the methyl xanthines, such as theophylline, and the catecholamines are thought to cause bronchodilatation by increasing intracellular levels of adenosine 3':5'-cyclic phosphate (cyclic AMP).

The xanthines inhibit its breakdown by phosphodiesterase, while catecholamines increase cellular levels by stimulating adenylyl cyclase. The cyclic AMP relieves bronchospasm either by a relatively direct effect on smooth muscle or by inhibiting release of mediators from mast cells. There is evidence that bronchodilator drugs may act through local receptors in the bronchial tree. Dautrebande and Heymons have shown that aerosol administration of sympathomimetic drugs can cause bronchodilatation in isolated lungs from guinea pigs. Lovejoy et al. have reported that very small doses of bronchodilator administered as a microaerosol (particles less than 0.5 µm in diameter) can have an effect equal to that produced by doses 30 times as great delivered by large-particle aerosols (particles 2 µm to 20 µm in diameter). Since the small particles of a microaerosol are thought to be deposited in the more peripheral airways, this suggests that local receptors may reside in these airways. If the response was related to systemic absorption alone, it would seem that the larger particle (and, therefore, larger dose) would have produced a greater effect. Evans and associates reported that salbutamol delivered as an aerosol can have its maximum effect within minutes, whereas the peak level in the blood...
occurs at three to four hours after administration. On the other hand, it is probable that aerosols may also work through a systemic effect following absorption into the bloodstream. One argument favoring this hypothesis is that aerosols are effective despite the fact that most of the material is deposited centrally and shunted away from the areas of most severe bronchoconstriction. Also, the systemic side effects which occasionally occur suggest that these drugs are absorbed and redistributed.

Although administration of theophylline might benefit the patient with bronchospasm, possible systemic toxic effects include headache, nausea, vomiting, diarrhea, convulsions, precordial pain, or arrhythmias. Patients with chronic obstructive pulmonary disease who are in a state of respiratory failure frequently have arrhythmias aggravated by hypoxemia, acidosis, and therapy with sympathetic amines. Parenteral administration of theophylline represents an additional potential hazard. Similarly, while patients with acute myocardial infarction and bronchospasm might benefit from therapy with theophylline, there exists the potential side effects of tachycardia and arrhythmias. Most toxic effects correlate well with serum levels of theophylline greater than 20 μg/ml. An effective means of delivering theophylline as an aerosol could avoid high serum levels and reduce toxic effects.

There are several possible explanations for our negative results. It might be that the dose delivered was inadequate, despite the fact that the concentration of the solution (12.5 mg/ml) was much higher than the known effective serum concentration of theophylline (greater than 10 μg/ml). Since only small volumes of material can be deposited in the peripheral airways by aerosol techniques, even higher concentrations of solutions (if available) also might have been ineffective. Nebulization of larger volumes of the available concentration would not be practical due to the time necessary for treatment. Although it might be argued that the micronebulizer is less effective than the propellant-driven aerosol, the particle size delivered by each method is similar, and they have been found to be equally effective in the nebulization of other bronchodilator drugs. A third possible reason for negative results is that the patients were refractory to therapy with theophylline. This seems unlikely, since their serum levels of theophylline were clinically insignificant, and they did respond significantly to administration of isoproterenol. A fourth reason for negative results might have been that the theophylline did reduce bronchospasm, but we were unable to detect it. For example, if bronchospasm were relieved only in a few local areas, the total air-flow obstruction may have remained essentially unchanged. Alternatively, a possible reduction in airway resistance might have occurred in the small airways and gone undetected by analysis of FEV₁. Although the latter might have occurred, we could still conclude that theophylline was much less effective than isoproterenol in reducing total airway obstruction. A last explanation is that the receptor for theophylline cannot be reached by the aerosol route. It might be that membrane transport does not take place to the receptor in the lung or that the receptor is removed from the lung, such as a location in the central nervous system.

Although negative results are sometimes frustrating, we believe that this experiment raises important theoretic questions about the mechanism of aerosol therapy. Are sympathomimetic amines effective as aerosols primarily because the respiratory mucosa allows systemic absorption? On the other hand, if aerosols of sympathomimetic amines work primarily via a local topical mechanism, why do not methyl xanthines work as well?

REFERENCES
9 Segal MS: Advances in inhalation therapy, with particular references to cardio-respiratory diseases. N Engl J Med 231:553-556, 1944
Elephant Tusks

It excites our imagination to hear of the immense weight and length of some of the largest known tusks. The longest are in the American Museum of Natural History. They measure 11 feet and 5½ inches and 11 feet, with a total weight of 293 pounds. The heaviest tusks, either as a pair or singly, are in the British Museum. The statistics of these tusks are: 10 feet 2½ inches long, 23½ inches in circumference, 214 pounds. As usual with elephant tusks, the longer one is thinner and lighter. The second heaviest pair of tusks were taken by Major Powell-Cotton in Uganda, early this century, though an elephant has recently been shot in Tanzania that rivals this in size and thickness. The Uganda tusks are the thickest on record: 9 feet long, 25 inches in circumference, 198 pounds; 8 feet 11 inches long, 23½ inches in circumference, 174 pounds.