**Oral Sustained-Release Aminophylline and Bronchodilator Response to Inhaled Fenoterol in Patients with Chronic Airflow Obstruction**

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The bronchodilator response to inhaled fenoterol (400 μg) was examined in the morning and in the afternoon before and during oral sustained-release aminophylline treatment in eight patients with chronic reversible airway obstruction. Bronchodilatation was evaluated by measuring serial peak expiratory flow rates (PEFR) for eight hours after inhaled fenoterol and calculating the area under the time-response curves and the percentage increment from the baseline values. The patients showed an enhancement of the bronchodilatation achieved with fenoterol in the morning during aminophylline treatment. In the afternoon, instead, the effect of the fenoterol was not improved by oral aminophylline. This different effect of oral aminophylline might depend on the variable degree of potential reversibility present or diurnal variation in the bronchial response.

It is common practice to use the combination of oral theophylline and beta-adrenergic agonist inhalers in the treatment of reversible airway obstruction. It has been assumed, in fact, that these drugs may, when used together, produce a greater bronchodilatation than that obtained by each drug alone. Both drugs have been shown to increase cyclic AMP in bronchial and bronchiolar smooth muscle. Adrenergic agonists mediate this by stimulating adenyl-cyclase and theophylline compounds by inhibiting phosphodiesterase.

Our study was designed to determine whether an oral sustained-release aminophylline treatment might improve the bronchodilatation normally achieved with fenoterol (a beta-adrenergic agonist) administered by pressurized aerosol in conventional dose.

**Patients and Method**

Eight patients (mean age 54.1 years) with stable chronic airway obstruction were studied. Table 1 summarizes their age, sex, diagnosis, duration of illness, and the results of screening spirometry. Patients with cardiovascular or liver diseases were excluded. None had received corticosteroids orally during the previous two months. All the patients were experienced users of metered-dose inhalers which, however, were discontinued 72 hours before the study. All had a baseline forced expiratory volume in the first second (FEV₁) under 75 percent of their predicted value and a sufficient reversibility to produce at least 15 percent incremental response in the FEV₁, 15 minutes after inhaling 400 μg of fenoterol given by metered-dose inhaler (two puffs) at 8:00 AM. All who entered the study gave their consent. Xanthine-containing foods and beverages were prohibited during the study.

The study design is shown in Table 2. Identi...
Table 2—Design of Studya

<table>
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<th>6</th>
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<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhalers</td>
<td>8:00 AM</td>
<td>F</td>
<td>P</td>
<td>F</td>
<td>F</td>
<td>P</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>P</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>P</td>
</tr>
<tr>
<td></td>
<td>4:00 PM</td>
<td>F</td>
<td>P</td>
<td>F</td>
<td>F</td>
<td>P</td>
<td>F</td>
<td>F</td>
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<td>F</td>
<td>P</td>
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<tr>
<td>Tablets</td>
<td>Placebo</td>
<td>A</td>
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<tr>
<td></td>
<td>Aminophylline</td>
<td>A</td>
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</table>

*P is placebo; F, fenoterol.

Table 3—Peak Expiratory Flow Rate (PEFR) Responses to Inhaled Fenoterol Assessed in Morning (M) and Afternoon (A) during Oral Placebo and Aminophylline Therapy

<table>
<thead>
<tr>
<th>Oral Treatment</th>
<th>AUC (0-8 hr) (L/min × hour)</th>
<th>Percentage Increment from baseline value</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>A</td>
<td>p</td>
</tr>
<tr>
<td>Placebo</td>
<td>330.2</td>
<td>106.6 (0.005)</td>
<td>33.1 (15.5)</td>
</tr>
<tr>
<td>Aminophylline</td>
<td>441.3</td>
<td>116.4 (0.02)</td>
<td>21.2 (15.5)</td>
</tr>
<tr>
<td>p</td>
<td>0.01</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Each value represents the mean of eight subjects. Relative standard deviation expressed as percentage in parentheses.

Metered-dose inhalers were used for inhaling fenoterol and placebo (consisting of propellant only).

On each of the 15 days, the responses to inhaled placebo or fenoterol (two puffs, 400 μg), administered in the morning (at 8:00 AM) and in the afternoon (at 4:00 PM) were assessed by measurement of peak flowmeter before, 30 minutes, one, two, four, six, and eight hours after dosing, and the best value obtained in three attempts was recorded.

The patients received placebo tablets twice daily (at 8:00 AM and 8:00 PM) on days 1 to 7 and oral sustained-release aminophylline (microencapsulated theophylline-ethylendiamine) using an average dose of 8.54 ± 1.23 mg/kg/dose administered twice at the same time as placebo on days 8 to 14. Active and placebo tablets were identical in appearance and taste. The serum theophylline concentration was evaluated in the morning of the 12th day and in the afternoon of the 14th day (the fifth and seventh day of theophylline administration, sufficient time to reach a steady state of serum theophylline concentration). Five-milliliter blood samples were taken before inhaling fenoterol, and at one, two, four, six, and eight hours afterwards. Blood samples were allowed to stand at room temperature for one hour, then centrifuged for 20 minutes. The serum was stored at −18°C until the time of analysis. All serum samples were assayed in duplicate within one week of collection. The radioimmunoassay system was used.

On days 4 to 7 and 11 to 14, bronchodilator responses were evaluated by calculation, using the trapezoidal rule method, of the areas under the time-response curves of PEFR over eight hours which defines both the magnitude and the persistence of the response without relating to baseline value. In the same days, the percentage maximum increment of the PEFR after inhaled fenoterol was calculated from the baseline value. The maximum level of the PEFR response was on average one hour after inhaled fenoterol. Placebo effects were subtracted and values analyzed by Student’s t-test for paired samples.

Results

All the patients completed the study. None of them required other drugs for their respiratory disease.

The afternoon baseline values were significantly higher (p<0.05) than the morning ones during the placebo period but not during the aminophylline treatment (p = 0.20). There was no significant difference between the maximum values of the PEFR achieved by fenoterol in the morning and in the afternoon before and during aminophylline treatment (Fig 1).

In the morning, the AUC of PEFR response to inhaled fenoterol was significantly greater during the aminophylline treatment than that during the placebo period. The percentage increment of the PEFR from the baseline value was lower during aminophylline treatment than during the placebo period (Table 3). The morning baseline value during the aminophylline treatment was, in fact, significantly (p<0.05) higher than during the placebo period (Fig 1). This pattern shows that aminophylline is very active in producing bronchodilatation in the morning, and this effect is only partly at the expense of the response to inhaled fenoterol.

In the afternoon, the AUC and the percentage mean increment of the PEFR response during aminophylline treatment were not significantly different from those during the placebo period (Table 3). The baseline value during the aminophylline treatment was not

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![Graph](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21490/ on 05/31/2017)
significantly different from that during the placebo period (Fig 1). This pattern shows the poor efficacy of aminophylline to improve the bronchodilatation achievable by fenoterol in the afternoon.

The difference between morning and afternoon serum theophylline concentrations were not significant at each sampling time after fenoterol.

**DISCUSSION**

The results of this study show that the treatment with oral sustained-release aminophylline, sufficient to give an adequate serum theophylline concentration, can significantly improve the bronchodilatation achievable with inhaled fenoterol in the morning. This effect is linked to the bronchodilating activity of aminophylline rather than an enhancement of the response to β-agonist inhaler. In the afternoon, instead, aminophylline, despite the therapeutic range of serum theophylline concentration, is unable not only to induce significant bronchodilatation, but also to increase the improvement in the lung function which was produced by fenoterol. We then infer that in the absence of a baseline response to aminophylline, no enhancement of bronchodilatation may be expected.

Interpreting this variable activity of oral aminophylline is difficult. Nevertheless, since the drug was effective in the morning when the baseline values of PEFR were lower, and it was ineffective in the afternoon when the baseline values were higher, it might be attributed to a different degree of potential reversibility of airway obstruction present, as shown by Hume and Rhys Jones. No relationship was found instead by Fanta et al and Rossing et al between severity of initial airway obstruction and the response to oral theophylline and inhaled isoproterenol.

It is, therefore, also possible that there is a diurnal variation in the bronchial response to aminophylline. The serum theophylline concentrations achieved in this study, although within therapeutic range, would be inadequate to produce bronchodilatation in the afternoon. This hypothesis suggests a chronopharmacologic activity of aminophylline which needs, however, to be confirmed by further investigations.

In conclusion, aminophylline can really improve the bronchodilator response to fenoterol, but this effect should be evaluated in the light of clinical response rather than serum theophylline concentration. At present, in fact, no simple predictive formula can be offered to relate clinical response to aminophylline with its serum level.

**REFERENCES**


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Response to Inhaled Fenoterol (Carpentiere et al)