Cardiac Arrhythmias Due to Oral Aminophylline in Patients with Chronic Obstructive Pulmonary Disease*

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The effect of orally-administered aminophylline on cardiac arrhythmias was studied in 15 patients with stable chronic obstructive pulmonary disease by continuous 24-hour ambulatory electrocardiographic recordings. During the control period, the mean frequency of ventricular ectopic beats (VEBs) per hour was 43 ± 26 (range 0.3 to 401), and heart rate was 80 ± 3 beats per minute. All grades of ventricular arrhythmias were seen with occasional VEBs in five patients, frequent in three, multifocal in four, coupled beats in two, and short runs of ventricular tachycardia in one patient. Seven patients had occasional atrial premature contractions, six paroxysmal atrial tachycardia, and one patient had stable atrial fibrillation. Mean frequency of VEBs per hour and heart rate were statistically similar in patients undergoing two 24-hour control recordings. Mean grade of atrial and ventricular arrhythmias also remained similar on two control recordings. After oral aminophylline, the mean frequency of VEBs per hour increased to 72 ± 41 (P = 0.006). Heart rate increased to 88 ± 4 beats per minute (P = <0.01). The mean grade of ventricular or atrial arrhythmias remained unchanged. We conclude that orally-administered aminophylline has both arrhythmogenic and chronotrophic effects, but does not change the grade of arrhythmia.

Cardiac arrhythmias are common in patients with chronic obstructive pulmonary disease (COPD) as documented by both routine 12-lead electrocardiogram and continuous electrocardiographic monitoring. The etiology of arrhythmia in COPD is multifactorial and includes hypoxemia, acidosis, alkalosis, electrolyte imbalance, and underlying cardiac disease. Many drugs may cause arrhythmias in patients with COPD and respiratory or cardiac failure, but digitalis is most frequently implicated. Sympathomimetic agents and xanthines commonly used in the treatment of COPD have cardiac-stimulating properties that also contribute to cardiac arrhythmias. The arrhythmogenic effect of aminophylline has been well documented during intravenous therapy, but the effect of oral administration has provided conflicting results. The purpose of this study was to evaluate the effect of oral aminophylline on cardiac arrhythmias in patients with stable COPD.

Materials and Methods

Study Population

The study included 15 ambulatory patients (14 men and 1 woman) with stable COPD in whom the forced expiratory volume at one second expressed as a percentage of forced vital capacity (FEV1/FVC%) was less than 60 percent. The mean age of the patients was 66 years (range: 52 to 78). Eight patients were on longterm treatment with oral aminophylline, two patients used low-flow continuous oxygen, and four patients were receiving digoxin, which was stopped seven to ten days prior to the study. Those patients requiring oxygen, diuretics, and potassium supplements continued their use throughout the study. All patients had normal electrolytes and hematocrit. The presence or absence of cardiac arrhythmia on the resting ECG was not a factor in patient selection. However, patients with cardiac disease (other than cor pulmonale) diagnosed by history, physical examination or resting ECG were excluded. All patients signed informed consent before participating in the study.

Protocol

Upon admission, each patient underwent a physical examination, including chest x-ray film, 12-lead ECG, blood
count, electrolytes, chemistry panel, and a complete medical history.

Each patient was studied during aminophylline therapy and one \( (n = 3) \) or two \( (n = 12) \) 24-hour control periods (control 1 and 2). Control periods preceded aminophylline therapy in seven patients. Aminophylline was then given orally at a 400 mg loading dose followed by 300 mg doses every six hours. After 24 hours of drug treatment, ambulatory ECG recording was performed for 24 hours.

In the eight patients who were already receiving aminophylline before starting the study, the drug was continued at a dosage of 300 mg every 6 hours and 24-hour ambulatory monitoring was carried out. The control periods were obtained after stopping the drug for at least 48 hours. Plasma theophylline measured concentration was measured two and four hours following drug administration on the day of ambulatory ECG monitoring in both groups by ultraviolet spectrophotometer methodology.

Spirometric and forced expiratory lung volumes were measured during control and aminophylline periods with a 13-liter water seal spirometer (Warren E. Collins, Inc., Braintree, MA). Arterial blood was obtained during both periods and analyzed for \( pH \), \( PCO_2 \), and \( PO_2 \).

**Ambulatory Electrocardiographic Recording and Data Analysis**

Continuous 24-hour ECG recordings were obtained using a two-channel model 425 Avionics Holter recorder (Del-Mar Avionics, Irvine, CA). Patients were coupled to the monitoring apparatus with standard disposable silver-silver chloride electrodes utilizing modified chest lead \( V_1 \) and lead \( V_6 \). The recorder was attached around the shoulder by a strap, and it did not interfere with routine activity. An hourly event record was provided for listing activities and types of symptoms.

An Avionics model 600 dynamic electroscanner with an Avionics model 662A arrhythmia computer was employed for analysis of the recordings. Audiovisual techniques utilized to detect ventricular ectopic beats (VEBs) included oscillographic display of two simultaneous channels of electrographic data and the R-R interval, and the use of an R wave-triggered sound system. The arrhythmia analyzer employed variable characteristics of prematurity, QRS width and QRS amplitude. These criteria were individually adjusted for each recording analysis to detect and assess automatically the frequency of VEBs. Ventricular ectopy was measured quantitatively as VEBs per hour and qualitatively according to the Lown grading classification.\(^{14}\) Lown grades are defined as grade 0 (absence of ventricular ectopy), grade 1 (less than 2 VEBs per minute or 30 per hour), grade 2 (2 or more VEBs per minute or greater than 30 per hour), grade 3 (multiform VEBs), grade 4A (couplets of VEBs), grade 4B (three or more consecutive VEBs), and grade 5 (early cycle VEBs with or on T phenomena).

Accuracy of this method for each tape was established by comparison of the arrhythmia-analyzer frequency count with a real-time frequency count performed for four separated 15-minute periods in each recording. When the accuracy was less than 85 percent, the variable criteria of the arrhythmia analyzer was readjusted until such accuracy was obtained. In two patients, this accuracy could not be obtained and a hand count of arrhythmia was obtained.

Because computer criteria for quantitative evaluation of atrial premature contractions (APCs) are suboptimal, only semi-quantitative analysis was carried out. They were recorded as isolated APCs (<100 per 24 hours), frequent APCs (>100 per 24 hours), paroxysmal atrial tachycardia, atrial flutter, and atrial fibrillation.

Statistical differences between means were determined by calculating the individual percentage of change relative to the control and applying the Wilcoxon sign rank test to these changes. Control 1 versus control 2 tested reproducibility. Since no systematic difference was noted between control 1 and control 2 \( (P > 0.1) \), the data were pooled and the mean of control 1 plus control 2 was compared to aminophylline.

**RESULTS**

**Pulmonary Function**

Moderate to severe obstructive airway disease was present during the control period with a mean \( FEV_1 \) of 0.97 ± 0.09 liters (34 ± 4 percent predicted value) and \( FEV_1/FVC \) of 40 ± 2 percent. Resting hypoxemia was present in most subjects with a mean \( PaO_2 \) of 67 ± 3 mm Hg (range 45 to 92 mm Hg). The mean \( PaCO_2 \) was 42 ± 2 mm Hg (range 33 to 55 mm Hg) with six patients chronically retaining carbon dioxide. During aminophylline therapy, the \( FEV_1 \) increased by 34 percent \( (P < 0.02) \) with an increase of greater than 20 percent in ten subjects, but \( pH \), \( PaCO_2 \), and \( PaO_2 \) did not change significantly \( (P > 0.05) \).

**Cardiac Arrhythmias**

**Baseline electrocardiograms.** The standard 12-lead ECG showed normal sinus rhythm in all patients except one who had persistent atrial fibrillation. VEBs, varying from one to four per tracing, were present in five patients. Two patients had intraventricular conduction abnormality with a complete right- and a left-bundle branch block, respectively. Five patients showed morphologic abnormalities suggesting chronic lung disease.

**Arrhythmia during the control period.** During the control period, without aminophylline therapy, the mean frequency of VEBs per hour was 43 ± 26 (range 0.3 to 401) (Table 1). All grades of ventricular arrhythmias were seen with occasional VEBs in five patients, frequent in three, multifocal in four, coupled beats in two, and short runs of ventricular tachycardia in one patient. All grades of APCs were also seen with the majority of the patients having sporadic APCs. One patient had frequent APCs, seven had short runs of asymptomatic paroxysmal atrial tachycardia, and one had stable atrial fibrillation.

We tested the between-day reproducibility of ambulatory electrocardiographic data from two 24-hour control periods. No systematic difference was noted between control periods in VEBs per hour, heart rate, or grade of arrhythmias \( (P > 0.1) \). Ran-
Table 1—Fibroticular Ectopic Beats and Heart Rate during Control and Aminophylline Therapy

<table>
<thead>
<tr>
<th>Patient</th>
<th>VEBs/hour Control</th>
<th>Aminophylline</th>
<th>% Change</th>
<th>VEBs/hour Control</th>
<th>Aminophylline</th>
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<tbody>
<tr>
<td>1*</td>
<td>12.0</td>
<td>17.0</td>
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<td>54</td>
<td>61</td>
</tr>
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<td>2</td>
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<td>0</td>
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<td>88</td>
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<td>118</td>
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<td>86</td>
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<tr>
<td>5</td>
<td>104.0</td>
<td>42.0</td>
<td>-60</td>
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<td>72</td>
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<td>75</td>
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<tr>
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<td>125.0</td>
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<td>64</td>
<td>86</td>
</tr>
<tr>
<td>9</td>
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<td>15.0</td>
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<td>+287</td>
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<td>78</td>
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<td>Mean</td>
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<td>71.7†</td>
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<td>80</td>
<td>88‡</td>
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<td>SE</td>
<td>26.4</td>
<td>41.0</td>
<td>+64</td>
<td>3</td>
<td>4</td>
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</tbody>
</table>

*Patients 1 through 7 were studied first during a control period, followed by aminophylline therapy.
†Patients 8 through 15 were studied first during aminophylline therapy, followed by a control period.
‡P < 0.01.

Random variability of differences between mean values for individual patients on two control periods was obtained by dividing the standard error of the differences by the grand mean. Random variability between two control periods for VEBs per hour and heart rate was ±25 percent and ±1 percent, respectively.

Effect of aminophylline on arrhythmias. During aminophylline therapy, heart rate increased from 80 ± 3 to 88 ± 4 beats per minute (P < 0.01). The mean and peak trough theophylline levels were 1.91 ± 0.57 and 1.34 ± 0.56 μg/ml, respectively.

VEBs increased from a mean of 43 ± 26 per hour during the control period to 72 ± 41 per hour after aminophylline (P = 0.006). VEBs increased in ten patients (range 57 to 900 percent), decreased in four (range 9 to 60 percent), and remained the same in one patient. The increase in VEBs per hour was similar whether the first study period was during aminophylline therapy (n = 8) or was the control period (n = 7) (P > 0.05). The grade of ventricular and atrial arrhythmias remained unchanged after administration of aminophylline (Table 2).

The increase in VEBs during aminophylline therapy did not correlate with theophylline levels, baseline pulmonary function studies, or the number of VEBs during control 24-hour monitoring (P > 0.05).

Discussion

The results of electrocardiographic monitoring in patients with stable COPD showed a high incidence of supraventricular and ventricular arrhythmias that were not apparent on the resting 12-lead ECG. Similar observations have been documented by other investigators. However, previous studies did not control for drugs or cardiac diseases that are known to cause cardiac arrhythmias. Nor has any attempt been made to quantitate or assess day-to-day variability in VEBs in previous studies. Our patient population was small, but was controlled for these variables and allowed us to assess the influence of oral aminophylline on cardiac arrhythmias.

Aminophylline increased the heart rate and frequency of VEBs in ambulatory patients with stable COPD. However, the grade of arrhythmia was not increased after aminophylline in any of the patients studied. A drug effect is usually difficult to document due to random variation in heart rate and arrhythmias. However, we documented the stability of cardiac arrhythmias in 12 patients on a day-to-day basis by showing no systematic difference between heart rate and VEBs per hour on control 1 versus control 2 (P > 0.1). Random variability between days was quantitated and a statistically significant difference between treatment and both control periods was documented. No difference in increased heart rate and VEBs during aminophylline therapy was noted, whether the patient received aminophylline therapy first followed.

Table 2—The Highest Grade of Cardiac Arrhythmia during Control and Aminophylline Therapy

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Aminophylline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular ectopic beats</td>
<td>5*</td>
<td>4</td>
</tr>
<tr>
<td>Frequent</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Multiform</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Paired</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Atrial arrhythmia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occasional APC†</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Frequent APC</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Paroxysmal atrial tachycardia</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*Number of patients
†APC = atrial premature contraction
by a control period or vice-versa. Therefore, we concluded that the increase in heart rate and VEBs represented a true chronotropic and arrhythmogenic effect of aminophylline.

The accuracy of counting VEBs during ambulatory electrocardiographic monitoring and analysis of the data by this technique have been documented in previous studies. Kennedy and Underhill, using a similar method of analysis, showed that this method has 80 to 90 percent accuracy of all VEB counts. In another study using a similar analytic technique, Morganroth and associates found an average error rate of 7.0 percent compared to real-time analysis. Therefore, the overall accuracy of our analytic technique is fairly good in assessing quantitative changes in VEBs in response to drug intervention.

The arrhythmogenic effect of aminophylline has been assessed in a variety of clinical situations. Aminophylline may cause malignant arrhythmias and sudden death when given intravenously. In prospective monitoring of 2,786 hospitalized patients who received derivatives of theophylline, severe cardiovascular reactions were reported in 1.2 percent of the patients. All patients who developed life-threatening cardiovascular complications and arrhythmias had received the drug intravenously.

Oral aminophylline has also been associated with worsening of cardiac arrhythmias in COPD, but this study did not control for digitalis which is known to exacerbate cardiac arrhythmias. In contrast, Banner and associates showed no significant increase in cardiac arrhythmias or heart rate after a single oral dose of aminophylline. Our study was carefully controlled for drugs known to exacerbate cardiac arrhythmias and showed that conventional oral doses of aminophylline enhance ventricular irritability, but do not cause a more severe grade of ventricular ectopy.

The mechanism of aminophylline-induced cardiac arrhythmias is speculative. Aminophylline infusion in anesthetized, open-chest dogs exerts a biphasic effect, i.e., the threshold for ventricular fibrillation is lowered during infusion, but after completion of infusion, aminophylline has a protective effect and reduces the ease with which ventricular fibrillation can be initiated. The arrhythmogenic effects are potentiated by respiratory failure, suggesting that patients with COPD and abnormal arterial blood gases may be more susceptible to cardiac arrhythmias after aminophylline.

We investigated factors that might identify patients who are at increased risk of developing cardiac arrhythmias with aminophylline. The presence or frequency of VEBs on resting ECG and 24-hour monitoring did not predict an increase in arrhythmias with aminophylline. Neither peak nor trough theophylline blood levels correlated with increased arrhythmias. Baseline pulmonary function or a change in function after aminophylline did not predict arrhythmogenesis. Therefore, we found no measurements that could predict susceptibility to arrhythmogenesis with aminophylline, although the numbers of patients studied were small.

The prognostic implication of worsening of cardiac arrhythmias during administration of aminophylline in these stable COPD patients is not clear. Survival in COPD is related to the severity of ventilatory impairment, and high mortality may reflect the severity of underlying COPD rather than any direct association with arrhythmias. Since most patients with COPD are in the group with a high incidence of coronary artery disease, this could account for some of the sudden deaths. Frequent and complex ventricular arrhythmias in patients with coronary artery disease provide important prognostic information with regard to sudden death. An average follow-up of 30 months in our patients showed no mortality. However, the number of patients and length of follow-up was small for a definitive conclusion. Only a long-term controlled study can determine whether the beneficial effect of slight improvement in pulmonary function during aminophylline therapy outweighs the multiple potential side effects such as worsening of arrhythmias.

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American Board of Internal Medicine–1982 Subspecialty Examination in Pulmonary Disease

The registration period for the 1982 Subspecialty Examination in Pulmonary Diseases is January 2-April 1, 1982. The examination will be held November 9. For further information and application forms, please contact: American Board of Internal Medicine, 3624 Market Street, Philadelphia 19104.