Kinetics of Theophylline*  
Variability and Effect of Arterial pH in Chronic Obstructive Lung Disease

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The pharmacokinetic behavior of theophylline was determined in 12 patients during an acute exacerbation of their chronic obstructive pulmonary disease. A 5.6 mg/kg loading dose of aminophylline was administered, followed three hours later by a 0.9 mg/kg/hr continuous infusion. The loading dose increased the serum theophylline level an average of only 5.77 μg/ml. After the loading dose, only five patients had levels greater than 10 μg/ml. Mean initial drug clearance was 0.077 L/kg/hr, half-life 9.1 hr, and apparent volume of drug distribution 0.877 L/kg. Wide inter- and intrapatient pharmacokinetic variability was observed. The variability of drug distribution was inversely correlated with the arterial pH. These patients with chronic obstructive pulmonary disease appeared to require more theophylline than theophylline when acidic than when alkaline to achieve similar serum theophylline concentrations.

Theophylline preparations, particularly the soluble salt aminophylline, have been a cornerstone in the treatment of reversible bronchoconstriction.1 For patients with acute exacerbation of obstructive lung disease (COPD), the administration of intravenous aminophylline is an important treatment modality. The dosage of intravenous aminophylline recommended by Mitenko and Ogilvie2 of a 5.6 mg/kg loading dose and a 0.9 mg/kg/hr continuous infusion was designed to increase serum theophylline levels by 10 μg/ml and maintain a therapeutic range of 10-20 μg/ml.3,4 This dosage regimen, however, disregards pharmacokinetic variability among patients, and may not be appropriate for middle-aged patients with COPD since the pharmacokinetic data used to calculate the regimen were obtained in young adults with asthma who were not acutely ill.5 It is not surprising then that the use of intravenous aminophylline has been associated with both inadequate and toxic theophylline levels.6,8 The present study was designed to examine pharmacokinetic values of theophylline in a group of middle-aged COPD patients during an acute exacerbation of their illness. The pharmacokinetic values, the variability of these values, and the relationship between arterial pH and the apparent volume of drug distribution are presented.

METHODS

Patient Selection

Twelve patients (ten men and two women) with an exacerbation of severe chronic obstructive pulmonary disease requiring intravenous administration of aminophylline were studied. The ten men had complete studies while the two women had only partial studies. Patients selected had prior evidence of COPD based upon previous pulmonary function tests with consistent FEV1/FVC ratios of 0.6 or less. No patient had clinical, historic or biochemical evidence of liver or heart disease. Patients weighing more than 150 percent ideal body weight (New York Life Insurance tables), as well as current smokers, were excluded. Patients signed consent forms approved by the University Human Subjects Committee.

Study Design

All patients were taking oral theophylline preparations prior to admission. Baseline levels of theophylline were drawn just prior to a loading intravenous dose of aminophylline of 5.6 mg/kg given over 20 minutes through a buretrol. Three levels of theophylline were drawn over three hours after the loading dose infusion, but prior to beginning a continuous infusion of 0.9 mg/kg/hr. While administering the continuous infusion, theophylline levels were drawn several hours apart twice daily. Independent of the investigators,
the clinical care team determined the duration of the continuous infusion depending upon patient response. After the infusion was discontinued, six theophylline levels were drawn over the next six hours prior to starting a regimen of oral theophylline preparations. Daily FEV₁ and FVC values were measured with a Collins spirometer. Arterial blood gas determinations, pH, liver function tests (SGOT, SGPT, LDH, alkaline phosphatase), electrocardiograms and chest radiographs were obtained on all subjects at the time of admission. The studies were repeated when indicated clinically. Six patients had repeat arterial blood gas determinations and pH at the time the continuous infusion of aminophylline was stopped. Relationships between various pharmacokinetic parameters were determined using the Pearson product-moment correlation method.

Sample Preparation

Blood samples were allowed to clot, centrifuged on a model HNS (International Equipment Co.) centrifuge at 5,000 RPM for 20 minutes, the serum frozen at 4°C, and quantitatively assayed for theophylline within one week. Aliquots of 500 µl were pipetted into 1.5 ml microfuge tubes (2591-EO8, Thomas Co, Philadelphia) and an equal volume of 10 percent trichloroacetic acid was added. Samples were thoroughly mixed for 15 seconds on a deluxe vortex mixer (Scientific Products). After mixing samples were centrifuged for four minutes on a Beckman microfuge. Serum standards of 0, 5, 10, 25 µg/ml of theophylline were prepared by adding 100 µl of the appropriate concentration of theophylline to 900 µl of serum containing no xanthines. Samples were then precipitated as above. Routinely 25 µl of the supernatant was injected into the column for analysis.

Analysis

The chromatographic analysis was carried out using a Waters model 6000A pump, model 440 absorbance detector and a model UK-6 septumless injector (Waters Associates, Milford, Ma.). The column employed was a µC₁₈ Bondapak reverse phase column, 300 mm x 3.9 mm ID. The technique was a modification of a Hewlett Packard assay using 94.5/5.5 percent aqueous/acetitrile at a flow rate of 3 ml/min. Detection was at 280nm. Peak height analysis was used to determine the serum concentration of theophylline. Unknown concentrations were calculated from the linear regression analysis of the standard curve. The assay is specific for theophylline. Other xanthines, such as caffeine, do not interfere. The assay is sensitive to 1 µg/ml and reproducible (± 5 percent).

Analysis of Data

The data were analyzed and plotted using a Hewlett Packard model 9830A calculator, 9866A printer and 9862A calculator plotter. Since the distribution phase of theophylline is brief and the first theophylline level was obtained one hour after the end of either the loading dose or continuous infusion, we ignored the alpha distribution phase and used a one compartment model. The plasma decay curve was plotted and the slope defined using the least squares linear regression method. The Y intercept was defined by the slope as the extrapolated plasma concentration at time zero (Cp0). Thus, distribution phase effects were ignored in calculations for the apparent volume of distribution (V₁). Initial volume of distribution (V₀) was determined by the equation:

\[ V₀ = \frac{D}{Cp} \]

Where D = loading theophylline dose in mg/kg and Cp = extrapolated initial theophylline concentration minus the measured baseline theophylline concentration. The terminal volume of distribution (VT) after discontinuing the aminophylline infusion V₀ was calculated by the equation:

\[ V_T = \frac{IR \cdot T-1/2}{0.693 \cdot \text{Cps}} \]

Where IR = infusion rate of theophylline in mg/hr, T-1/2 is the half-life, the Cps is steady state theophylline level (calculated as the average of the last three levels during the continuous infusion, the level prior to discontinuation of the infusion, and the Y intercept calculated from the six levels after the continuous infusion was stopped; using a paired t test, there was no significant difference in the means or standard deviations in these steady state values). Apparent V₀ values were reported in standard terms of L/kg by dividing by patient weight in kg. The half-life was determined from the six hour decay after the continuous infusion was stopped. The elimination rate constant Kel was obtained from the slope of the decay curve by: Kel = −Slope/2.303 Kel is calculated using the equation: Cl (L/kg/hr) = V₀ or 1/ Kel

RESULTS

The admission morphometric and laboratory data, mean and ranges are summarized in Table 1. The patient population was predominantly middle-aged men with severe COPD, moderately hypoxic and slightly hypercapnic. Measured theophylline levels at various time points during the study are presented in Figure 1. Two patients had only baseline and post-loading theophylline levels determined. These patients felt subjectively better after the loading dose and refused further study. Although all 12 patients were taking oral theophylline preparations before admission, nine had baseline levels below 10 µg/ml. Two of the three patients with baseline levels above 10 µg/ml achieved levels of 28 and 32 µg/ml after the loading dose. Only two of nine patients with baseline levels below 10 µg/ml achieved levels

<table>
<thead>
<tr>
<th>Table 1—Mean and Ranges for Morphometric and Laboratory Data in 12 Patients on Admission to the Study</th>
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<td>Data</td>
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<tr>
<td>Age</td>
</tr>
<tr>
<td>Weight</td>
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<tr>
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</tr>
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<td>PCO2</td>
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greater than 10 μg/ml after the loading dose. In fact, seven of 12 patients remained under 10 μg/ml. Of the ten patients who were given both a loading dose and a continuous infusion, two had levels less than 10 μg/ml throughout the study (48-120 hours depending upon patient response). Six hours after the continuous infusion was stopped, only three of ten still had levels greater than 10 μg/ml.

No patient exhibited signs of toxicity, although three patients had theophylline levels greater than 20 μg/ml. The mean, standard deviation, and range for the pharmacokinetic values are presented in Table 2 for both the initial and repeat (discharge) studies. The average (ΔCp) was 5.19 μg/ml ± 1.66 (range 2.9-8.3 μg/ml) which is consistent with a theophylline dose of 4.5 mg/kg (5.6 mg/kg of aminophylline) distributed into an initial VDI of 0.9503 L/kg. The mean initial clearance was 0.0834 L/kg/hr and the mean initial half-life was 8.66 hours. The VD, the half-life and the clearance differ from previous studies in adults, although differences in methodologies preclude a statement as to the significance of this variation. Mean pharmacokinetic values for the group did not differ between initial and discharge studies (Table 2). Despite this apparent uniformity, wide intrapatient differences were found between initial and discharge studies for individual patients. The percentage of change in VDI, half-life and clearance from admission to discharge study for each patient, is presented in Figure 2. Repeat drug clearance values increased an average of 44 percent in four of the ten patients and decreased an average of 31 percent in the remainder when compared to admission studies. Similarly, drug half-life increased an average of 68 percent in five, decreased an average of 42 percent in four, and remained constant in one patient. The VD decreased an average of 30 percent in seven patients and increased an average of 61 percent in three.

Various laboratory and morphometric values were examined for possible relationships to the pharmacokinetic variability observed in our patients. The Pco2, Po2, lean body weight and ideal body weight showed no significant correlation with pharmacokinetic variability. Arterial pH did correlate significantly (P < 0.001, r = -0.824) with the VD, as did [H+] (P < 0.001, r = 0.820). The correlation was noted in two subpopulations: all 12 patients on admission and the six of these patients who had pH determinations also done at the time the continuous infusion was stopped. The arterial pH versus the VD for the combined 18 data points are presented in Figure 3. An even higher correlation (r = 0.994, P < 0.001) was found between the changes in pH and VD within the same individual (Fig 4).

**DISCUSSION**

This study describes the pharmacokinetic values,

**Table 2—Initial and Terminal Pharmacokinetic Values**

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<th>Volume of Distribution</th>
<th>Clearance</th>
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<tr>
<td></td>
<td>Half-Life (hr)</td>
<td>(L/kg)</td>
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<tr>
<td><strong>Initial (N=12)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>8.66</td>
<td>0.9503</td>
</tr>
<tr>
<td>SD (N-1 weighting)</td>
<td>±3.83</td>
<td>±0.3014</td>
</tr>
<tr>
<td>Range</td>
<td>3.8-15.5</td>
<td>0.538-1.545</td>
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<tr>
<td><strong>Terminal (N=10)</strong></td>
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<td></td>
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<tr>
<td>Mean</td>
<td>8.51</td>
<td>0.8917</td>
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<tr>
<td>SD (N-1 weighting)</td>
<td>±3.21</td>
<td>±0.4016</td>
</tr>
<tr>
<td>Range</td>
<td>5.4-15.5</td>
<td>0.3963-1.540</td>
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variability and the correlation of arterial pH with theophylline $V_D$ in selected patients with severe COPD during acute exacerbation. Patients with liver or heart disease, obesity or a current smoking habit were excluded.

Ogilvie recently summarized pharmacokinetic data from several studies employing normal subjects, asthmatic patients and COPD patients. Comparison of the pharmacokinetic data from the present study with other studies is difficult because of
dissimilar groups, small study populations, varied study designs and different pharmacokinetic analysis techniques.

The results of the present study differ from other studies, especially in the larger apparent VD. It is probable that the reasons the serum levels of the patients in this study tended to be generally lower than those reported in other studies13-18 was due to this larger apparent volume of distribution. This cannot be stated with certainty since there is a great deal of interpatient variability in all of these studies. Normal adults5,16,17 and two groups with COPD have smaller values for VD,17,18 although the other COPD groups did manifest larger VD than normal subjects. Several explanations can be offered for the larger volumes. Since some reported groups with COPD and the COPD group in the present study had larger VDs than published normals, our group with COPD may have even larger values because of patient selection. The present study demonstrates a high correlation between arterial pH and the apparent VD. It is possible that our patients had increased VDs because they were acidemic (or relatively so) when compared to other study populations. Jenne et al18 did not exclude current smokers. Smoking increases theophylline clearance (by increasing metabolism) and decreases half-life.19 In steady state calculations, the apparent volume of distribution at steady state (Vdss) related directly to the half-life.20 Hence, smoking may decrease the apparent Vdss.

The mean theophylline clearance was slightly higher in this study than those reported in either normals or COPD patients. Also, the half-life in the present study is slightly longer, possibly a result of patient selection since smokers were not excluded in the other studies. The importance of patient selection on theophylline pharmacokinetic values is demonstrated by the markedly different clearance reported in pediatric patients without liver or heart disease when compared to normal adults.16

Although all the patients in this study were taking oral theophylline preparations at doses ranging from 800-1,600 mg each day, baseline levels of theophylline were below therapeutic range in nine of 12 patients. These low levels at baseline may reflect patient noncompliance. They may also be a result of the slightly higher drug clearance observed. The failure of the loading dose to increase serum theophylline concentration by 10 μg/ml as projected by Mitenko and Ogilvie is directly related to the larger VD.21 The larger the VD, the larger the dose of aminophylline required to increase serum theophylline levels.

Only one patient increased his serum theophylline concentration by 10 μg/ml or greater, while eight of ten achieved at least 10 μg/ml during the constant infusion. This variability in reaching projected serum theophylline levels results from both the inter- and intrapatient variability in theophylline pharmacokinetic values. Such variability decreases the usefulness of any fixed dosage regimens or nomograms. As demonstrated in this study, any fixed dosage regimen, such as those reported by Zwillich and others,6,7 potentially may produce either subtherapeutic or toxic levels in some patients.

Interpatient variability is known to occur between patient groups as a function of disease states such as congestive heart failure or liver disease,22 but is less well known in apparently homogenous patient groups. The wide interpatient variability seen with our select group with COPD has been observed in other select groups.23

Even less appreciated is the intrapatient variability seen over a few days or several months.23 Intrapatient variability has profound consequences if a single set of pharmacokinetic values is used to calculate individual theophylline dosages on a chronic basis.

A significant portion of the intra- and interpatient variability seen in our patients’ Vdss was correlated with changes in the arterial pH. If studies on larger groups of subjects bear out this relationship, clinicians may be able to adjust loading dosages on the basis of arterial pH, since the serum concentration after the loading dose is inversely related to the VD. However, until the relationship between theophylline levels, therapeutic effects and toxicity are described, it is not possible to say whether doses should be altered in acidemic patients.

To date, time delays and unavailability have plagued the routine use of theophylline levels. The availability of arterial pH measurements may provide a useful addition to dosage evaluation in certain circumstances. In our patients, a pH of 7.50 was correlated to a VD roughly equivalent to that found by Mitenko and Ogilvie in normal adults. It is possible that since intravenous aminophylline causes an increase in total and alveolar ventilation and a decrease in arterial carbon dioxide tension,24 their patients had an unrecognized slight alkalosis. This would provide an explanation for the similarity in VD found in their normal subjects and in our patients at pH 7.50.

At a pH of 7.30, for example, two times as much aminophylline would be required to increase the serum theophylline concentration by 10 μg/ml compared to that required at a pH of 7.5. These dosages are not recommendations; they only illustrate how greatly aminophylline loading dosage can vary when
the \( V_D \) changes over such a wide range.

The relationship between arterial pH and apparent volume of distribution has been noted for other drugs, such as salicylates\(^2\) and phenobarbital,\(^3\) but a different mechanism is certainly involved. These drugs have large differences in percentage of unionized drug in this pH range which is not true for theophylline. The relationship we found between \( V_D \) and arterial pH has only been shown in a small select group of patients with COPD. The reliability of this observation and its cause must be studied and verified in other patients and patient groups before definite statements about therapeutic practice can be made.

In summary, we found a good correlation between arterial pH and the apparent \( V_D \) for 18 arterial pH measurements in 12 patients. Perhaps of greater interest was the excellent correlation we found between the change in pH and the change in the apparent \( V_D \) in the six patients who had repeat matched blood gas determinations and clearance studies. This change may be associated with changes in protein binding,\(^27\) as suggested by Vällner et al.\(^27\) However, no recommendation as to dosage modification can be made without investigating whether lower blood levels possess greater, lesser or equivalent efficacy in the presence of respiratory acidosis. Vällner and colleagues\(^27\) have reported acidemic patients may have more free and, therefore, more active drug.

References