Volume of Distribution of Theophylline in Acute Exacerbations of Reversible Airway Disease*  

Effect of Body Weight  
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The literature is unclear as to whether theophylline loading doses should be based on total body weight (TBW) or ideal body weight (IBW). The objective of this study was to determine the most appropriate body weight for estimation of volume of distribution (Vd) in calculating theophylline loading dose in patients with acute bronchospasm. Fifty-four adult patients with acute bronchospasm requiring intravenous (IV) theophylline therapy were entered into the study. Patients were randomized into three theophylline loading dose groups based on (1) TBW, (2) IBW, and (3) adjusted body weight (ABW). Initial serum theophylline concentrations were used to determine an IV loading dose to reach a plasma concentration of 12 to 15 μg/ml. Percent prediction error was used to determine the appropriateness of each dosing group. Volumes of distribution were also determined for each group. There was a statistically significant difference at p<0.01 in the percent prediction error when patients in the TBW group were compared to the IBW and ABW groups. A statistically significant difference in the Vd was observed between the TBW and IBW group (p<0.01). We conclude that IBW is more appropriate than TBW or ABW for determining theophylline loading dose in patients with acute bronchospasm.

The effect of obesity in altering the pharmacokinetics of most drugs is unknown. Distribution, biotransformation, and excretion may be altered in obese but otherwise healthy patients. Hydrophilic agents such as digoxin and the aminoglycoside antibiotics do not readily distribute into fat, whereas lipophilic drugs distribute to varying degrees into fat depending on their lipophilicity. Theophylline has been used for its bronchodilatory effects for over half a century in the treatment of both acute and chronic reversible airway disease. It is recommended that theophylline plasma concentrations be maintained within the 10 to 20 μg/ml range to maximize the therapeutic effect while minimizing toxicity. Headache and gastrointestinal symptoms including nausea, anorexia, and vomiting rarely occur at theophylline plasma concentrations less than 13 μg/ml, but occur with increasing frequency as the concentration increases above 20 μg/ml. Zwillich et al reported seizure activity in seven of eight patients whose theophylline concentrations ranged between 47 and 70 μg/ml. Supraventricular tachycardias have been reported when theophylline plasma concentration exceeds 30 μg/ml.

This narrow range between the theophylline therapeutic and toxic plasma concentrations necessitates dosage regimens which will reliably maintain patients in the therapeutic range. Since several factors, including obesity, potentially alter theophylline disposition, it is imperative that the effects of these factors on theophylline dosage requirements be quantified. There are conflicting properties which make it difficult to predict the distribution of theophylline into fat. Factors suggesting that theophylline does not readily distribute into fat include its small volume of distribution and its slight solubility in ether, chloroform, and alcohol. A contrasting property that favors its distribution into fat is its extensive metabolism which usually correlates with high lipid solubility.

Gal and co-workers investigated the effect of obesity on the pharmacokinetics of theophylline. In the 14 patients studied, the volume of distribution was similar for obese and nonobese patients (0.38 and 0.48 L/kg, respectively) when normalized to total body weight. However, when normalized to ideal body weight, there was a large difference in the volumes of distribution between the two groups (0.77 and 0.52 L/kg, respectively).

In contrast, Rohrbaugh et al reported that theophylline did not extensively distribute into adipose tissue. The mean volume of distribution of theophylline in eight lean subjects was 0.472 L/kg, while in eight obese subjects, the mean volume of distribution was 0.321 L/kg when normalized to total body weight following an oral theophylline loading dose. The authors of this study concluded that theophylline loading dose calculations should be based on ideal body weight.

The large number of patients with acute asthma seen

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in our emergency services area necessitated the development of appropriate guidelines for determining theophylline loading doses. Because of the conflicting results in the aforementioned studies and the fact that the majority of subjects were not asthmatic, no specific guidelines could be derived from the present literature. The objective of this study was to determine the most appropriate body weight for estimation of volume of distribution in calculating theophylline loading doses in patients with acute bronchospasm.

**Materials and Methods**

All patients with acute bronchospasm who presented to the Emergency Services Area of the University of Illinois Hospital were evaluated for inclusion into the study over an eight-month period. Study exclusions were hypersensitivity to theophylline, self-administration of a sustained or nonsustained release theophylline preparation within eight hours or four hours, respectively, an initial theophylline plasma concentration greater than 10μg/ml, less than 18 years of age and pregnancy.23

Fifty-four patients ranging in age from 18 to 64 years were entered in the study. Informed consent was obtained from all patients. Baseline serum theophylline concentrations were determined in duplicate by a clinical pharmacist.24 This sample was obtained no sooner than 30 minutes prior to administration of the loading dose. Patients were randomized into one of three dosing groups based on the following: 1, total body weight (TBW); 2, ideal body weight (IBW); or 3, adjusted body weight (ABW) using the formula 0.6 (TBW−IBW) + IBW. The 60 percent factor was derived from previously reported literature for theophylline,25 and was used to account for a partial distribution of theophylline into adipose tissue similar to that reported for the aminoglycosides.26 Ideal body weight was determined using the formula27

\[
\text{IBW} = 50\text{kg} + 2.3\text{kg for every inch over 5 feet (males)}
\]

\[
\text{IBW} = 45\text{kg} + 2.3\text{kg for every inch over 5 feet (females)}
\]

Aminophylline loading doses were calculated using the formula:

\[
D = \frac{(Cp_d - Cp_i)V_d \times BW}{0.79}
\]

where

- \(D\) = loading dose
- \(Cp_d\) = desired plasma concentration
- \(Cp_i\) = initial plasma concentration
- \(V_d\) = volume of distribution = 0.5L/kg
- \(BW\) = IBW, TBW, or ABW

Standard aminophylline concentration for administration of the loading dose was prepared beforehand at 5 mg/ml in 5 percent dextrose in water. The loading dose was infused intravenously over 30 minutes using a volumetric 927 infusion pump. A blood sample was drawn from the contralateral arm five minutes after completion of the infusion to evaluate the predicted (\(Cp_d\)) and observed (\(Cp_i\)) serum theophylline concentrations. These serum samples were also assayed in duplicate on a 24-hour basis by the emergency services area clinical pharmacist. The appropriateness of each of the dosing groups was determined by the percent prediction error (\(\text{CP}_{\text{pred}}/Cp_i\)). The volumes of distribution were also calculated for each of the three groups using the following formula:

\[
V_d = \frac{D (0.79)}{(Cp_d - Cp_i)} BW
\]

The equations for calculation of the loading dose and volume of distribution assume that theophylline disposition following the IV infusion can be adequately characterized by a first order, one compartment pharmacokinetic model.28 The assumption of a one compartment model was verified in 11 of our patients in whom a second theophylline serum concentration was obtained 30 to 60 minutes following the loading dose prior to initiation of any mainte-

<table>
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<th>Table 1—Summary of Patient Data for Each Group</th>
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<td>No. of Subjects</td>
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<td>% Predicted FEV</td>
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**Results**

A total of 54 patients were evaluated during the study with 17 patients in the TBW group, 19 in the IBW group, and 18 in the ABW group. No significant difference was observed between the three groups with regard to age, sex, smoking history, percent greater than IBW, or pulmonary status (Table 1). None of the patients had significant hepatic, renal, or cardiovascular disease.

The mean percentage difference between predicted and observed serum concentrations for each of the three groups is listed in Table 2. A statistically significant difference (p<0.01) was found between patients in the TBW group when compared to the IBW and ABW groups. No significant difference in prediction error was found between the IBW and ABW groups. The mean volumes of distribution for the three groups, normalized for their respective body weight, are listed in Table 3. A statistically significant difference (p<0.01) was observed in the volume of distribution between the TBW and IBW group. No significant difference was found between either the TBW and ABW or ABW and IBW groups.

<table>
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<th>Table 2—Percent Difference Between Predicted and Observed Serum Concentrations</th>
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<td>Mean ± SD</td>
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<td>TBW vs IBW, p&lt;0.01</td>
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<th>Table 3—Calculated Volume of Distribution for Each Group</th>
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Figures 1, 2, and 3 illustrate the relationship in the percent prediction error as total body weight exceeds ideal body weight for each of the three groups. For both the TBW and ABW groups, the prediction error increased significantly (p<0.05) as the patient’s total body weight exceeded their ideal body weight. As demonstrated by the larger negative slope, this trend was more prominent in the TBW group. No significant relationship between these two variables was found for the IBW group. This relationship was further examined by combining the three groups. The percent prediction error was then determined between predicted and observed serum levels for each patient using each of the three body weights, (TBW, ABW, IBW) to estimate the volume of distribution. The patients were then subdivided into one of five groups depending on the percentage their total body weight exceeded ideal body weight (Fig 4). When TBW and ABW were used to determine the loading dose, a significantly larger (p<0.01) prediction error was found for the 50 percent to 70 percent and 70 percent to 100 percent groups when compared to the 0 percent to 10 percent group. With the use of IBW, no significant difference in prediction error was found among the five weight groups.

**DISCUSSION**

The volume of distribution for theophylline has been reported to range from 0.3 to 0.7 L/kg with a mean of 0.5 L/kg.\(^{10,21}\) Our results showed a significant difference when the mean volume of distribution in the TBW group (0.39 ± 0.10 L/kg) was compared with the IBW group (0.48 ± 0.10 L/kg). The clinical significance of this difference is illustrated by the fivefold greater prediction error in the TBW group. This is consistent with the data obtained by Rohrbaugh et al.\(^{11}\) In contrast, our results disagree with the findings of Gal et al\(^{10}\) who recommend the use of TBW. Possible explanations for these opposing results include the following: (1) the majority of obese subjects studied by...
Gal et al. were otherwise healthy, while the patients in our study were diagnosed as having acute bronchospasm; (2) possible bioavailability problems with the oral aminophylline preparations in the Gal et al. study; and (3) the lack of patient data for the normal patients studied by Gal et al. makes the determination of the group homogeneity difficult.

No significant difference was observed in either the mean volume of distribution or prediction error between the ABW and IBW groups. However, as illustrated in Figures 1 and 3, the TBW and ABW groups demonstrated significant trends toward increasing the negative prediction error as the patient's TBW exceeded their IBW. A significant difference in the prediction error was found for patients greater than 50 percent of their IBW for both TBW and ABW when compared to the patients between 0 percent to 10 percent of their IBW (Fig 4). No such biases were found with the use of IBW.

The volume of distribution is the pharmacokinetic parameter used to determine the loading dose required to achieve an appropriate plasma concentration. Our results demonstrate that the use of TBW, and to a lesser extent an ABW, in estimating the volume of distribution may result in a significant overdosing of moderately obese patients. The use of the patient's IBW in determining the loading dose appeared to be the most appropriate from our data. It would appear from our results that theophylline does not extensively distribute into adipose tissue following a loading dose.

REFERENCES
7 Jacobs MH, Senior RM, Kessler G. Clinical experience with theophylline: relationships between dosage, serum concentration, and toxicity. JAMA 1976; 235:1983-86

Distribution of Theophylline in Reversible Airway Disease (Zell et al)