Assessment of Clinical Application of Test-Dose Concept for Theophylline in Patients with Respiratory Failure

Mitsuyoshi GOTO, Hiroshi YOSHIDA, Toshio TERASHIMA,* Hiromitsu KUSAFUKA,* Tadashi HORIUCHI,** Ichiro MIZUGAKI,** * * Ikuo JOHNO**,*4 and Shikifumi KITAZAWA**,*5

Department of Hospital Pharmacy, and *Department of Internal Medicine, Nagoya Memorial Hospital, Hirabari, Nagoya, 468, Japan, and **Department of Hospital Pharmacy, School of Medicine, Nagoya University, Tsurumai, Nagoya, 466, Japan

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The possibility of clinical application of test-dose concept for theophylline was assessed in 11 patients with serious underlying disease who required theophylline. Based on the pharmacokinetic parameters calculated from the single intravenous aminophylline administration, they received a continuous infusion of aminophylline in order to maintain about 10 μg/ml plasma which is considered to be the lowest therapeutic level. Plasma levels during a constant rate infusion were assayed at 6:00, noon, 18:00 and midnight on the 3rd or 4th day after the infusion had started. There were no significant differences among plasma levels at each sampling time, but plasma levels varied ranging from 5.1 to 24.8 μg/ml (12.1 ± 5.5 μg/ml: mean ± S.D.), which values were in disagreement with the predicted value in some cases. The correlations of the theophylline clearance ratio to dose, pH, arterial partial pressures of oxygen (Pao₂) and carbon dioxide (Paco₂) ratios, which were calculated by dividing the value during continuous infusion by the value at the test dose, were investigated to evaluate which factor largely contributed to the failure of this dosing method. Although the clearance ratio did not correlate to pH and Pao₂ ratios, significant negative relationships were observed between the clearance ratio and the dose (p < 0.05) or Paco₂ ratios (p < 0.02). In other words, the alternation of dose or Paco₂ resulted in the change of theophylline clearance. These findings suggest that the test-dose concept should not be used in the seriously ill patients whose theophylline clearance can change easily in relation to dose and/or Paco₂ change.

Keywords — theophylline; clearance; test-dose concept; dose-dependent kinetics; blood gas

Introduction

Because of large individual variations in theophylline systemic clearance,1–3 it is difficult to recommend a dosage regimen according to the predictive algorithm including nomogram,4–6 especially in seriously ill patients.2,7 Since theophylline has a narrow therapeutic range,1,2 the test-dose concept for theophylline on the basis of linear kinetics has been developed to improve therapeutic effectiveness.3,8–11 A number of authors have presented successful results in clinical applications of this method.3,8–11

However, it has also been reported that theophylline clearance is affected by various factors such as age, diet, smoking, other drugs, concomitant disease, disease state,1,2 elapsed time after doing,12 and its concentration.13–16 In spite of such individual variations in theophylline clearance, decisive reports which restricted the clinical application of this method were not found.

The present work was conducted to assess the possibility of the clinical application of theophylline test-dose concept in the critically ill patients, and to investigate factors influencing theophylline clearance.

*** Present Address: Department of Hospital Pharmacy, Nagoya Hospital, Hirakata, Osaka, 573-01, Japan.
*4 Present Address: Pharmacy Services, Kishiwa City Hospital, Kishiwa, Osaka, 596, Japan.
*5 Present Address: Department of Hospital Pharmacy, Keio University Hospital, Shinjuku-ku, Tokyo, 160, Japan.
Address correspondence and reprint requests to Dr. Mitsuyoshi Goto: Department of Hospital Pharmacy, Nagoya Memorial Hospital, Hirabari, Tenpaku-ku, Nagoya, 468, Japan.
TABLE I. Patient Profile

<table>
<thead>
<tr>
<th>Subject</th>
<th>Diagnosis</th>
<th>Sex</th>
<th>Age (Y)</th>
<th>Weight (kg)</th>
<th>Disease state (^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Chronic bronchitis</td>
<td>M</td>
<td>59</td>
<td>36.5</td>
<td>Improved</td>
</tr>
<tr>
<td>2</td>
<td>Pulmonary emphysema</td>
<td>M</td>
<td>64</td>
<td>57.0</td>
<td>Not improved</td>
</tr>
<tr>
<td>3</td>
<td>Drug intoxication</td>
<td>F</td>
<td>80</td>
<td>43.5</td>
<td>Not improved</td>
</tr>
<tr>
<td>4</td>
<td>Pulmonary tuberculosis, Congestive heart failure</td>
<td>M</td>
<td>82</td>
<td>60.5</td>
<td>Not improved</td>
</tr>
<tr>
<td>5</td>
<td>Cerebral infarction, Congestive heart failure</td>
<td>M</td>
<td>73</td>
<td>80.0</td>
<td>Not improved</td>
</tr>
<tr>
<td>6</td>
<td>Pneumonia, Congestive heart failure</td>
<td>F</td>
<td>83</td>
<td>28.0</td>
<td>Not improved</td>
</tr>
<tr>
<td>7</td>
<td>Chronic bronchitis</td>
<td>M</td>
<td>63</td>
<td>44.0</td>
<td>Not improved</td>
</tr>
<tr>
<td>8</td>
<td>Pneumonia, Congestive heart failure</td>
<td>M</td>
<td>72</td>
<td>33.0</td>
<td>Not improved</td>
</tr>
<tr>
<td>9</td>
<td>Uterus cancer, Congestive heart failure</td>
<td>F</td>
<td>70</td>
<td>30.0</td>
<td>Not improved</td>
</tr>
<tr>
<td>10</td>
<td>Pulmonary tuberculosis</td>
<td>M</td>
<td>80</td>
<td>42.0</td>
<td>Not improved</td>
</tr>
<tr>
<td>11</td>
<td>Cerebral bleeding</td>
<td>F</td>
<td>51</td>
<td>55.0</td>
<td>Not improved</td>
</tr>
</tbody>
</table>

Mean 70.6 46.3  
S.D. 10.4 15.6

\(^a\) Underlying disease state at blood sampling day during continuous infusion.

Methods

Patients — Eleven patients (7 males and 4 females), ranging in age from 51 to 83 years and in weight from 28 to 80 kg, who were admitted to the Intensive Care Unit of Nagoya Memorial Hospital, were the study subjects (Table I). The intravenous administration of aminophylline (Neophylline®, parenteral, Eisai Co., Ltd., Tokyo, Japan), which contains 80% theophylline, was used to improve chronic respiratory failure due to underlying diseases and/or to discontinue oxygen inhalation (Table II) because theophylline has various pharmacological actions in addition to its bronchodilative effect.\(^17-19\) Although cimetidine, a drug metabolizing enzyme inhibitor,\(^20\) was intravenously given at the same dose in subject 2 throughout the study, the patient was included in this study, because the extent of the inhibition is almost identical in the

TABLE II. Arterial Blood Gas Analysis at Test-Dose and during Continuous Infusion of Aminophylline

<table>
<thead>
<tr>
<th>Subject</th>
<th>Oxygen inhalation</th>
<th>(P_{aO_2})^a)</th>
<th>(P_{aCO_2})^b)</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test-dose</td>
<td>Continuous infusion</td>
<td>Test-dose</td>
<td>Continuous infusion</td>
</tr>
<tr>
<td>1</td>
<td>+</td>
<td>−</td>
<td>94</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>+</td>
<td>64</td>
<td>68</td>
</tr>
<tr>
<td>3 (^c)</td>
<td>+</td>
<td>+</td>
<td>166</td>
<td>128</td>
</tr>
<tr>
<td>4</td>
<td>−</td>
<td>+</td>
<td>64</td>
<td>74</td>
</tr>
<tr>
<td>5</td>
<td>−</td>
<td>+</td>
<td>69</td>
<td>182</td>
</tr>
<tr>
<td>6</td>
<td>+</td>
<td>+</td>
<td>115</td>
<td>127</td>
</tr>
<tr>
<td>7</td>
<td>−</td>
<td>+</td>
<td>28</td>
<td>47</td>
</tr>
<tr>
<td>8</td>
<td>+</td>
<td>+</td>
<td>119</td>
<td>106</td>
</tr>
<tr>
<td>9</td>
<td>+</td>
<td>+</td>
<td>156</td>
<td>162</td>
</tr>
<tr>
<td>10</td>
<td>+</td>
<td>+</td>
<td>81</td>
<td>85</td>
</tr>
<tr>
<td>11 (^c)</td>
<td>+</td>
<td>+</td>
<td>142</td>
<td>88</td>
</tr>
<tr>
<td>Mean</td>
<td>100</td>
<td>104</td>
<td>42</td>
<td>39</td>
</tr>
<tr>
<td>S.D.</td>
<td>44</td>
<td>41</td>
<td>13</td>
<td>8</td>
</tr>
</tbody>
</table>

\(^a\) Arterial partial pressure of oxygen. \(^b\) Arterial partial pressure of carbon dioxide. \(^c\) Intubation had been made in this patient.
case of the same dose.\textsuperscript{20} The others did not receive any drugs known to affect the metabolism of theophylline such as macrolide antibiotics, phenobarbital,\textsuperscript{1,2} and enoxacin.\textsuperscript{21} Any other theophylline preparations were not administered before the study. All of them were non-smokers, and neither hepatic nor renal dysfunctions were observed. Since oxygen inhalation had been made in these patients, arterial partial pressure of oxygen (\(P_{\text{aO}}\)) and carbon dioxide (\(P_{\text{aCO}}\)) in some patient were already within normal range as shown in Table II.

**Protocol** — Since the state of respiratory failure in all of our subjects was chronic and the dosage regimen of theophylline in patients suffered from congestive heart failure has been reported to be difficult,\textsuperscript{1,2} we chose the test-dose concept for theophylline.

The test dose of 250 to 500 mg aminophylline, which could be expected to result in the plasma concentration within the lower therapeutic range of 10 to 15 \(\mu\text{g/ml}\), was infused over 1 h by using an infusion pump (Terufusin\textsuperscript{®}, model STC-503, Terumo Co., Ltd., Tokyo, Japan) because the population mean of the volume of distribution of theophylline, 0.45 l/kg, is known to be relatively stable between individuals.\textsuperscript{6} Blood samples (3 ml each) were drawn from an arm vein by using a heparinized vacuum tube (Venoject\textsuperscript{®}, Terumo Co., Ltd., Tokyo, Japan) at 1, 3, 6 and 11 h after the infusion ceased. Samples were always withdrawn from the arm contralateral to that used for infusion. Plasma was immediately separated by centrifugation. After the last sample was obtained, plasma theophylline levels were immediately assayed by fluorescence polarization immunoassay (FPIA) using TDX\textsuperscript{®} analyzer (Dainabot Co., Ltd., Tokyo, Japan).\textsuperscript{22} The sensitivity limit of FPIA method for theophylline is said to be as low as 0.3 \(\mu\text{g/ml}\).

Postinfusion plasma levels \((C_t)\) were fitted to the following eq.\textsuperscript{23}

\[
C_t = \frac{k_0}{V_d K} (1 - \exp(-KT)) \exp(-Kt)
\]  

(1)

where \(k_0\) is the infusion rate in the test dose (mg/h/kg), \(V_d\) is the volume of distribution (l/kg), \(K\) is the elimination rate constant (h\(^{-1}\)), \(T\) is the infusion time (h), and \(t\) is the postinfusion time (h). Systemic clearance \((Cl_{\text{sys}})\) in the test dose was calculated as follows.\textsuperscript{23}

\[
Cl_{\text{sys}} = KV_d
\]  

(2)

Based on the kinetic parameters obtained from the test dose, a loading dose of aminophylline was made and subsequently continuous infusion of the drug adequate to maintain around 10 \(\mu\text{g/ml}\) of plasma level. Plasma theophylline levels were determined at 6:00, noon, 18:00 and midnight on the 3rd or 4th day after continuous infusion had been initiated. Unfortunately, the levels were measured only at noon and 18:00 for subject 10 and at noon for subject 11. Systemic clearance in the continuous infusion \((Cl_{\text{sys}})\) was calculated according to the following formula.\textsuperscript{23}

\[
Cl_{\text{sys}} = \frac{k_0}{C}
\]  

(3)

where \(k_0\) is the continuous infusion rate (mg/h/kg), and \(C\) is the average plasma concentration (\(\mu\text{g/ml}\)).

The best values of the various pharmacokinetic parameters were calculated by using the iterative least-squares computer program, MULTI,\textsuperscript{24} adapted for a personal computer FM-16β (Fujitsu, Tokyo, Japan).

\(P_{\text{aO}}\), \(P_{\text{aCO}}\) and pH were monitored at the test dose and at noon or 18:00 on the blood sampling day during continuous infusion with blood gas and pH analyzer (ABL-2\textsuperscript{®}, Radiometer Co., Ltd., Denmark).

In order to normalize the extent of the changes of dose and blood gases, we used the dose ratio (daily dose during constant infusion/test dose), the clearance ratio \((Cl_{\text{sys}}/Cl_{\text{sys}})\), the \(P_{\text{aO}}\) ratio, \(P_{\text{aCO}}\) ratio and pH ratio (the values of \(P_{\text{aO}}\), \(P_{\text{aCO}}\) and pH during continuous infusion/those at the test dose) in Results.

**Statistical Analysis** — All data are given as mean ± S.D. Statistical comparison of the mean value was performed by one-way analysis of variance (ANOVA) and Fisher’s pairing t-test to identify the difference. \(p\) values of less than 0.05 were considered statistically significant.
### TABLE III. Theophylline Pharmacokinetic Parameters after Intravenous Test-Dose over 1 h and during Continuous Infusion

<table>
<thead>
<tr>
<th>Subject</th>
<th>Test-dose</th>
<th>Continuous infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose (a)) (mg)</td>
<td>(K) (h(^{-1}))</td>
</tr>
<tr>
<td>1</td>
<td>200</td>
<td>0.149</td>
</tr>
<tr>
<td>2</td>
<td>200</td>
<td>0.061</td>
</tr>
<tr>
<td>3</td>
<td>200</td>
<td>0.057</td>
</tr>
<tr>
<td>4</td>
<td>200</td>
<td>0.072</td>
</tr>
<tr>
<td>5</td>
<td>400</td>
<td>0.073</td>
</tr>
<tr>
<td>6</td>
<td>200</td>
<td>0.064</td>
</tr>
<tr>
<td>7</td>
<td>300</td>
<td>0.021</td>
</tr>
<tr>
<td>8</td>
<td>200</td>
<td>0.039</td>
</tr>
<tr>
<td>9</td>
<td>200</td>
<td>0.063</td>
</tr>
<tr>
<td>10</td>
<td>300</td>
<td>0.038</td>
</tr>
<tr>
<td>11</td>
<td>400</td>
<td>0.160</td>
</tr>
<tr>
<td>Mean</td>
<td>255</td>
<td>0.072</td>
</tr>
<tr>
<td>S.D.</td>
<td>82</td>
<td>0.044</td>
</tr>
</tbody>
</table>

\(a\) Dose is presented as theophylline. \(b\) Calculated as \(K \times V_d\). \(c\) Calculated as infusion rate/average observed level. \(d\) The concentration at 18:00.

### Results

#### Predictability of Plasma Level during Continuous Infusion by the Intravenous Test-Dose Method

The theophylline pharmacokinetic parameters following intravenous administration over 1 h and during a constant rate of infusion are given in Table III. Although approximately 10 µg/ml of plasma level could be expected on the basis of the kinetic parameters in the test dose, the average observed levels revealed a large individual variation, ranging from 5.1 to 24.8 µg/ml. The observed plasma level at steady state was under- and overestimated in 5 and 6 cases, respectively, as compared with the predicted levels. In view of the other successful reports with respect to the theophylline test-dose method, the unpredictability, especially in subjects 1 and 10, seems surprising.

Reflecting a large individual difference between the predicted and the observed levels, \(Cl_{sys}\) also varied between 17.7 and 60.0 ml/h/kg. Although the mean of clearance ratio (\(Cl_{sys}/Cl_{sys}\)) was close to unity, the large individual variations of the ratio, ranging from 0.389 to 2.372, strongly indicate a necessity to take special care of the clinical application of the theophylline test-dose concept in these patients.

#### Factors Affecting Theophylline Disposition

In order to examine factors resulting in the failure of theophylline test-dose method, we investigated the causes as follows.

Although data on diurnal variation of theophylline elimination are conflicting,\(^{25,27}\) some authors have reported a 30 to 40% increase in half-time of theophylline following morning in comparison with evening administration in the intravenous studies.\(^{26,27}\) If the disposition profile of theophylline, which has a relatively short half-time,\(^{1,2}\) can change within a day, it would appear to be difficult to estimate a steady state plasma level based on the kinetic parameter from a single dosing only at a day or night time. Therefore, we have investigated the contribution of circadian change of clearance to the unpredictability of \(Cl_{sys}\).

The mean plasma concentrations with S.D. at steady state during continuous infusion were 13.2±6.6 at 6:00, 12.3±5.6 at noon, 12.3±5.1 at 18:00 and 12.8±5.2 µg/ml at midnight (subjects 10 and 11 were excluded.) as shown in Fig.
Assessment of Theophylline Test-Dose Method

Fig. 1. Plasma Theophylline Concentration during a Constant Rate Infusion of Aminophylline

There were no significant differences among concentrations at each blood sampling time by ANOVA and Fisher's pairing t-test.

1. No significant differences were observed using ANOVA and Fisher's pairing t-test. This observation is in good agreement with the previous study on circadian change of theophylline metabolism. If the under- or overprediction of clearance was due to circadian variation of theophylline metabolism, the concentration at 6:00, at least, would be different from that at 18:00. This implies that the disagreement of the prediction may not result from the diurnal change of theophylline metabolism.

Since the dosage regimen in the constant rate infusion was adjusted by the application of the test-dose method, the administered dose was different between the test dose and the continuous infusion in the most cases. The reports have

Fig. 2. Relationship between the Ratios of Dose and Clearance $n = 11, Y = -0.339X + 1.641, r = -0.621 (p < 0.05)$

The ratios were calculated by dividing the value during continuous infusion by the value at the test.

Fig. 3. Relationships between the Ratios of Clearance and $P_aO_2$, $P_aCO_2$ or pH

Significant correlation was observed only between the $P_aCO_2$ ratio and clearance ratio as follows: $n = 11, Y = -2.038X + 2.980, r = -0.685 (p < 0.02)$.

The ratios were calculated by dividing the value during continuous infusion by that at the test dose.
been accumulated that theophylline obeys non-linear elimination kinetics in some patients.\textsuperscript{13–16} Therefore, the relationship of the dose ratio to the clearance ratio was plotted in Fig. 2. A significant negative correlation between both ratios was observed. This observation demonstrated that theophylline clearance was influenced by dose as reported previously,\textsuperscript{13–16} and that its non-linearity contributed to the difficulty of clinical application of the test-dose concept. However, no significant relationship was found between the ratios except the data of subjects 1 and 10, and clearance ratio was around 1.0. This result also shows that the theophylline pharmacokinetics in most patients is linear.

It has been reported that theophylline clearance varied in association with the change of \textit{P}ao\textsubscript{2} and/or \textit{P}aco\textsubscript{2} in rabbits\textsuperscript{24} and of \textit{pH} in humans.\textsuperscript{29} The relationships of the clearance ratio to the \textit{P}ao\textsubscript{2} ratio, \textit{P}aco\textsubscript{2} ratio and \textit{pH} ratio were illustrated in Fig. 3. Although there were no significant correlations between the clearance ratio and the \textit{P}ao\textsubscript{2} or the \textit{pH} ratios, the ratio of \textit{P}aco\textsubscript{2} showed a significant negative relationship with that of clearance. Furthermore, after excluding subjects 1 and 10 who contributed to the demonstration of dose-dependency of theophylline, a better relationship between the \textit{P}aco\textsubscript{2} ratio and the clearance ratio was obtained ($r = -0.806; p < 0.01$). These suggest that the change of \textit{P}aco\textsubscript{2} affected theophylline clearance, and subsequently fail to predict a steady state plasma level.

**Discussion**

The use of measured theophylline levels has been settled to be clearly superior to predictive algorithm including nomograms in its dosage regimen calculation.\textsuperscript{30} Based on the linear kinetics, a number of authors have presented satisfactory data for the prediction of the plasma level at steady state from the first dosing.\textsuperscript{3,8–11} Horai \textit{et al.} have shown that the observed minimum concentrations at steady state after oral dosing were in quite accordance with the levels estimated from an intravenous test-dose in 60 patients, and that only 3 of them were found to be outside $\pm 2$ S.D. of the mean.\textsuperscript{3}

No decisive reports have been published that attention must be paid to the clinical application of the test-dose concept for theophylline, except for our recent study, in which we have concluded that theophylline test-dose concept must be practiced carefully because its clearance can reduce with elapsed time.\textsuperscript{12} The present study, performed under actual clinical conditions, has shown that the measured steady state plasma levels ranged from 5.1 to 24.8 $\mu$g/ml (12.1 $\pm$ 5.5 $\mu$g/ml) which was different from the expected value of around 10 $\mu$g/ml in some patients (Table III and Fig. 1). This implies that the test-dose concept for theophylline is difficult to apply to the aged seriously ill patients and that such observed lower or higher levels can be caused by the change of dose and/or \textit{P}aco\textsubscript{2} (Figs. 2 and 3).

There are an increasing number of clinical studies appearing in the literature suggesting that the elimination kinetics of theophylline is non-linear in some cases.\textsuperscript{13–16} This phenomenon has been accepted to result from the saturation of theophylline metabolism, particularly in the 3-methylxanthine formation pathway.\textsuperscript{13,15} Ishizaki and Kubo have recently reported that the values of Michaelis-Menten parameters calculated from 21 adult Japanese who showed non-linearity, ranging in $K_m$ from 3.8 to 42.3 $\mu$g/ml (12.9 $\pm$ 8.1 $\mu$g/ml) and in $V_{max}$ from 14.7 to 39.3 mg/kg/d (21.8 $\pm$ 6.7 mg/kg/d), were almost a half of those obtained from Caucasians,\textsuperscript{16} indicating that dose-dependent kinetics for theophylline can be seen more frequently in Japanese than in Caucasians. In other words, the disproportional increase of plasma level can occur even within the low therapeutic range as reported previously.\textsuperscript{14} Furthermore, it seems likely that drug metabolizing activity decreased in the critically ill patients as compared with stable patients in whom the test-dose method gave a good prediction.\textsuperscript{3,8–11} The observation by Ishizaki and Kubo supports our results that the clinical application of the test-dose method failed owing to its clearance alteration by dose-dependency, although the target concentration was at the lowest therapeutic level.

The role of arterial blood gases, especially \textit{P}ao\textsubscript{2}, on theophylline metabolism has become
of major recent interest. Letarte and Souich have demonstrated that theophylline clearance reduced in rabbits with hypoxemia.\textsuperscript{28} Miller and Oliver have, more recently, shown that the decrease of oxygen tension increased theophylline half-life in a rat liver perfusion study.\textsuperscript{31} These findings are in accordance with the observation that a 2-to 3-fold increase in the theophylline clearance paralleled to the elevation of $P_{ao2}$ in some patients.\textsuperscript{32} However, the change of $P_{ao2}$ did not relate to that of theophylline clearance in this work. This disagreement might be due to the fact that most of the patients had already received oxygen inhalation before theophylline dosing and that the tension shown in Table II did not reflect their own disease state.

Of interest found in our present study is that the change of $P_{aco2}$ other than $P_{ao2}$ influences theophylline clearance in humans. In rabbits with hypercapnia as well as hypoxemia, theophylline serum concentration has been reported to increase in relation to the reduction of its renal clearance.\textsuperscript{29} The decrease of theophylline clearance in the low $P_{ao2}$ condition has been regarded as the consequence of insufficient oxygen supply to drug metabolizing systems which require oxygen for metabolic oxidation of theophylline.\textsuperscript{29,31} However, this speculation can not be applied in the case of $P_{aco2}$. In view of no relationships between the changes of pH throughout the study, it seems unlikely that the elevation of pH, which could be subject to the decrease of $P_{aco2}$, resulted in the decrease of theophylline clearance owing to the decrease of free levels.\textsuperscript{29,33} Now, it is unclear how the variation of $P_{aco2}$ could influence theophylline disposition.

In any case, further investigation is necessary to elucidate the role of $P_{aco2}$ in theophylline elimination in detail.

In conclusion, theophylline test-dose concept may not be always useful in the seriously ill patients with respiratory failure because theophylline clearance can be easily changed by dose and $P_{aco2}$. Moreover, $P_{aco2}$ must be taken into account in theophylline dosage regimen calculation as a physiological parameter affecting theophylline clearance.

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**References**


