Theophylline Disposition in Patients with COLD with and without Hypoxemia*


This study aimed to assess the effect of hypoxemia on theophylline disposition. Ten patients with a mean (± SEM) of 58 ± 3 years with COLD (PaO₂, 55 ± 1 mm Hg; PaCO₂, 46 ± 2 mm Hg; and pH of 7.39 ± 0.01) were hospitalized to have oxygen therapy. Before starting O₂, they received intravenously, 4 mg/kg of theophylline over a 20-minute period; blood samples and urine were collected for six hours. The results suggested that hypoxia does not influence the disposition of theophylline or its metabolites.

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Theophylline systemic clearance is decreased in a variety of disease states, eg, severe airway obstruction, COLD in the elderly, pneumonia, cor pulmonale, congestive heart failure, acute pulmonary edema, and hepatic failure. Theophylline hepatic extraction ratio, expressed as the ratio of the rate of extraction (arterial less venous concentrations) to the rate of presentation (arterial concentration), is low and its plasma protein binding is only 50 percent. Thus, one may speculate that a decrease in theophylline clearance should be related to a reduction in its rate of biotransformation. In all the above diseases states except hepatic failure, the mechanism explaining this decrease remains obscure. It has already been proposed that hypoxia might cause a reduction in theophylline rate of biotransformation.

This hypothesis was supported by several reports showing that hypoxia decreased the in vivo biotransformation of several substrates. More recent studies, using hepatocytes, isolated perfused liver or conscious rabbits, have also shown that the clearance of theophylline was decreased under hypoxic conditions.

Studies conducted in man, however, have been contradictory and have not established definitely whether hypoxia causes a decrease in the activity of the cytochrome P-450. One study, comprised of patients with COLD, showed that arterial PaO₂ values below 55 mm Hg increased antipyrine half-life; however, these results were not confirmed by a more recent report.

Other studies have shown that in patients with COLD, tolbutamide half life was reduced. On the other hand, in a pediatric population, as well as in critically ill patients, no correlation was found between arterial blood gases and theophylline clearance. Moreover, no decrease in theophylline clearance was observed in ten patients, with advanced COLD, when their chronic O₂ therapy was discontinued.

The present study further investigated the effect of arterial blood gases on theophylline disposition. The experimental protocol differed from that of the earlier studies in two critical areas: first, the disposition of theophylline was assessed in the same patients with hypoxia and later on oxygen therapy, and second, theophylline and its three major metabolites were assayed in urine so as to document how hypoxia influenced theophylline biotransformation.

METHODS

Subjects

The selection of the patients was based on the following two criteria: (1) hypoxic patients requiring oxygen therapy; and (2) patients presenting no obvious cause, other than the disease itself, able to alter theophylline disposition. Ten patients (nine men and one woman) with COLD were selected for the study. Special care was taken to exclude patients older than 70 years old, or patients with cor pulmonale, congestive heart failure or hepatic disease. None of the patients exhibited acute decompensation but rather a gradual deterioration of their ventilatory status. The patients did not smoke; however, three of them gave up smoking two, four, and five weeks before the admission to the hospital.

Patients were hospitalized for clinical evaluation and possible oxygen therapy in the Respiratory Section of the C.H.U. de Brabois, Vandoeuvre-lès-Nancy (France). Each candidate gave informed consent for inclusion in the study. Mean patients’ age was 58.2 ± 3.1 years (± SEM) and their mean weight was 66.0 ± 3.2 kg. Clinical data concerning the ventilatory status of the patients are shown in Table 1. Arterial blood gases, FVC, and FEV₁, were measured just prior toophylline administration, using an automated and comput-
Table 1—Mean (± SEM) Arterial Blood Gases and Ventilatory Function of Ten Patients with COLD

<table>
<thead>
<tr>
<th></th>
<th>Before O2 Therapy</th>
<th>After O2 Therapy</th>
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<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>75 ± 12</td>
<td>83 ± 3</td>
</tr>
<tr>
<td>Respiratory rate, insp/min</td>
<td>20 ± 1</td>
<td>18 ± 1</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>54.9 ± 1.3</td>
<td>73.6 ± 1.9*</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>46.4 ± 2.3</td>
<td>49.3 ± 3.2</td>
</tr>
<tr>
<td>pH</td>
<td>7.39 ± 0.01</td>
<td>7.39 ± 0.01</td>
</tr>
<tr>
<td>FVC, L</td>
<td>1.88 ± 0.27 (4.18)</td>
<td>1.76 ± 0.27</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>0.78 ± 0.14 (2.91)</td>
<td>0.68 ± 0.08</td>
</tr>
<tr>
<td>FEV/FVC, %</td>
<td>40.7 ± 2.7 (69.6)</td>
<td>40.2 ± 3.5</td>
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*p<0.001 compared to values before O₂ therapy (analysis of variance).

†predicted values

erized gas microanalyzer and an electronic spirometer, respectively.

Drug therapy had been used in these patients prior to the study. This included oral theophylline (eight patients), salbutamol (two patients), amoxicillin (two patients), almitrine (two patients), cysteine derivatives (five patients) and furosemide, K⁺ supplements, oxtiropium and occasionally nitrates (one patient). Only four patients received theophylline between the two experiments. In all cases, theophylline was interrupted 24 hours prior the experiment. Prior and during the study, the patients drank the same amount of coffee (one to two cups per day) and none of them ate chocolate. Eight of the subjects were occasional wine drinkers (one to three cups per day).

All subjects had normal hepatic function tests. Renal function was appropriate for their age group as creatinine clearance was 97 ± 7 ml/min, prior to oxygen therapy.

Protocol

Once full clinical and laboratory examination was completed, the candidates were asked to empty their bladders prior to receiving 4 mg/kg of theophylline infused intravenously over a period of 20 minutes with a syringe pump. Blood samples were drawn prior to and 0.5, 1, 1.5, 2, 4, and 6 hours after the administration of theophylline. Urine was collected for the six-hour period. Following this first phase, the patients received oxygen through a nasal cannula at a rate of 1.5 to 2 L/min to obtain a PaO₂ of at least 65 mm Hg. After 48 hours, and still on oxygen, theophylline kinetics were reassessed following the same protocol as described above.

Theophylline in plasma was assayed by HPLC as described elsewhere. Theophylline and its three major metabolites in urine, 1,3-dimethyluric acid (1,3-DMU), 3-methylxantine (3-MX) and 1-methyluric acid (1-MU), were assayed by HPLC as described by St. Pierre et al. Pharmacokinetic Analysis

Theophylline plasma concentrations-time curve was best described by a two compartment model, with first order distribution and elimination. Pharmacokinetic parameters were calculated using conventional model independent method by means of a nonlinear regression curve-fitting program. In order to calculate the apparent volume of distribution (Vd) and the apparent systemic clearance (Clᵢ), we subtracted the area under theophylline plasma concentrations curve function of time (AUC) corresponding to the decline of theophylline plasma concentration at time 0 (calculated as C₀/B) from the total value of theophylline AUC (AUC₀∞). Theophylline renal clearance (Clᵢ) was calculated by dividing the amount recovered in urine for six hours by the AUC₀∞. Theophylline metabolic clearance (Clᵢ) was estimated from the equation Clᵢ = Clᵢ - Clᵢₐ.

The comparison of the effects of the two experimental conditions was carried out using a one-way analysis of variance. The minimal level of significance was p = 0.05.

RESULTS

As shown in Table 1, patients presented severe hypoxia and a mild hypercapnia secondary to obstructive lung disease. These showed considerable reduction in both the FEV₁ and the FVC, as well as in the FEV₁/FVC percentage. After 48 hours of oxygen therapy, PaO₂ increased significantly, while PaCO₂ increased only slightly and the indices of ventilatory function showed no change at all.

Theophylline plasma concentrations showed a sim-

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21593/ on 06/26/2017)

Table 2—Mean (± SEM) Distribution and Elimination Kinetic Parameters Following 4 mg/kg IV Dose of Theophylline in Ten Patients with COLD

<table>
<thead>
<tr>
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<th>Before O₂ Therapy</th>
<th>After O₂ Therapy</th>
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<tbody>
<tr>
<td>AUC₀∞, μg·min/ml</td>
<td>2709 ± 410</td>
<td>2607 ± 347</td>
</tr>
<tr>
<td>Vdᵢ, L/kg</td>
<td>0.45 ± 0.03</td>
<td>0.48 ± 0.03</td>
</tr>
<tr>
<td>Clᵢ, ml/min/kg</td>
<td>1.03 ± 0.11</td>
<td>1.14 ± 0.17</td>
</tr>
<tr>
<td>Clᵢₐ, ml/min/kg</td>
<td>0.13 ± 0.01</td>
<td>0.13 ± 0.02</td>
</tr>
<tr>
<td>t 1/2, h</td>
<td>5.90 ± 0.59</td>
<td>5.81 ± 0.75</td>
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Chest 95/5/MAV, 1989 1029
ilar pattern before and after oxygen therapy in all subjects, whether they exhibited a low ($n=2$) or a high ($n=8$) level of theophylline at the beginning of the experiment. For convenience, the two groups were pooled (Fig 1). The $AUC_{\text{R}}$ of theophylline was not modified by oxygen therapy (Table 2) and theophylline apparent volume of distribution remained constant.

Theophylline systemic clearance increased in only four of the ten patients which resulted in only a slight increase in the average value. This finding was secondary to a slight increase in theophylline metabolic clearance, as renal clearance did not change with oxygen therapy. Theophylline half life was not affected by oxygen therapy.

There was no relationship between the slight changes in theophylline clearance and the variations in $PaO_2$. However, when the patients were divided into two groups according to their $PaCO_2$ values, with 45 mm Hg as the cutoff, it was apparent that subjects with normal $PaCO_2$ values (lower than 45 mm Hg), had significantly higher values of theophylline clearance than patients with $PaCO_2$ values above 45 (Fig 2). Moreover, when considering the ten patients before and after therapy, the changes in theophylline clearance were inversely correlated ($r = -0.5264$; $p<0.02$) with the values of $PaCO_2$ (Fig 3).

The six-hour urinary recoveries of theophylline and its metabolites (3-MX, 1,3-DMU and 1-MU) are depicted in Table 3. As shown, oxygen therapy did not affect the pattern of urinary excretion of theophylline or its metabolites. On the other hand, the urinary recovery of theophylline metabolites was independent of previous treatment with theophylline but appeared weakly related to individual values of $PaO_2$ ($r = -0.53$, $p<0.02$ for 3-MX; $r = -0.46$, $p<0.05$ for 1,3-DMU; and $r = -0.47$, $p<0.05$ for 1-MU).

**DISCUSSION**

The results of this study showed that prior to oxygen therapy, theophylline clearance in our patients was not lower than that reported in healthy volunteers.\(^27\) The average value of theophylline clearance was not significantly decreased if the three exsmokers were excluded, eg, $Cl_t = 0.90 \pm 0.11$ ml/min/kg. On the other hand, after oxygen therapy, the changes in $PaO_2$ in our patients with COLD did not significantly alter the apparent systemic clearance of theophylline, and that was also true when the three exsmokers were excluded, eg, $Cl_t = 0.93 \pm 0.15$ ml/min/kg. Six of our patients showed a theophylline clearance of less than 1 ml/min/kg and after oxygen therapy, only one of them showed an increase; the values of the other five patients remained essentially unchanged. The study of the changes in the amounts of theophylline and its metabolites in urine (Table 3) does confirm that oxygen therapy did not affect the biotransformation of theophylline.

The present results in humans are in agreement with previous reports.\(^27\) Theophylline is a weak base (pKa = 11.6) and its renal clearance is essentially unchanged when the $Cl_t$ is increased.\(^6,27\)

**Table 3—Mean (± SEM) Recovery of Theophylline and Its Metabolites in a Six Hour Urine Collection, Following a 4 mg/kg IV Dose of Theophylline in Ten Patients with COLD**

<table>
<thead>
<tr>
<th></th>
<th>Before $O_2$ Therapy</th>
<th>After $O_2$ Therapy</th>
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<tbody>
<tr>
<td>Theophylline, mg</td>
<td>20.8 ± 2.2</td>
<td>19.4 ± 2.0</td>
</tr>
<tr>
<td>3-MX, mg</td>
<td>12.6 ± 2.1</td>
<td>10.0 ± 1.9</td>
</tr>
<tr>
<td>1,3-DMU, mg</td>
<td>59.1 ± 6.5</td>
<td>49.0 ± 6.2</td>
</tr>
<tr>
<td>1-MU, mg</td>
<td>33.9 ± 4.9</td>
<td>27.3 ± 3.4</td>
</tr>
<tr>
<td>Total, mg</td>
<td>126.5 ± 13.3</td>
<td>106.7 ± 11.0</td>
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\*3-MX is 3-methylxanthine; 1,3-DMU, 1,3-dimethyluric acid; and 1-MU, 1-methyluric acid.
with results obtained in conscious dogs, where neither acute nor chronic (six days) hypoxia affected theophylline disposition.20 However, these results differ from those obtained in a rabbit study, where it was shown that short term hypoxia (mean PaO2 of 55 mmHg) significantly decreased theophylline clearance.17 This discrepancy may be due to species differences or to protocol differences (in the rabbits, hypoxia was acute and of short duration and in addition, the rabbits had slight respiratory alkalosis). The discrepancy may also have been caused by other factors related to the patients' chronic respiratory disease, which may have influenced theophylline disposition. It is unlikely, however, that our results were biased by the experimental protocol (eg, blood sampling for only six hours), as the estimated theophylline kinetic parameters are in total agreement with those reported in the literature.8,27,29-31

It is interesting to note that in our patients, oxygen therapy slightly increased the PaCO2 with no noticeable decrease in arterial pH. The theophylline apparent volume of distribution was not increased by these slight changes. However, the changes in PaCO2 were inversely related to theophylline clearance values (Fig 3). Keeping in mind that the average theophylline clearance was slightly lower in subjects with a high PaCO2 (Fig 2), we are tempted to speculate that, in man, primarily hypercapnia and/or the pathology associated with hypercapnia is able to influence theophylline clearance.

Our results agree with those reported by Westerfield et al,22 and by Cusack et al,23 who, using a different approach, were unable to demonstrate that hypoxia could reduce the rate of biotransformation of theophylline. On the other hand, in their patients, the individual PaCO2 values did not correlate with theophylline clearance. This could be due to the fact that their patients had multiple additional conditions, including cor pulmonale, congestive heart failure, pneumonia, and liver disease, all of which are capable of reducing theophylline clearance. In addition, these patients were receiving several drugs which could alter the disposition of theophylline. Thus, when numerous factors are present within the same patient, which are capable of influencing theophylline clearance, correlations between changes in arterial blood gases and the values of theophylline apparent clearance may be masked.

In summary, in patients with COLD and severe hypoxia, the biotransformation of theophylline does not appear to be affected by hypoxia, since oxygen therapy did not alter significantly the clearance of theophylline. Our results do not support the hypothesis that in man, hypoxia affects the oxidation or the demethylation of theophylline. Therefore, the decrease in theophylline clearance reported by many investigators1-6 may be due instead to other factors such as inflammation secondary to viral22,33 or bacterial24,35 processes, liver disease, or perhaps hypercapnia.

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