IMPAIRED THEOPHYLLINE CLEARANCE IN PATIENTS WITH COR PULMONALE

N. VICUNA,¹ J.L. McNAY,¹ T.M. LUDDEN² & H. SCHWERTNER³

¹Division of Clinical Pharmacology, Departments of Medicine and Pharmacology

²College of Pharmacy, University of Texas-Austin, Austin, Texas, and

³Department of Pathology, UTHSCSA, and Audie Murphy Veterans Administration Hospital, San Antonio, Texas.

- 1 The relationship between serum theophylline concentration and daily dose was studied in 45 patients receiving aminophylline orally and in 36 patients receiving it by constant intravenous infusion.
- 2 Patients were categorized as uncomplicated chronic obstructive pulmonary disease (COPD) or COPD with cor pulmonale (CP).
- 3 Serum theophylline concentration relative to daily theophylline dose was significantly higher in patients with COPD plus CP than in patients with COPD alone.
- 4 Total body clearance of theophylline estimated from data obtained during constant intravenous infusion was significantly lower in COPD plus CP than in patients with COPD alone.
- 5 We conclude that reduced maintenance doses of theophylline are indicated in patients with COPD when complicated with CP.

Introduction

There is known to be a wide intersubject variation in the relationship of serum concentration of theophylline to dosage (Jacobs, Senior & Kessler, 1976; Jenne, Wyze, Rood & MacDonald, 1972; Loughnan, Sitar, Ogilvie, Eisen, Fox & Neims, 1976; Mitenko & Ogilvie, 1973). This is partially attributable to differences in rate of metabolism. Factors which have been shown to affect theophylline metabolism include age (Loughnan *et al.*, 1976), smoking habits (Hunt, Jusko & Yurchak, 1976), and liver disease (Piafsky, Sitar, Rangno & Ogilvie, 1977b). Left ventricular heart failure sufficient to produce pulmonary edema also decreases the rate of metabolism of theophylline (Piafsky, Sitar, Rangno & Ogilvie, 1977a). In one study, a high proportion of patients with a diagnosis of COPD in combination with cor pulmonale and/or congestive heart failure was found to have an increased serum theophylline concentration relative to daily dose (Zwillich, Sutton, Neff, Cohn, Matthay & Weinberger, 1975). However, no systematic study has been performed which permits quantitative estimation of the extent to which cor pulmonale in combination with COPD affects theophylline metabolism.

The present study was undertaken to determine the influence of cor pulmonale, in combination with COPD, on the relationship of serum theophylline to dosage. Theophylline administered by either the oral or intravenous route to patients with COPD uncomplicated by CP provided a reference group with which comparison was made. In the subgroup of

patients who received the drug by constant intravenous infusion, the apparent serum clearances of theophylline in patients with and without CP were compared. We established that the serum concentration of theophylline relative to the dose is increased in patients with COPD plus CP when compared to patients with COPD alone. The increase in concentration relative to the dose was shown to be associated with a reduction in apparent serum clearance in patients with COPD plus CP, when compared to the clearance of patients with uncomplicated COPD.

Methods

Subjects of this study were inpatients at the Bexar County and Audie Murphy Veterans Administration Hospitals with the clinical diagnosis of chronic obstructive pulmonary disease (COPD) or COPD and cor pulmonale (CP). The diagnoses were accepted by the authors on the basis of inclusion in the problem list of patients' records and therefore represented the clinical assessment of the attending physician or house-officers of The University of Texas Health Sciences Center at San Antonio.

Oral route of administration

Forty-five patients received oral theophylline as aminophylline tablets in equally divided doses every

6 h. Of this group, thirty-nine patients (four females) had COPD alone. The mean age was 56.1 years. Six patients (three females), mean age of 63.8 years, had COPD and CP. For the entire group the mean daily dose was 15.4 mg/kg (range 6.3–29.7 mg/kg). Serum samples for assay of theophylline concentration were obtained 0.5 h predose after at least 48 h of continuous therapy.

Intravenous administration

Thirty-six patients received a loading dose of aminophylline via intravenous infusion over 20 to 30 min and were subsequently placed on an infusion of aminophylline at a constant rate. Twenty-eight of these patients (three females), mean age of 62.5 years, had COPD. The remaining eight patients (two females) had both COPD and CP. The mean age of these patients was 64.5 years. Serum theophylline concentrations were determined after at least 36 h of constant infusion. The mean rates of intravenous theophylline infusion for patient groups with COPD alone and COPD with CP were 0.756 mg kg⁻¹ h⁻¹ (range: 0.312–1.27 mg kg⁻¹ h⁻¹) and 0.665 mg kg⁻¹ h⁻¹ (range: 0.376–0.849 mg kg⁻¹ h⁻¹), respectively.

Xanthine containing beverages were not restricted since a specific gas-liquid chromatographic method was used for the assay of serum theophylline (Schwertner, Ludden & Wallace, 1976). Caffeine, theobromine or metabolites of caffeine, theobromine, and theophylline do not interfere with the determination of theophylline by this technique. Although theophylline itself is a metabolite of caffeine, ingestion of the usual amounts of caffeine produces serum theophylline concentrations less than 3 µg/ml (Jacobs *et al.*, 1976).

Apparent theophylline plasma clearance was calculated for patients receiving a constant intravenous infusion of aminophylline by dividing the infusion rate (expressed in terms of theophylline) by the apparent steady state serum theophylline con-

centration. It is necessary to refer to these calculated clearances as apparent values since multiple sampling was not performed to confirm that the observed serum theophylline concentrations were truly steady state.

Comparison of group means was carried out using the unpaired *t*-test. Regression analysis was performed using the technique of least squares.

Results

Oral route of administration

The dose of theophylline was lower and the predose serum concentration of theophylline higher in patients with CP plus COPD than in patients with COPD alone. However, in neither instance was the difference significant. Mean values for each clinical group are presented in Table 1.

When, however, serum concentration was related to total daily dose and expressed as (µg/ml) / (mg kg⁻¹ 24 h⁻¹), ratio was significantly ($P < 0.02$) greater in patients with COPD plus CP than in patients with COPD alone. The mean values for each group are presented in Table 2.

Table 1 Daily theophylline doses and predose serum concentrations (C_p) in patients with chronic obstructive pulmonary disease (COPD) with and without cor pulmonale (CP); oral route.

<i>n</i>	<i>Clinical group</i>			
	<i>COPD</i>		<i>COPD + CP</i>	
	39		6	
	<i>Dose*</i>	<i>C_p</i>	<i>Dose*</i>	<i>C_p</i>
	<i>(mg kg⁻¹ 24 h)(µg/ml)</i>		<i>(mg kg⁻¹ 24 h⁻¹)(µg/ml)</i>	
Mean	12.56	11.06	10.68	15.23
s.e. mean	0.81	0.85	1.16	1.76

*Dose expressed as theophylline
n signifies number of patients per group

Table 2 Serum theophylline concentrations relative to 24 h doses in patients with chronic obstructive pulmonary disease (COPD) with and without cor pulmonale (CP).

<i>Clinical class</i>	<i>Route of administration</i>			
	<i>Oral</i>	<i>Intravenous</i>		
	<i>COPD</i>	<i>COPD + CP</i>	<i>COPD</i>	<i>COPD + CP</i>
<i>n</i>	39	6	28	8
Mean plasma concentration: dose ratio*	0.939	1.434 ⁺	0.932	1.73 ⁺
s.e. mean	0.073	0.100	0.049	0.300

* Plasma concentration: dose ratio expressed as (µg/ml)/(mg kg⁻¹ 24 h⁻¹)

n number of patients per group

⁺ Significance of intergroup differences; oral COPD—oral COPD + CP, $P < 0.02$, i.v. COPD—i.v. COPD + CP, $P < 0.01$

Intravenous route of administration

The rate of intravenous administration of theophylline was virtually identical in the patient groups with and without cor pulmonale. In contrast, the serum theophylline concentration was significantly ($P < 0.001$) greater in the patients with cor pulmonale than in those with COPD alone. A comparison of the two groups is presented in Table 3.

In addition, when serum concentration was related to total daily dose, and expressed as $(\mu\text{g/ml})/(\text{mg kg}^{-1} 24 \text{ h}^{-1})$, the ratio was significantly ($P < 0.01$) greater in patients with COPD plus CP than in patients with COPD alone. The mean values for each group are presented in Table 2. It is of interest that the ratios of serum concentration to administered dose were of similar magnitude to those obtained during oral administration.

Pooled oral and intravenous results

Serum concentrations of theophylline in patients with COPD with and without CP were related to the rate of administration by least squares regression analysis independent of the route of administration. There was a significant correlation between serum concentration and the administration rate both for patients with COPD ($P < 0.001$) and with COPD plus CP ($P < 0.05$).

In addition, the slopes of the two linear regression lines differed with the probability < 0.06 , being greater in patients with COPD plus CP than in patients with COPD alone. The relationship of serum concentration to dose for each group of patients is presented in Figure 1.

Figure 1 The relationship of serum theophylline concentration to rate of administration, according to clinical group independent of route of administration. ● Patients with COPD alone, ○ patients with chronic obstructive pulmonary disease plus cor pulmonale. Lines represent the correlations between serum concentrations and doses, calculated by least squares regression. A significant correlation was present for each group. A comparison of the slopes of the two linear regression lines was suggestive of a difference, with a probability < 0.06 .

	COPD	COPD + CP
slope	0.79	1.53
intercept	1.49	0.23
<i>r</i>	0.68	0.56
<i>n</i>	67	14
<i>P</i>	< 0.001	< 0.05

Table 3 Intravenous infusion rates and serum theophylline concentrations in patients with chronic obstructive pulmonary disease (COPD) with and without cor pulmonale (CP).

	Clinical class	
	COPD	COPD + CP
<i>n</i>	28	8
Theophylline infusion rate ($\text{mg kg}^{-1} \text{ h}^{-1}$)		
Mean	0.756	0.664
s.e. mean	0.030	0.058
Serum concentration ($\mu\text{g/ml}$)*		
Mean	16.6	26.8
s. e. mean	1.09	4.4

* Significance of difference between groups, $P < 0.001$

n number of patients per group

Table 4 Comparison of average apparent plasma clearances of theophylline, according to clinical class: intravenous route only.

	Clinical group	
	COPD	COPD + CP
<i>n</i>	28	8
Mean apparent plasma clearance ($\text{ml kg}^{-1} \text{ min}^{-1}$)*	0.798	0.481
s.e. mean	0.041	0.070

COPD signifies chronic obstructive pulmonary disease; CP signifies cor pulmonale

* Significance of intergroup differences; COPD–COPD + CP, $P < 0.001$

n number of patients per group

Apparent serum clearance of theophylline

We compared the observed clearances of theophylline from sub-groups having a diagnosis of COPD with or without cor pulmonale. Only patients who had received the drug intravenously were included in this comparison, which is presented in Table 4. The mean clearance of the group of patients with COPD plus CP was significantly ($P < 0.001$) less than that of the patients with COPD alone.

Discussion

We have established that patients with cor pulmonale associated with COPD constitute an additional group of patients predisposed to elevated plasma theophylline concentration. Although our classification of patients was based exclusively on clinical observations, this is the usual situation in practice and should serve to alert physicians to the need for dosage individualization in this type of patient.

The increased plasma concentration relative to dose in patients with cor pulmonale was found to be attributable quantitatively to a decrease in plasma clearance of theophylline. The average total body clearance of theophylline in patients receiving intravenous infusion with the diagnosis of COPD alone was $0.798 \text{ ml kg}^{-1} \text{ min}^{-1}$. Patients with COPD plus CP had on average total body Clearance of $0.481 \text{ ml kg}^{-1} \text{ min}^{-1}$. Thus, the clearance rate in the latter group of patients was 60% of that in the former group of patients.

We found that the most feasible approach by which to identify the effect of cor pulmonale on theophylline clearance was by comparison of patient groups with COPD alone and COPD concomitant with cor pulmonale. This comparison tends to eliminate other factors which may separate patients with COPD *per se* from the normal population. An example of such a factor would be the amount and duration of cigarette consumption, a factor which in itself enhances theophylline disposition clearance (Hunt, Jusko & Yurchak, 1976). However, it should be noted that the total body clearance of theophylline which we observed in patients with COPD plus CP was not only

significantly less than that observed in our own series of patients with COPD, but also significantly less than values reported for normal subjects in the literature (Mitenko & Ogilvie, 1973).

Literature published to date suggests that COPD complicated by heart disease may be associated with toxic plasma theophylline concentrations. In a report of patients with theophylline-induced seizures, there was a clear association of elevated plasma concentration with toxic effects (Zwillich *et al.*, 1975). Of twelve patients with toxic manifestations, the average serum concentration of theophylline relative to average oral dose was elevated. Seven of these twelve patients had a clinical diagnosis of congestive heart failure. This suggests that the presence of cardiac insufficiency predisposes to reduced metabolism of theophylline. It has been demonstrated that theophylline clearance is reduced in pulmonary edema (Piafsky *et al.*, 1977a). However, the effect of cor pulmonale *per se* to reduce theophylline clearance has not been previously documented.

While it has been suggested that passive congestion of the liver in patients with heart failure might alter the hepatic capacity to extract and metabolize theophylline (Piafsky *et al.*, 1977b), this possibility has not been experimentally verified. Our observation that cor pulmonale, as well as pulmonary edema, reduces theophylline clearance would be compatible with this mechanism of decreased hepatic clearance, since cardiac output *per se* and possibly liver perfusion, are normal in cor pulmonale (Parker, Kelkar & West, 1966).

In conclusion, we observed that the plasma concentration of theophylline in COPD plus CP was higher relative to orally or intravenously administered doses than was the case in patients with COPD alone. A significantly lower total body clearance of theophylline was also established in the patients with COPD plus CP. The combination of COPD and CP was associated with an average decrease in clearance to 38% of that observed in a selected normal series (Mitenko & Ogilvie, 1973). In light of these findings, it would seem prudent to appropriately adjust oral and intravenous maintenance doses of theophylline in the present of these clinical diagnosis, and to individualize dosage regimens by serum theophylline assays.

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