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Hypoxia, Arterial pH and Theophylline Disposition

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Summary

Theophylline is a bronchodilator used extensively in the management of obstructive pulmonary disease. Factors implicated in altered theophylline clearance include smoking, age, concomitant drug intake, liver disease and left ventricular heart failure. However, evidence now suggests that theophylline clearance may be altered by changes in severity of the pulmonary obstruction, hypoxia and variation in arterial pH.

The *in vitro* disposition of theophylline has been evaluated in isolated rat livers and mouse hepatocytes. *In vivo* studies have assessed the metabolism of theophylline under hypoxia in rats, rabbits and dogs. In isolated mouse hepatocytes and rat livers, low oxygen concentrations resulted in higher theophylline concentrations, a longer elimination half-life and a decrease in the production of the metabolite 1,3-dimethyl uric acid, suggesting impaired metabolism of theophylline. In rabbits, hypoxia, hypercapnia and respiratory acidosis decreased total body clearance and increased plasma theophylline concentrations. On the other hand, experiments involving dogs showed no significant changes in theophylline concentrations or pharmacokinetic parameters with hypoxia. At present, animal studies remain inconclusive. This can be attributed to the use of different animal models and variations in study methodology, including the extent and duration of hypoxia and acidaemia, concurrent acid-base disorders such as hypercapnia, as well as the severity of pulmonary obstruction.

Human studies assessing alterations in theophylline disposition secondary to the hypoxia present in pulmonary disease are few and include mostly case reports and observational studies. There is evidence suggesting decreased theophylline clearance and protein binding during acute illness and some consensus can be achieved using case reports and controlled studies. There is additional evidence that drug clearance decreases with age and that elderly patients may have a decreased theophylline clearance at baseline. However, the most obvious markers appear to be the severity of pulmonary disease and the rate of change in the patient's condition. Caution should be exercised when administering theophylline to elderly patients with chronic obstructive pul-

monary disease presenting with acute exacerbations of a concomitant respiratory illness, as these patients appear to be most likely to exhibit altered theophylline metabolism. Therefore, they would be at increased risk for toxicity should conventional dosages be used during an acute respiratory event.

Theophylline is a bronchodilator used extensively in the management of obstructive pulmonary disease. Wide interindividual variability exists in the dose-concentration relationship of theophylline, and interindividual differences in the rate of metabolism are most often cited as the cause of this variation. Factors implicated in altered theophylline clearance include smoking, age, concomitant drug intake, liver disease and left ventricular heart failure (Cusack et al. 1986; Edwards et al. 1992; Lee et al. 1987; Powell et al. 1978; Vicuna et al. 1979).

Until recently, little attention had been paid to the influence of pulmonary disease on theophylline disposition in patients in the acute or chronic phases of chronic obstructive pulmonary disease (COPD) and asthma. However, evidence now suggests that theophylline clearance may be altered by changes in the severity of pulmonary obstruction, hypoxia and variation in arterial pH. This review focuses on the effects of hypoxia and variation in arterial pH on the disposition of theophylline.

1. Pulmonary Disease and Pharmacokinetics

Pathological changes associated with pulmonary diseases can influence drug disposition through changes in normal organ physiology, hepatic enzyme activity, blood flow to the liver and kidneys, plasma protein binding and tissue pH. Most pulmonary disease will result in altered arterial blood gas tension, hypoxia, acid-base imbalance or increased pulmonary vascular resistance (du Souich et al. 1978). While these manifestations are closely linked, patients usually present with either vascular or gas exchange abnormalities.

There are 2 major haemodynamic consequences of increased pulmonary vascular resistance: decreased cardiac output and increased venous congestion of the peripheral circulation. This results in decreased perfusion of the liver, kidneys and other vascular beds. Although reduced splanchnic blood flow can decrease perfusion of the gastrointestinal tract, there is little clinical evidence to substantiate that these changes are clinically significant in terms of altered drug absorption.

Alterations in plasma pH may change the degree of ionisation and distribution of drugs. Depending on their hepatic extraction characteristics, drugs that are primarily metabolised by the liver may also be expected to exhibit altered elimination in patients with pulmonary diseases. Elimination of drugs with a high hepatic extraction ratio (>0.7), such as propranolol and lidocaine (lignocaine), would be delayed secondary to decreased liver blood flow. Drugs with low hepatic extraction ratios (<0.3), such as theophylline and phenazone (antipyrine) would also be expected to have a reduced clearance as a result of changes in hepatic enzyme activity induced by the hypoxic state (see section 2). Renal excretion of drugs may also be altered in pulmonary disease as a consequence of changes in plasma protein binding as well as a decrease in renal blood flow and glomerular filtration rate (du Souich et al. 1978).

The effect of acute hypoxia on liver function has been predominantly studied in animals. In humans, changes caused by respiratory disease on drug absorption, distribution, metabolism and elimination have been studied and reviewed for procainamide, corticosteroids, phenazone, tolbutamide, amikacin, amoxicillin, digoxin and ephedrine (du Souich et al. 1978).

Phenazone is a marker used extensively to study the effect of different patient-specific variables on oxidative drug metabolism. A decrease in phenazone clearance of 21% was noted in 30 men with lung disease when compared with healthy normal

volunteers ($p < 0.01$) [Laybourn et al. 1986]. There was only a low correlation between the spirometric lung function values and the phenazone clearance ($r = 0.5$, $p < 0.005$), which suggested that the reduction in phenazone clearance is partially related to the lung disease *per se*. However, blood gas analysis was not performed and therefore the effect of changes in oxygen tension on phenazone clearance could not be determined.

In another study, patients with decreased arterial partial oxygen tensions (paO_2) secondary to pulmonary disease were given phenazone orally or intravenously (Cumming 1976). The investigator reported a trend towards longer phenazone elimination half-lives in patients with a paO_2 less than 60mm Hg. However, the clinical value of these results is questionable. The number of patients evaluated was not reported and some of the patients received enzyme inducers as concomitant medication. In addition, information regarding the severity of disease and selection of controls was also not presented. On the other hand, in 8 patients with chronic pulmonary disease exposed to both room air and supplemental oxygen, phenazone clearance values were reported to be higher than literature values for healthy volunteers (Agnihotri et al. 1978).

2. Hypoxia and Drug Metabolism

Hepatic lobules are anatomically and traditionally described as periportal or centrilobular. From a morphological standpoint, the term liver acinus has been used to describe the microvascular unit. This unit is divided into 3 zones: 1, 2 and 3 according to cell morphology, rather than by distribution of blood flow (Gumucio & Miller 1981). It has been proposed that a significant oxygen concentration gradient exists between zone 1 and zone 3, the latter having the most critical concentration (Gumucio & Miller 1981). In addition, it is thought that zone 3 may contribute predominantly to cytochrome P450-dependent drug metabolism. Many variants of cytochrome P450 enzymes exist, however, and their zonal distribution has not been elucidated.

Distribution of enzymes in the acinus is not the only contributing factor to drug metabolism. The rate of drug elimination by hepatic mixed function oxidases is a function of the amount of enzyme activity, the rate of drug delivery to the enzyme, the accessibility of drug to the enzyme located in various parts of the acinus and the availability of oxygen as a cosubstrate (Gumucio & Miller 1981; Nakatsu 1985). Oxygen is required as a substrate for drug oxidation and as a terminal electron acceptor in processes dependent upon cellular redox state and in the mitochondrial synthesis of high energy bonds required for drug transport and conjugation reactions (Jones 1981). Cytochrome oxidase is the enzyme responsible for the use of most of the oxygen that is consumed by cells.

In mammalian cells, the apparent concentration at which the rate of use of oxygen is at half maximum value (Km_{O_2}), is approximately 5 μmol/L. Since the mean oxygen concentration in the liver is about 30 μmol/L, cytochrome oxidase is typically saturated and, thus, its function is mostly independent of oxygen. However, a small decrease from 30 μmol/L is sufficient to cause a change in the oxidation-reduction state of cytochromes. Consequently, even mild hypoxia can result in changes in mitochondrial function (Jones et al. 1989). Hypoxia, a state of subnormal intracellular oxygen concentration, is therefore an important consideration in pharmacology, as a decrease in oxygen concentration can alter biochemical, physiological or pathological functions. Impaired cellular function can modify the *in vivo* effectiveness of a drug, increase drug-induced toxicity and alter the rate of drug metabolism (Jones 1981).

Two types of hypoxia have been described: bioenergetic and metabolic hypoxia (Jones 1981). Bioenergetic hypoxia results when high energy phosphate supply is depleted and the oxidation-reduction state of pyridine nucleotides is altered due to abnormal cytochrome oxidase function in light of decreased oxygen concentrations. When oxygen concentrations are inadequate to maintain other oxidases and oxygenases in a functional state, the result is metabolic hypoxia. Based on the enzyme affinity for oxygen determined in animal

studies, the metabolism of a large number of cytochrome P450 substrates will decrease during mild hypoxia. Subsequent *in vivo* studies have demonstrated that drug metabolism of certain drugs is dependent upon oxygen supply, and the effect is dependent on the severity of the hypoxia.

As discussed previously, results on the disposition of phenazone in chronic hypoxia are conflicting. Propranolol uptake was unchanged by acute hypoxia but its overall elimination was greatly reduced in isolated perfused rat livers (Jones et al. 1984). However, caution must be used when defining the severity of hypoxia at the cellular level since arterial measurement does not always assess organ supply. This applies particularly to the liver, which is primarily supplied by low oxygenated venous blood.

Hypoxia has not been shown to have an effect on nicotinamide adenine dinucleotide (NAD^+) - linked dehydrogenases, another type of phase 1 reaction (Jones et al. 1989). Phase 2 reactions such as glucuronidation and sulphonation are dependent, to some extent, on oxygen concentration. Glucuronidation of paracetamol (acetaminophen) is oxygen dependent below paO_2 values of 75mm Hg, while sulphonation of paracetamol is affected by acute but not by chronic hypoxia (Jones et al. 1989).

3. Clinical Pharmacokinetics of Theophylline

For many years theophylline has been used as a bronchodilator in the treatment of acute asthma, in the management of neonatal apnoea, as well as in the control of symptoms of chronic asthma. This dimethylated xanthine is similar in structure to caffeine and theobromine. It is consistently and completely absorbed without first-pass metabolism (Edwards et al. 1992). Theophylline is a low extraction drug due to its low intrinsic clearance with respect to liver blood flow. Its hepatic clearance and terminal elimination half-life are independent of changes in liver blood flow but highly sensitive to the liver's ability to metabolise the drug (Wilkinson & Shand 1975). This in turn can be interpreted as changes in theophylline concentrations associated with interindividual differences in rates of drug metabolism, enzyme induction or inhibition, and changes in disease states.

Theophylline is eliminated by hepatic biotransformation into mostly inactive metabolites that are rapidly excreted in the urine. Approximately 85 to 90% of a dose of theophylline is metabolised by the hepatic cytochrome P450 enzyme system (Edwards et al. 1992; Robson et al. 1987). This metabolism involves both first-order and capacity-limited pharmacokinetic processes (fig. 1).

The major metabolic route is 8-hydroxylation to 1,3-dimethyluric acid (1,3-DMU) which represents 45 to 55% of total theophylline clearance (Robson et al. 1987). The other metabolites are 1-methyluric acid (1-MU) and 3-methylxanthine (3-MX), which account for 20 to 25% and 13 to 16% of total theophylline clearance, respectively. The biotransformation of theophylline to 1-MU via formation of 1-methylxanthine (1-MX) is mediated by xanthine oxidase. On the basis of the lack of V_{max} correlation for metabolite production, it is postulated that 1- and 3-demethylation of theophylline are predominantly mediated by one cytochrome P450 isozyme, and 8-hydroxylation of theophylline to 1,3-DMU by another (Robson et al. 1987). Using different human cytochrome P450 enzymes expressed in HepG2 cells, Gu et al. (1992) recently identified cytochromes CYP1A2 and CYP2E1 as responsible for *N*-demethylation and 8-hydroxylation of theophylline, respectively.

Pharmacological activity of 3-MX has been demonstrated in isolated preparations of human and guinea-pig airway, guinea-pig hearts and anaesthetised cats (Persson & Andersson 1977). However, *in vivo* concentrations of 3-MX are approximately 10 times less than corresponding concentrations of the parent compound theophylline. This explains the clinically insignificant pharmacological action of the metabolite (Tang-Liu et al. 1982). Based on urinary excretion patterns and the area under the curve (AUC) of the 3 major metabolites, there were no significant circadian differences in theophylline metabolism when the drug was infused as a single intravenous dose to 8 healthy nonsmoking males (St-Pierre et al. 1985).

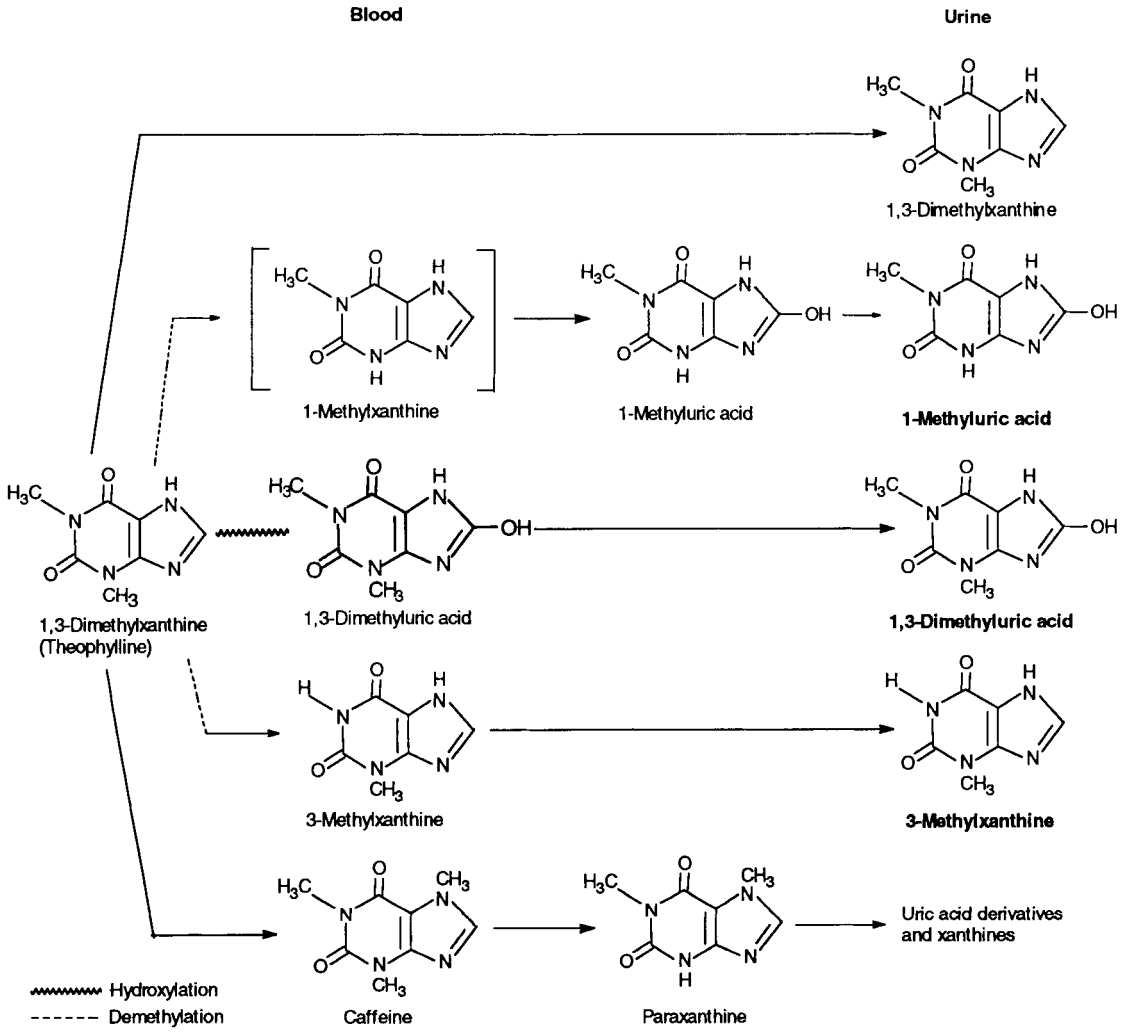

Fig. 1. Metabolism of theophylline.

Different studies reported that 40 to 60% of theophylline is bound to plasma proteins, predominantly albumin, of healthy adults and those with obstructive pulmonary disease. Binding was concentration independent but pH dependent (Buss et al. 1983; Shaw et al. 1982; Vallner et al. 1979). Shaw et al. (1982) investigated the effect of arterial pH on protein binding of theophylline *in vitro*. The theophylline bound fraction increased from 28.2% ± 4.3 at pH 7.0 to 46.8% ± 4.9 at pH 7.8. Vallner et al. (1979) observed a dependence of theophylline binding on pH, with the bound fraction increasing from 30% at pH 7.0 to 65% at pH 7.8. Buss et al. (1983) also found a relationship between plasma pH and percentage theophylline in the bound form. The bound fraction ranged from 30% at pH 7.0 to 45% at pH 7.8. The results of these studies showed that theophylline binding increases as the pH increases, although the results of Vallner et al. (1979) showed a higher bound fraction at pH 7.8.

This difference in result may be related to the temperature at which the binding study was performed. Buss et al. (1983) and Shaw et al. (1982), but not Vallner et al. (1979), performed the binding experiments at 37°C. Shaw et al. (1982) evaluated the effect of temperature and reported that binding of theophylline decreased as temperature increased. All 3 studies showed that the binding of theophylline at different pH values was independent of the concentration of theophylline.

Beyond the neonatal period, less than 15% of a theophylline dose is excreted as unchanged drug by the kidney. Renal clearance of theophylline is dependent upon urine flow rates and there is evidence that renal clearance of metabolites exceeds glomerular filtration rate, implicating secretion as an additional mechanism of theophylline elimination (Tang-Liu et al. 1982). These conclusions were derived following oral administration of theophylline and measurement of plasma and urine concentrations of the metabolites.

4. Hypoxia, Acid-Base Disorders and Theophylline Disposition

4.1 *In Vitro* and Animal Studies

Using mouse hepatocytes and isolated rat livers, Nakatsu (1985) evaluated the effect of oxygen availability on the rate of metabolism of theophylline. Hepatocytes were incubated with theophylline at a concentration of 15 mg/L and were supplied with a gas mixture of 7, 14, 28, 40, 70 or 95% oxygen over a period of 2 to 4 hours. Isolated rat livers were perfused with 15 mg/L of theophylline for the first and third hour of perfusion. During the second hour the oxygen concentration was varied between 14 and 70%. In mouse hepatocytes, a decrease in the metabolism of theophylline, as measured by theophylline concentration in the incubation bath after exposure, was most obvious when oxygen content of the gas mixture was $\leq$ 40% (table I). In the isolated rat livers, theophylline metabolism was assessed solely by the production of 1,3-DMU, the predominant metabolite in rats. Correlation analysis showed a high degree of association ($r = 0.87$, $p < 0.001$) between an elevated oxygen concentration of the gas mixture and 1,3-DMU production. Upon restoration of high oxygen concentrations, inhibition of 1,3-DMU production was reversible.

The influence of oxygen tension and perfusate flow rate on the clearance of theophylline (80 mg/L in the perfusate) was evaluated in another study using rat isolated perfused livers (Miller & Oliver 1986). Perfusion rate was varied from 8 to 15 ml/min; oxygen tension was altered to give 115mm Hg (treatment I), 50mm Hg (treatment II) and finally 115mm Hg oxygen (treatment III). Results showed no significant difference in the theophylline extraction ratio at flow rates varying from 8 to 15 ml/min. One-way analysis of variance showed a significant increase in theophylline half-life between treatment I and II and between treatment II and III (table I). No significant difference was noted between theophylline half-life during treatments I and III, indicating that the change in half-life was not due to irreversible change in hepatocellular function.

Theophylline was administered as a bolus injection or as a bolus injection followed by a constant infusion in normal hypoxic rats (8% oxygen and paO_2 of 34.2 $\pm$ 2.9mm Hg) [Kishimoto et al. 1989]. The pharmacokinetic parameters are reported in table II.

Analysis of plasma theophylline concentration after bolus injection revealed an elimination half-life of 2.4 hours in the control group *vs* 7.7 hours in the hypoxic group. In the hypoxic group there was evidence of significantly reduced total, hepatic and renal clearance. The percentage of the theophylline dose excreted in the urine as unchanged drug was decreased from 22.5 to 13.0% in hypoxic rats. The percentages of the theophylline dose excreted in the urine as 1-MU and 1,3-DMU were decreased by hypoxia from 21.2 to 8.1%, and from 21.4 to 7.4%, respectively, compared with control rats. The altered pharmacokinetics of theophylline did not result from altered distribution, as reflected by the similar steady-state volume of distribution and unbound fraction. After 4 hours of continuous infusion, plasma concentrations were significantly higher in the hypoxic group (15.4 $\pm$ 2.4 mg/L in

Table I. Summary of *in vitro* studies of the effects of hypoxia and arterial pH on theophylline disposition

Reference	Species and preparation	Theophylline concentration (mg/L)	Oxygen content or paO_2 (%)	Theophylline recovery (mg/L)	1,3-DMU concentration[b] (mg/L)	Elimination half-life[c] (min)
Nakatsu (1985)	Mouse hepatocytes	15	7	15 (2h)[a]		
			14	15 (2h)[a]		
			28	8 (4h)[a]		
			40	7 (4h)[a]		
			70	4.5 (4h)		
			95	3 (4h)		
	Perfused rat liver	15	14		0-0.02	
			28		0-0.13	
			40		0.03-0.25	
			70		0.175-0.375	
Miller & Oliver (1986)	Perfused rat liver	80	(I) 115mm Hg			60
			(II) 50mm Hg			90
			(III) 115mm Hg			60

a $p < 0.05$ with reference to hepatocytes provided with 95% oxygen.
b Correlation coefficient (r) = 0.87 and $p < 0.001$.
c $p < 0.01$ between treatments I and II, and treatments II and III.
Abbreviations: paO_2 = oxygen tension; 1,3-DMU = 1,3-dimethyluric acid.

hypoxia; 9.7 ± 0.5 mg/L in controls). Theophylline plasma concentrations approached control group values when the rats were re-exposed to room air (Kishimoto et al. 1989).

In another study, 5 groups of 6 male New Zealand white rabbits were exposed to different experimental conditions: room air, metabolic acidosis induced by the administration of 0.3N HCl to attain a pH of 7.25, elevated CO_2 concentration [arterial partial tension of carbon dioxide ($paCO_2$): 60mm Hg], low paO_2 concentration (55mm Hg), and low paO_2 in conjunction with elevated $paCO_2$ concentrations (Letarte & du Souich 1984). Blood, urine and cerebrospinal fluid (CSF) were collected. Theophylline pharmacokinetics were not influenced by metabolic acidosis, but hypercapnia and respiratory acidosis increased theophylline AUC by 34.2% (table II). The presence of hypoxia alone and hypoxia with hypercapnia significantly increased theophylline AUC by 40.4 and 39.7%, respectively. This was attributed to a decrease in theophylline elimination rate constant and a decrease in the total clearance. Renal clearance was not affected but nonrenal clearance was significantly decreased by hypercapnia alone (25.7%), and to a greater extent by hypoxia alone (28.3%), and a combination of hypoxia and hypercapnia (32.9%). Hypoxia alone decreased the volume of distribution during the terminal elimination phase by 21.3%. The theophylline CSF : plasma ratio was increased by 16.1% when hypercapnia was combined with hypoxia.

On the other hand, theophylline disposition was unaltered during acute and chronic hypoxia in conscious dogs (Saunier et al. 1987). The experiment used 3 different experimental conditions: air; acute hypoxia (10% O_2, 4% CO_2, 86% N_2) with normocapnia, in which theophylline was administered 1 hour after the beginning of exposure; and chronic hypoxia with normocapnia (same gas concentrations as acute hypoxia), in which theophylline was administered 96 hours after the beginning of exposure. From data supplied in graphical form, the urinary recovery of theophylline, 1,3-DMU and 3-MX, appeared similar in all 3 experimental conditions. The results demonstrated that, in the dog, acute and chronic hypoxia did not alter theophylline AUC, total, renal or hepatic clearance, volume of distribution, or elimination half-life. It appears

Table II. Summary of animal studies of the effects of hypoxia and acidaemia on theophylline pharmacokinetics. All numbers are mean ± SE except the study of Clozel et al. (1981), in which the data are expressed as ± SD. Studies are performed using controlled gas delivery. All studies assume a 2-compartment model except the study of Clozel et al. (1981), which used a 1-compartment model

Reference [animal species]	Model	Dose (mg/kg)	O_2 content (%)	paO_2 (mm Hg)	$t_{½}$ (h)	k_{el} (min^{-1})	Vd (ml/kg)	V_z (ml/kg)	CL (ml/kg/min)	CL_R (ml/kg/min)	CL_{NR} (ml/kg/min)	AUC (mg · min/L)	CSF/P (%)
Kishimoto et al. (1989) [rat]	Hypoxia/ hypercapnia[a]	5 (bolus)	8	34.2 ± 2.9	7.71 ± 1.52[b]		572 ± 22		0.93 ± 0.10[b]	0.27 ± 0.035[c]	0.65 ± 0.11[b]		
	Respiratory alkalosis[d]	inf 0.4 mg/kg/h	8	34.2 ± 2.9									
Letarte & du Souich (1984) [rabbit]	Room air	2.5			5.17 ± 0.26	0.0036 ± 0.0003		701 ± 29[c]	1.57 ± 0.05[c]	0.04 ± 0.01	1.52 ± 0.05	1595 ± 78	31 ± 1.0
	Metabolic acidosis	2.5			4.78 ± 0.17	0.0037 ± 0.003		708 ± 42	1.72 ± 0.12[c]	0.10 ± 0.05	1.61 ± 0.11	1484 ± 93	31 ± 1.0
	Hypercapnia	2.5		$paCO_2$: 60	6.50 ±0.37[c]	0.0032 ± 0.0002		668 ± 30	1.21 ± 0.12[b]	0.08 ± 0.04	1.13 ± 0.13[b]	2140 ± 206[c]	34 ± 2.0
	Hypoxia	2.5		55	5.64 ± 0.36	0.0021 ± 0.0001		552 ± 21[b]	1.16 ± 0.09[b]	0.05 ± 0.01	1.09 ± 0.09[e]	2239 ± 193[b]	33 ± 2.0
	Hypoxia/ hypercapnia	2.5		$paCO_2$: 60 paO_2: 55	6.68 ± 0.19[e]	0.0029 ± 0.0001		653 ± 19	1.13 ± 0.05[e]	0.04 ± 0.02	1.02 ± 0.02[e]	2229 ± 97[e]	36 ± 1.0[c]
Saunier et al. (1987) [dog]	Room air	8			5.15 ± 0.83	0.0033 ± 0.0004	510 ± 30		1.69 ± 0.26	0.18 ± 0.04	1.53 ± 0.24	89 ± 11[f]	
	Acute hypoxia	8	10		4.48 ± 0.55	0.0037 ± 0.0006	510 ± 30		1.82 ± 0.25	0.26 ± 0.05	1.57 ± 0.22	80 ± 10[f]	
	Chronic hypoxia	8	10		4.8 ± 0.60	0.0037 ± 0.0006	500 ± 50		1.77 ± 0.22	0.15 ± 0.04	1.61 ± 0.20	82 ± 10[f]	
Clozel et al. (1981) [dog]	Normocapnia	8	21 CO_2: 0.2		4.93 ± 1.43	0.0023 ± 0.0006	775 ± 130		1.8 ± 0.483				
	Hypercapnia	8	21 CO_2: 10		4.32 ± 1.48	0.0026 ± 0.0007	829 ± 122		2.23 ± 0.8				

a Fraction excreted unchanged by the kidney = 0.452 ± 0.057; % of theophylline dose excreted as 1,3-dimethyluric acid = 25.2 ± 2.1; % of theophylline dose excreted as 1-methyluric acid = 27.0 ± 2.7.

b $p < 0.01$ compared with room air data.

c $p < 0.05$ compared with room air data.

d Plasma theophylline concentration = 15.38 ± 2.4 mg/L ($p < 0.05$ compared with room air data).

e $p < 0.001$ compared with room air data.

f Units: mg · h/L.

Abbreviations: inf = infusion; paO_2 = oxygen tension; $paCO_2$ = carbon dioxide tension; $t_{½}$ = elimination half-life; k_{el} = elimination rate constant; Vd = volume of distribution; Vz = volume of distribution in the elimination phase; CL = total clearance; CL_R = renal clearance; CL_{NR} = nonrenal clearance; AUC = area under the plasma concentration-time curve; CSF/P = (cerebrospinal fluid to plasma concentration ratio) × 100%.

that, in the dog, a paO_2 of approximately 48mm Hg, as a result of exposure to 10% oxygen, was sufficient to maintain the normal function of selected cytochrome P450 enzymes.

Clozel and colleagues evaluated the effects of respiratory acidosis on theophylline pharmacokinetic parameters in dogs (Clozel et al. 1981). Respiratory acidosis (10% CO_2) did not significantly alter volume of distribution, elimination half-life and total clearance when compared with the normocapnic condition. Different results obtained from other studies may reflect species specificity or be related to differences in study methodology.

4.2 Human Studies

The report of several cases of unexpected elevations in serum theophylline concentrations and decreases in clearance in patients presenting with acute respiratory illness (Jacobs & Senior 1974; Jenne et al. 1977; Vožeh et al. 1978) has triggered an interest in the role of pulmonary disease in the disposition of theophylline (table III). Speculations about these decreases in clearance include reduced renal clearance of theophylline, accumulation of metabolites falsely measured as theophylline, changes in volume of distribution, saturation of elimination pathways, hypoxic liver dysfunction, drug interactions and impaired theophylline metabolism. From these isolated cases reports, it appears that theophylline disposition is unpredictable in selected patients presenting with acute exacerbation of primary respiratory disease or pulmonary involvement secondary to congestive heart failure. However, all these reports must be evaluated with caution because of the complicated pathophysiology, the different theophylline dosage regimens and the severity of the respiratory illness.

Clinical studies have also assessed theophylline disposition in both the acutely ill patients and stable patients with chronic obstructive pulmonary disease or evidence of pulmonary involvement secondary to congestive heart failure. The data reported for all the human studies are detailed in table IV. No correlation was observed between sex, age, race, diagnosis of asthma or chronic bronchitis and theophylline clearance or volume of distribution in 26 mildly ill to acutely ill patients with airway obstruction, when compared with 31 healthy volunteers (Powell et al. 1978). 65% of the patients and 23% of the control study participants were smokers. The presence of smoking (10 or more cigarettes/day for at least 2 years), severe congestive heart failure (evidence of pulmonary oedema, cardiomegaly and prominence of blood vessels in upper lung zones), pneumonia (clinical, bacteriological and radiological evidence) and severe bronchial obstruction [forced expiratory volume in 1 second (FEV_1) <45% of forced vital capacity (FVC), or FEV_1 <1L, or peak expiratory flow (PEF) <100 L/min, or $paCO_2$ >45mm Hg] was associated with significant changes in theophylline clearance. Smoking increased average theophylline clearance by 57%.

Clearance was decreased by 43% in congestive heart failure and by 37% in pneumonia. Hypoxia and hypercapnia are common manifestations of airway obstruction. Unfortunately, those parameters were not evaluated with respect to alterations in theophylline clearance. In severe bronchial obstruction, clearance was decreased by 84% when compared with healthy volunteers. When compared with moderate bronchial obstruction (FEV_1 45 to 60% of FVC, or FEV_1 1 to 2L, or PEF 100 to 300 L/min) and mild bronchial obstruction (FEV_1 60% of FVC, or FEV_1 >2L, or PEF >300 L/min), patients with severe bronchial obstruction had lower theophylline clearance values (16%), but this was not statistically or clinically significant.

50 hospitalised patients received a continuous intravenous infusion of theophylline and were evaluated for manifestations of drug toxicity (Hendeles et al. 1977). Ten patients had nearly complete reversible airway obstruction, the remainder had longstanding chronic obstructive airway disease. A theophylline infusion (0.89 ± 0.29 mg/kg/h) resulted in excessive plasma theophylline concentrations (21.9 ± 12 mg/L, range 7 to 52 mg/L) in 29% of patients. The severity of toxicity strongly correlated with plasma theophylline concentrations in 18 patients. Cardiac decompensation, liver dysfunction or acute respiratory failure, alone or in

Table III. Summary of case reports of patients with hypoxia or acidaemia-induced changes in theophylline (frusemide) pharmacokinetics. All patients had a history of smoking

Reference	Age (y) and sex	Disease	pH	paO_2 (mm Hg)	$paCO_2$ (mm Hg)	Theophylline dosage (mg/kg/h)	Additional medication	Theophylline concentration (mg/L)	$t_{½}$ (h)	Clearance (L/h)	Adverse effects	Possible drug interaction
Jacobs & Senior (1974)	72M	COPD, arterial emboli	Day 0: 7.39 Day 18: 7.42	Day 0: 35 Day 18: 66	Day 0: 54 Day 18: 49	Day 0: 0.7 6 weeks: 0.3	Allopurinol Warfarin Tetracycline	Day 10: 59 Day 13: 86 6 weeks: 18			Seizures on days 10 and 13	Allopurinol
Jenne et al. (1977)	63M	Heart disease, chronic bronchitis, mild CHF		Hypoxia		Day 0: 0.7	Furosemide (frusemide)	Day 3: 50	0-12 h: 16 12-48 h: 65 48-84 h: 9		Sinus tachycardia	
Vožeh et al. (1978)	67M	Chronic asthma/ acute exacerbation	Day 0: 7.4 Day 5: 7.18	Day 0: 68 Day 5: 52	Day 0: 37 Day 5: 95	42 mg/h	Phenobarbital Hydrocortisone Isoprenaline (isoproterenol) Ampicillin	Day 5: 17.6		Day 1: 4.05 Day 8: 2.06		Phenobarbital Isoproterenol
	70F	Asthma, bronchitis, emphysema/ exacerbation, pneumonia	Day 0: 7.34 Day 4: 7.46	Day 0: 45 Day 4: 70	Day 0: 34 Day 4: 28	21 mg/h	Terbutaline Ampicillin			Day 1: 1.11 Day 7: 3.61		
	65M	Chronic bronchitis, CHF	Day 0: 7.22 Day 10: 7.37	Day 0: 24 Day 10: 78	Day 0: 45 Day 10: 56	42 mg/h	Methyldopa Furosemide Ampicillin			Day 1: 2.09 Day 11: 4.22		

Abbreviations: paO_2 = oxygen tension; $paCO_2$ = carbon dioxide tension; $t_{½}$ = elimination half-life; M = male; F = female; COPD = chronic obstructive pulmonary disease; CHF = congestive heart failure.

combination, predisposed patients to excessive plasma concentrations of theophylline. The mean plasma concentration in 27 patients with risk factors was significantly higher ($p < 0.002$) and the mean plasma clearance significantly lower ($p < 0.05$) than that in the 23 patients without risk factors (28.6 ± 15.0 *vs* 16.7 ± 6.7 mg/L and 0.58 ± 0.38 *vs* 0.83 ± 0.38 ml/min/kg, respectively). This occurred despite a lack of significant difference in the mean doses for the 2 groups (0.86 ± 0.22 mg/kg/h in patients with risk factors *vs* 0.92 ± 0.29 mg/kg/h in patients without risk factors). The smoking status of the patients was not reported. Multiple regression analysis was unable to delineate the contribution of the different risk factors to variation in plasma clearance estimates. Again, in this study, the extent of hypoxia and hypercapnia was not evaluated with respect to theophylline clearance.

The effect of hypoxia on the disposition of theophylline in 10 patients with chronic obstructive lung disease and gradual deterioration in ventilatory status was assessed by du Souich et al. (1989). Smokers, patients with cor pulmonale, congestive heart failure or hepatic disease, and patients over 70 years old were excluded. A theophylline 4 mg/kg bolus dose was infused intravenously and theophylline pharmacokinetic parameters were determined during the hypoxic state and after oxygen therapy at 1.5 to 2.0 L/min to obtain a paO_2 of ≥65mm Hg. The variability in theophylline clearance was not related to paO_2 in the patients. On the other hand, the investigators reported that patients with $paCO_2$ values >45mm Hg had significantly lower theophylline clearance values than patients with $paCO_2$ values <45mm Hg ($p < 0.01$). In addition, the amount of theophylline and its metabolites were also determined in urine on both occasions. Oxygen administration did not affect theophylline biotransformation because the amounts of unchanged theophylline and its metabolites recovered in the urine were similar before and after oxygen therapy.

Arnold et al. (1981) determined theophylline pharmacokinetic parameters in 8 asthmatic children during 3 different periods (acute exacerbation of asthma, postacute phase and remission period of 1 to 4 months) following a bolus dose (2 to 4 mg/kg) of aminophylline. None of the children had fever, hepatic failure or renal failure. The plasma theophylline clearance values were decreased in 3, remained the same in 1, and increased in 4 children when comparing the acute phase with the remission period. The severity of disease varied greatly among the children during the initial acute phase. Overall, there were no significant differences in theophylline clearance, half-life and apparent volume of distribution among the 3 periods. The investigators concluded that a change in dosage during acute asthma exacerbation is unnecessary.

In another study, patients with both COPD and cor pulmonale manifested a significant decrease in total body clearance (0.029 ± 0.004 L/kg/h) of intravenously administered aminophylline leading to an increase in serum theophylline concentration (26.8 ± 4.4 mg/L) compared with patients with COPD alone (0.048 ± 0.002 L/kg/h and 16.6 ± 1.1 mg/L, respectively). Theophylline was administered orally at an average dosage of 15.4 mg/kg/day or intravenously at an average dosage of 0.756 mg/kg/h for patients with COPD or 0.665 mg/kg/h for patients with COPD and cor pulmonale. Unfortunately, severity of disease was not reported and neither were respiratory parameters, smoking status or arterial blood gas values (Vicuna et al. 1979).

In another study, 9 patients with acute pulmonary oedema had prolonged plasma half-lives (mean of 22.9 hours) and reduced clearance (mean of 0.041 L/kg/h) of theophylline compared with 19 healthy volunteers (6.7 hours and 0.062 L/kg/h, respectively). The higher than expected plasma clearance of theophylline in the 9 patients with acute pulmonary oedema may be related to smoking. Four of the 9 patients with pulmonary oedema and 10 of the 19 control individuals were smokers (Piafski et al. 1977).

Theophylline pharmacokinetics were evaluated in 39 men with moderately severe but stable COPD following a loading dose of 5.6 mg/kg and a maintenance dose of 0.9 mg/kg/h for 5.5 hours (Au et al. 1985). 21 patients were nonsmokers. The groups

Table IV. Summary of human studies comparing theophylline disposition in acutely ill and stable patients. All results are ± SD unless otherwise specified

Study	Age (y)	pH	paO_2 (mm Hg)	$paCO_2$ (mm Hg)	Vd (L/kg)	CL (L/kg/h)	$t_{½}$ (h)	AUC (mg · min/L)	U_T (mg)	Urine 3-MX (mg)	Urine 1,3-DMU (mg)	Urine 1-MU (mg)
Powell et al. (1978)	P: 51.5 ± 17.2 C: 29.6 ± 20.5				A or B = 0.46 ± 0.15 CHF and B = 0.52 ± 0.12	A or B (S) = 0.064 ± 0.039 A or B (NS) = 0.041 ± 0.018 CHF and B = 0.027 ± 0.008						
Hendeles et al. (1977)	59 ± 15					RF = 0.035 ± 0.023 No RF = 0.05 ± 0.023[a]						
du Souich et al. (1989)[b]	58.2 ± 3.1	Pre-O_2 7.39 ± 0.01 Post-O_2 7.39 ± 0.01	Pre-O_2 54.9 ± 1.3 Post-O_2 73.6 ± 1.9[c]	Pre-O_2 46.4 ± 2.3 Post-O_2 49.3 ± 3.2	Pre-O_2 0.48 ± 0.03 Post-O_2 0.48 ± 0.03	Pre-O_2 0.062 ± 0.007 Post-O_2 0.068 ± 0.010[d]	Pre-O_2 5.9 ± 0.59 Post-O_2 5.81 ± 0.75	Pre-O_2 2709 ± 410 Post-O_2 2607 ± 347	Pre-O_2 20.8 ± 2.2 Post-O_2 19.4 ± 2.0	Pre-O_2 12.6 ± 2.1 Post-O_2 10.0 ± 1.9	Pre-O_2 59.1 ± 6.5 Post-O_2 49.9 ± 6.2	Pre-O_2 33.9 ± 4.2 Post-O_2 27.3 ± 3.4
Arnold et al. (1981)	7-12				Group 1: 0.40 ± 0.06 Group 2: 0.39 ± 0.08 Group 3: 0.44 ± 0.05[e]	0.079 ± 0.04 0.073 ± 0.03 0.082 ± 0.03	4.2 ± 1.6 4.1 ± 1.2 4.1 ± 1.4					
Vicuna et al. (1979)[b]	PO COPD: 56.1 COPD/CP: 63.8 IV COPD: 62.5 COPD/CP: 64					0.048 ± 0.002 0.029 ± 0.004[c]						
Piafsky et al. (1977)[f]	53-87				P: 0.562 C: 0.508	P: 0.041 C: 0.062[a]	P: 22.9 C: 6.99					
Au et al. (1985)[h]	50-83	60/NS: 7.40 ± 0.02 61/NS: 7.41 ± 0.01	69.6 ± 3.7 65.1 ± 3.0	42.5 ± 2.6 43.7 ± 1.6	0.478 ± 0.025 0.481 ± 0.015	0.051 ± 0.009 0.033 ± 0.003[ij]	7.4 ± 0.8 11.0 ± .8[ik]	212.4 ± 30.7 306.7 ± 26.3[ij]				

		60/S: 7.40 ± 0.01	64.9 ± 2.6	44.7 ± 2.2	0.508 ± 0.029	0.066 ± 0.008	5.8 ± 0.8	152.1 ± 18.4
		61/S: 7.40 ± 0.01	63.9 ± 2.6	43.6 ± 1.7	0.514 ± 0.034	0.057 ± 0.005	6.5 ± 0.5	170.2 ± 13.4
		60: 7.4 ± 0.01	67.4 ± 2.2	43.5 ± 1.7	0.492 ± 0.019	0.058 ± 0.006	6.7 ± 0.6	184.2 ± 19.6
		61: 7.41 ± 0.01	64.6 ± 2.1	43.7 ± 1.2	0.496 ± 0.018	0.044 ± 0.004[j]	9.0 ± 0.7[l]	244.4 ± 20.8
		NS: 7.41 ± 0.01	66.8 ± 2.4	43.2 ± 1.4	0.480 ± 0.013	0.04 ± 0.004	9.6 ± 0.7	270.8 ± 22.1
		S: 7.40 ± 0.01	64.3 ± 1.6	44.1 ± 1.3	0.511 ± 0.023	0.060 ± 0.004[m]	6.3 ± 0.4[m]	163.2 ± 10.8[m]
		All: 7.40 ± 0.01	65.8 ± 1.5	43.6 ± 1.0	0.494 ± 0.013	0.05 ± 0.003	8.1 ± 0.5	221.1 ± 15.4
Zarowitz et al. (1985)	P: 61.2 ± 9.9 C: 57.5 ± 14.9							
Resar et al. (1979)	58	7.43	53.6	44.7	Initial: 0.950 ± 0.301	0.05 ± 0.004	8.66 ± 3.83	
					Final: 0.892 ± 0.402	0.048 ± 0.005	8.51 ± 3.21	
Cusack et al. (1986)[b]	64 ± 2	RA: 7.43 ± 0.01	43 ± 3	47 ± 4	0.429 ± 0.024	0.05 ± 0.004	6.8 ± 0.6	
		O_2: 7.40 ± 0.01[g]	69 ± 4[c]	56 ± 3[n]	0.450 ± 0.021	0.048 ± 0.005	7.6 ± 0.8	
Westerfield et al. (1981)	62.3 ± 9.4					0.043 ± 0.015		

a $p < 0.05$.
b ± SE.
c $p < 0.001$.
d Renal clearance CL_R (L/kg/h): pre-O_2 0.008 ± 0.0006; post-O_2 0.008 ± 0.0006. Metabolic clearance CL_m (L/kg/h): pre-O_2 0.054 ± 0.006; post-O_2 0.06 ± 0.009.
e Group 1: acute; Group 2: post-acute; Group 3: chronic.
f Peak theophylline plasma concentration (mg/L): 12.9 (P); 13.9 (C).
g $p < 0.01$.
h ± SEM.
i $p < 0.01$ compared with 60 NS, 60 S, 61 S.
j $p < 0.05$ compared with 60 NS.
k $p < 0.001$ compared with 60 NS.
l $p < 0.05$ compared with 60.
m $p < 0.01$ compared with NS.
n $p < 0.02$ compared with room air.

Abbreviations and symbols: paO_2 = oxygen tension; $paCO_2$ = carbon dioxide tension; Vd = volume of distribution; CL = total clearance; $t_{½}$ = elimination half-life; AUC = area under the plasma concentration-time curve; U_T = urine theophylline recovered over 6 hours; 3-MX = 3-methylxanthine; 1,3-DMU = 1,3-dimethyluric acid; 1-MU = 1-methyluric acid; P = patients; C = control group; A = asthma; B = bronchitis; CHF = congestive heart failure; RF = risk factors; PO = oral administration; IV = intravenous administration; COPD = chronic obstructive pulmonary disease; CP = cor pulmonale; NS = nonsmokers; S = smokers; 60 = <60 years old; 61 = >61 years old; RA = room air.

were further subdivided into those over 61 years of age and those 60 years of age and less. Elderly nonsmokers had a 36% reduction in mean clearance and a 40% prolongation in half-life compared with middle-aged nonsmokers, although there were no differences in the volumes of distribution between the 2 groups. These differences were also noted between the elderly and middle-aged groups irrespective of smoking status. Smokers had a 34% decrease in mean half-life and a 52% increase in clearance compared with nonsmokers. Middle-aged and elderly patients who smoked did not show age-related differences in theophylline pharmacokinetics. In this study, the effect of theophylline on paO_2, $paCO_2$ and pH was also evaluated. There was small improvement in paO_2, $paCO_2$ and pH in all patients after theophylline treatment. The effect of the same parameters (paO_2, $paCO_2$ and pH) on theophylline disposition was not evaluated, but the baseline paO_2, $paCO_2$ and pH appeared comparable in all the groups.

The concentration of unbound drug in plasma is generally the pharmacologically active fraction. Consequently, clinical conditions that affect protein binding might alter the therapeutic and toxic effects of theophylline, as well as its disposition. Clinical relevance of these findings was evaluated in 13 adult patients with stable COPD (9 of 13 patients were smokers) and 9 acutely ill patients (6 of 9 patients were smokers) with COPD requiring ventilatory assistance (Zarowitz et al. 1985). There was no significant difference in total unbound concentration or plasma pH between the 2 groups (percentage bound theophylline: patients 30.3 ± 5.3%, controls 45.4 ± 4.6%, $p < 0.005$). However, the mean albumin concentration was reportedly different in the severely ill patient (2.7 ± 0.6 mg/dl) than in the stable group (4.0 ± 0.5 mg/dl). This resulted in a significantly lower bound fraction in the acutely ill patient ($p < 0.005$), linking the altered binding to the severity of pulmonary disease.

Different investigators evaluated the effect of arterial pH on apparent volume of distribution of theophylline. Resar et al. (1979) studied 12 nonsmoking patients with exacerbation of severe COPD requiring intravenous administration of theophylline. The $paCO_2$ and paO_2 showed no significant correlation with pharmacokinetic variability. Arterial pH correlated inversely with the volume of distribution for the group as a whole ($r = -0.824$, $p < 0.001$). For patients with arterial pH determined at different times, an even higher correlation was found between intraindividual changes in pH and volume of distribution ($r = -0.994$, $p < 0.001$). Mean volume of distribution (0.95 ± 0.30 L/kg) and clearance (0.083 ± 0.027 L/kg/h) did not change significantly during the study but were larger than average population values. The investigators attribute these changes to the severity of the disease and the presence of acidaemia. As a consequence of the larger volume of distribution, these COPD patients with acidaemia appeared to require more theophylline than patients with alkalaemia in order to achieve similar serum concentrations of theophylline. It is important to take into account the wide interpatient pharmacokinetic variability (range of volume of distribution 0.54 to 1.55 L/kg and range of clearance 0.043 to 0.14 L/kg/h) when evaluating this study.

A randomised, crossover study showed no significant difference between the mean volume of distribution, half-life and clearance when oxygen was administered or withheld in 10 male patients with severe, stable COPD and cor pulmonale receiving continuous home oxygen therapy. However, there was a significant decrease in volume of distribution with increasing pH in both the hypoxic ($r = -0.71$, $p < 0.05$) and oxygen therapy states ($r = -0.74$, $p < 0.05$). Unfortunately, the changes in volume of distribution were not uniform in the group as a whole (Cusack et al. 1986).

Theophylline clearance was also evaluated in 20 patients (16 of whom were ventilator dependent) requiring intravenous aminophylline in a medical intensive care unit (Westerfield et al. 1981). All were smokers and had multiple medical problems including congestive heart failure, liver dysfunction and sepsis. There was a wide variation in the initial theophylline clearance with a range of 19.6 to 61.3 ml/kg/h. No relationship was found between the mean clearance and changes in pH, $paCO_2$ or paO_2, initially and throughout the study period for the

group as a whole. Volume of distribution and the extent of protein binding were not evaluated.

5. Discussion and Conclusions

Theophylline still occupies a central role in the management of airway obstruction. There are many studies describing the pharmacokinetics of theophylline but few have focused on disposition of theophylline in severely ill or stable patients with hypoxia or alterations in arterial blood gases. At present, the body of literature encompasses mostly animal studies, a few human studies and case reports.

Rats, mice, rabbits and dogs metabolise theophylline to different extents both when exposed to normal oxygen concentrations and during hypoxia. In isolated mouse hepatocytes and rat livers, low oxygen concentrations resulted in higher theophylline concentrations, longer elimination half-lives and decreased 1,3-DMU production, suggesting decreased metabolism of theophylline. In New Zealand rabbits, plasma theophylline concentrations as well as total body clearance were influenced by hypoxia, hypercapnia and respiratory acidosis. On the other hand, experiments involving dogs showed no significant changes in theophylline concentrations or pharmacokinetic parameters. Consensus could not be reached on the effect of hypoxia on renal, nonrenal and total body clearance of theophylline, partly due to the confounding effect of hypoxia on decreasing renal blood flow and the diuretic effect of theophylline after short term administration. In addition, distinguishing between a decrease in nonrenal clearance secondary to hypoxia *vs* the manifestation of capacity-limited elimination could pose a problem. However, most investigators attempted to determine a Michaelis-Menten constant and maximum rate of metabolism before the start of experimentation and the theophylline dosage was adjusted accordingly.

An important point to remember is that the liver is supplied in part by low oxygenated venous blood. Therefore, in order to validate experimental results, the extent of experimental hypoxia must be defined and standardised. At present, the use of different animal models and variations in study methodology, including the extent and duration of hypoxia and acidaemia, concurrent acid-base disorders such as hypercapnia, as well as severity of disease are the main reasons why animal studies remain inconclusive.

Human studies assessing alteration in theophylline disposition secondary to the hypoxia present in pulmonary disease are few and conclusions are discrepant. In addition, extrapolation of animal data to humans is complicated by the additional 1-demethylation of theophylline in humans (Gu et al. 1992; Robson et al. 1987). There is evidence for decreased theophylline clearance, and some consensus can be achieved using case reports along with controlled studies. The most obvious markers appear to be the severity of pulmonary disease and rate of change in the patient's condition.

It becomes apparent that caution should be exercised when administering theophylline to patients with COPD presenting with acute exacerbations of a concomitant respiratory illness such as pneumonia. These are the patients who appear to be most likely to exhibit altered theophylline metabolism. Close monitoring of serum theophylline concentrations during the first 24 to 48 hours of the acute illness and on improvement of clinical status is necessary, since it can be expected that metabolism might return to baseline at that time. On the basis of a study reporting a decrease in theophylline clearance by an average of 37% in pneumonia, and 84% in severe bronchial obstruction, maintenance doses could tentatively be decreased accordingly when there is a concern about theophylline toxicity (Powell et al. 1978). There is additional evidence that drug clearance decreases with age and that elderly patients may have a decreased theophylline clearance at baseline. Therefore, they would be at increased risk for toxicity should conventional doses be used during an acute respiratory event.

There is some evidence, albeit weak, that protein binding of theophylline decreases during acute respiratory illness. However, consensus has not been reached on changes in theophylline volume of distribution with abnormal arterial pH and clin-

icians should be careful in adjusting the loading dose in patients with acidaemia or alkalaemia. It is unfortunate that most available studies did not evaluate parameters such as pH, paO_2 and $paCO_2$, which might correlate with changes in theophylline metabolism. Additional studies are needed to characterise theophylline disposition in these select group of patients. When designing such studies, severity and pathophysiology of illness, choice of control groups, choice of monitoring parameters and concurrent drug therapy are all factors that require careful consideration.

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