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Original Article

Pharmacokinetic Behavior of Theophylline following PEEP in Critically Ill Patients with Acute Lung Injury

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Abstract

The effect of Positive End Expiratory Pressure (PEEP) on the hepatic elimination of low to moderate extraction ratio drugs has not been clearly defined. We prospectively investigated the effect of PEEP on the clearance of theophylline in 30 (20 males and 10 females) intubated critically ill adult patients with acute lung injury/acute respiratory distress syndrome (ALI/ARDS). The Mean (±SD) age was 57±17 years, creatinine clearance 86±36 ml/min, serum albumin 3.2±0.57 mg/dl and the median APACHE (acute physiology and chronic health evaluation) II score was 25 (with a range of 16 to 34). Critically ill patients who had met the diagnostic criteria for ALI/ARDS were enrolled on PEEP in low (5-9 cmH_2O) and high (10-15 cmH_2O) levels. All patients received the ordered dose of aminophylline infusion (3 mg/kg over 30 min and then 15 mg/h) after 2 h of initiating PEEP. Blood samples were collected after the loading dose, 2 and 6 h the aminophylline continuous infusion. Vital signs were recorded before and after 2 h of PEEP and each blood sampling interval. Cirrhotic patients and those who had received any drug which could interact with the metabolism and clearance of theophylline, were not included. The Mean(±SD) value of the pharmacokinetic key parameters of theophylline in high (n=17) and low (n=13) PEEP groups were as follows: V_d=0.42(±0.15) L/kg and 0.54(±0.13) L/kg, clearance = 0.035(±0.024) L/h/kg and 0.056 (±0.025) L/h/kg. Mean measured theophylline concentrations following loading dose were 7.08 mg/L and 5.09 mg/L. The calculated volume of distribution ($P<0.03$), clearance ($P<0.05$) and theophylline serum concentration ($P<0.05$), in high versus low peep group, were found to be significantly different. Positive ventilation tends to reduce Vd and clearance of theophylline in critically ill patients.

Keywords: Theophylline; Pharmacokinetic; ALI/ARDS; PEEP.

Introduction

The acute respiratory distress syndrome (ARDS) represents a severe form of acute lung injury (ALI) and remains a significant burden in the care of critically ill patients (1). They face a 30% to 60% chance of dying and often require prolonged courses of mechanical ventilation, nutrition support and pharmacotherapeutic interventions (2). Theophylline via numerous mechanisms improves oxygenation and its anti-inflammatory effects would be useful. It is often being used in ALI/ARDS. Theophylline has a narrow therapeutic index and application of its pharmacokinetic and pharmacodynamic

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information in conjunction with readily available serum assay has allowed theophylline to be used with improved efficacy and an acceptable risk of toxicity. Many factors such as age, tobacco, ethanol, drugs and some diseases can alter hepatic metabolism and clearance of theophylline (3-8). In patients with ALI/ARDS, mechanical ventilatory support with Positive End Expiratory Pressure (PEEP), can improve and increase oxygenation. This was first described by Ashbaugh et al (9) for use in these patients and remains a mainstay in its management. On the other hand, the use of mechanical ventilation and PEEP is a well-documented cause of decrease in cardiac output and venous return (10, 11), decrease in right and left ventricular end-diastolic volume (12), drop in the mean arterial blood pressure (MAP), and central venous pressure (CVP), altered regional blood flow (13) decrease hepatic and renal blood flow, decrease in glomerular filtration rate (GFR), reduction in urine output and sodium excretion, as well as an increase in antidiuretic hormone (ADH) (14, 15). These diverse extrapulmonary effects may alter the disposition of several pharmacological agents. Richard et al (16), compared lidocaine pharmacokinetic, as a high hepatic-extracted drug, in critically ill patients before and after weaning from mechanical ventilation with a washout period of 48 h between mechanical and spontaneous ventilation. They found an increase in the peak and steady-state plasma concentration and a decrease in the clearance of patients on mechanical ventilation.

The aim of the present study was to determine the pharmacokinetic parameters of theophylline in critically ill patients with ALI/ARDS who required positive ventilation.

Experimental

This research was a prospective cross-sectional study in which the pharmacokinetic characteristics of theophylline were investigated in 30 (20 male and 10 female) critically ill adult patients with ALI/ARDS, whom were admitted to a general intensive care unit (G-ICU) of a teaching referral hospital affiliated with the Tehran University of Medical Sciences. The study was approved by the investigational review board for human study. The diagnosis of ALI/ARDS was established according to the criteria reported previously by Ashbaugh et al (9) and was confirmed by the European-American Consensus Conference on ARDS (1). Patients were not on any medication affecting metabolism and clearance of theophylline. Those with established diagnosis of hepatic cirrhosis, renal failure requiring hemodialysis, hemoperfusion or peritoneal dialysis and congestive heart failure, were also excluded. Following 2 h of initiating PEEP (ranging from 5-15 cmH_2O), aminophylline was administered intravenously (3 mg/kg over a 30 min infusion period by a microinfusion set as a loading dose and then 15 mg/h, by an infusion pump as a maintenance dose). This regimen is the most popular dosing regimen for the drug being used locally. For all patients, there were three sampling time to determine theophylline concentrations. The first was taken 5 min after the end of the loading dose. The second and third blood samples were taken 2 and 6 h into the maintenance dose. Vital signs and other physiological parameters were recorded at each sampling as well as before and 2 h after starting the PEEP. Paraclinical parameters such as arterial blood gas (ABG), serum electrolytes, creatinine, blood urea nitrogen (BUN), albumin, hemoglobin, glucose, red blood cell and white blood cell were measured before starting PEEP and at the time of taking the last blood sample. Samples were centrifuged and frozen at -30ºC until analysis.

The severity of the condition of each patient was characterized by using the Acute Physiology and Chronic Health Evaluation (APACHE II Score) (18). This score was calculated for each patient separately before starting PEEP and 8 h after PEEP. The ideal body weight (IBW) was calculated for each patient as described by Devine (19):

$$IBW_{kg} = 50_{male}(45_{female}) + 2.3(Height_{inch}\text{-}60) \quad \text{(Equation 1)}$$

After measurement of theophylline concentration in samples, theophylline Vd and clearance were calculated with Chiou equation for non steady-state situation (3), for each patient.

$$Cl_{(L/h)}=2Ro/(C_1+C_2)+2Vd(C_1-C_2)/(C_1+C_2)(t_2-t_1) \quad \textit{(Equation 2)}$$

These parameters were compared between patients in high and low PEEP groups.

Serum theophylline quantification

Theophylline serum concentrations were measured by a high performance liquid chromatography technique (Knauer HPLC: K-1500 mixing chamber, K-1001 high pressure pump, K-2600 Ultraviolet detector and Teknokroma C18 column) (17). Intra-assay and inter-assay coefficient of variation were <7% for serum concentrations, ranging from 1 to 20 μg/ml.

Statistical analysis

Statistical significance was determined by using the student and paired student *t*-test. A P value less than 0.05 was considered statistically significant. The Statistical package for Social Sciences (SPSS version 11.5) was used for data analysis.

Results and Discussion

A total of 35 patients meeting the inclusion criteria were enrolled in the study. Five of them were excluded due to inaccurate documentation of the time of drug infusion or blood sampling. The main clinical, laboratory and physiological parameters of the patients are shown in table 1.

The mean±SD age was 57±17 years, weight 70.8±11.2 kg, ideal body weight 65±8 kg, creatinine clearance 86±36 ml/min and serum albumin 3.2±0.57 mg/dl. There was no significant difference between these parameters in the two groups. The median for APACHE II score was 25 (with a range of 16-34).

Based on the patients ventilation and oxygenation profiles (e.g. PaO_2/FiO_2, O_2 sat) they were divided as either low PEEP (5-9 cmH_2O) or high PEEP (10-15 cmH_2O).

Table 1. Demographic data of the patients took part in this study.

	MEAN	SD	SEM	MAX	MIN
Age (years)	57	18	3	76	16
Height (cm)	170.2	7.3	1.3	180	158
Weight (kg)	71	11	2	90	50
APACHE II Score	25.3	5.6	1.0	34	16
Serum Albumin (g/dl)	3.2	0.6	0.1	4.2	2.3

APACHE II = Acute Physiology and Chronic Health Evaluation Score II.

Table 2. Clinical and Para-clinical data of the patients took part in this study.

	Group	Before PEEP (Mean±SD)	After 2h PEEP (Mean±SD)	After 8h PEEP (Mean±SD)
MAP(mm Hg)	HP	102±16	85±18*	93±15
	LP	101±15	96±19	98±16
HR(bpm)	HP	99±17	111±16*	107±14*
	LP	87±22	93±21	89±19
pH	HP	7.37±0.091	7.35±0.087	7.39±0.062
	LP	7.43±0.088	7.38±0.070	7.37±0.12

HP = High PEEP; LP = Low PEEP; PEEP = positive end expiratory pressure, MAP = mean arterial pressure; HR = heart rate per minute; PH = arterial blood acidity; *=P<0.05 statistically different between high and low PEEP

Seventeen patients (57%) were on high PEEP, and thirteen patients (43%) had a low PEEP mechanical ventilation mode.

While a decrease in MAP, 2 h after PEEP was noted in both groups, it was more significant in the high PEEP group.

Clinical and paraclinical parameters of patients are shown in table 2.

Body temperature, serum creatinine, creatinine clearance, and serum albumin and pH of patients in the high and low PEEP groups were not significantly different (p>0.05 repeated measure analysis of variance test). In contrast, there was a significant difference in the serum concentration, volume of distribution and clearance of theophylline between the two groups.

Pharmacokinetic parameters of theophylline in patients under study are presented in table 3.

The aim of this study was to investigate the possibility of a pharmacokinetic interaction between PEEP and theophylline, following the concurrent use of PEEP and continuous infusion of theophylline in critically ill patients with ALI and ARDS. Several studies have reported the potential effect of PEEP on the

Table 3. Statistical description of the pharmacokinetic parameters of theophylline in the patients took part in this study.

	HP group (Mean±SD)	LP group (Mean±SD)	All patients (Mean±SD)
Vd(L/Kg)	0.42 ±0.15*	0.54 ±0.13	0.47 ±0.15
CL(L/h/kg)	0.035±0.024*	0.056±0.025	0.044±0.026
C1(mg/L)	7.08 ±3.23*	5.09 ±1.30	6.22 ±2.73
C2(mg/L)	6.27 ±3.48	4.35 ±1.49	5.43 ±2.92
C3(mg/L)	6.24 ±3.50*	3.98 ±1.04	5.26 ±2.92

HP=high PEEP group; LP=low PEEP group; Vd=Volume of distribution; CL=clearance; C1=theophylline plasma concentration after loading dose; C2=theophylline plasma concentration after 2h of maintenance dose; C3=theophylline plasma concentration after 6h of maintenance dose; *=P<0.05 statistically different between high and low PEEP

pharmacokinetic of high extraction ratio and drugs excreted in the urine.

Richard et al (16), compared lidocaine pharmacokinetic as a high hepatic-extracted drug in critically ill patients before and after weaning from mechanical ventilation. They found an increase in the peak and steady-state plasma concentration and a decrease in the clearance of patients on mechanical ventilation. The volume of distribution, however, did not change significantly.

Lugo and Hernardez (20) have studied the relationship between hemodynamic measures and pharmacokinetic behavior of amikacin in 30 critically ill septic patients. They found a poor, but significant, relationship between the use of PEEP mode of ventilation and V_d (r^2=0.29, p=0.002). A similar result was reported, regarding the clearance of amikacin and application of PEEP (r^2=0.39 and p=0.0001).

Theophylline has a low to moderate extracted ratio which is primarily metabolized in the liver by the cytochrome P-450 enzyme system. Since the theophylline metabolism is dependent on the integrity of the liver and on hepatic blood flow (21), many factors such as gender, age, diet, obesity, cigarette smoking, within-subject variability, drugs and concurrent diseases (e.g. cirrhosis, congestive heart failure, infections, thyroid diseases, cystic fibrosis, down syndrome and hypoxemia) can alter hepatic metabolism, clearance, volume of distribution and serum concentration of theophylline (3-4, 22-25). We decided to evaluate the effect of PEEP on the theophylline pharmacokinetic in our groups of critically ill patients.

In this study, the mean±SD peak theophylline serum concentration after the loading dose in high PEEP group was 7.08±3.23 mg/L, which was significantly greater than the value of 5.09±1.30 mg/L in the low PEEP group (P<0.05). V_d was 0.42±0.15 L/kg in the high PEEP and 0.54±0.13 L/kg in the low PEEP group (p<0.03). These differences are probably related to the extrapulmonary effects of PEEP on the circulated blood volume. The use of positive end expiratory pressure in mechanical ventilation is a well-documented cause of reduction in the cardiac index, cardiac output and venous return (10, 11), decrease in right and left ventricular end-diastolic volume (12), drop in the mean arterial blood pressure (MAP) and central venous pressure (CVP), decrease in hepatic and renal blood flow, glomerular filtration rate and urine output (14-15, 26), altered regional blood flow such as skeletal muscles, brain, small intestine and fat-free tissues, due to a MAP decreased (13). These effects are directly related to the amount of PEEP.

Mulla et al (24) determined the population pharmacokinetic of theophylline during the extracorporeal membrane oxygenation (ECMO) in term neonates and children. They concluded that an increase in the V_d and a decrease in the clearance of theophylline, are probably related to the expanded circulating volume during ECMO and altered renal and hepatic physiology.

Theophylline distributes into the fat-free tissues and body water. Its mean volume of distribution in adults is 0.45 L/kg (0.35-0.7 L/kg). The volume of distribution increases linearly with the total body weight in both non-obese and obese subjects. Theophylline binds approximately 40% to plasma proteins, predominantly albumin. Protein binding reduces as the pH decreases and the temperature rises. Each 0.10 unit decrease in pH decreases theophylline binding by 4% and increases the apparent volume of distribution by 0.2 L/kg. Alterations in the theophylline protein binding have been reported in critically ill adult patients, ventilated mechanically. This may also occur with acid/base disturbances, hypoxemia, cirrhosis, protein-calorie malnutrition, and in pregnant women (3). Albumin generates an oncotic pressure because of its high molecular weight. Hypoalbuminemia may cause a shift of body fluid from the intravascular to the extravascular space by decreasing the oncotic pressure.

In this study there was no difference between the mean serum albumin levels, arterial pH, total weight, ideal body weight, body temperature, and creatinine clearance in low and high PEEP groups. The mean serum albumin levels in all patients were 3.25±0.59

mg/dL, which was a little less than the lower normal limit (3.3-4.5 g/dL).

In a previous report on theophylline pharmacokinetic in the Iranian critically ill patients receiving similar doses, it was shown that the theophylline serum level was less than the therapeutic levels, averaging between 2.5-7.5 mg/L (27). In this study, except for three patients in the high PEEP group, whom had theophylline levels within the therapeutic range (14.6, 12.2 and 10.1 mg/L), the rest of the levels were sub-therapeutic (2.2-8.3mg/L). The usual theophylline loading dose of 6 mg/kg and a maintenance dose of 30-60 mg/h (0.6 mg/kg/h) seems to cause numerous cardiovascular and neurological adverse effects in our patients, usually not receiving more than half of the recommended doses.

The effects of PEEP, especially reduction of the MAP and hepatic blood flow, may be the cause of clearance reductions. In the current study the high PEEP group had a significantly larger decrease in MAP after 2 h PEEP.

The mean±SD theophylline clearance in patients on high PEEP was 0.035±0.024 L/h/kg, which was lower than that of the low PEEP group, 0.056±0.025 L/h/kg ($p<0.05$). Theophylline clearance in healthy adult is about 0.039 (0.016-0.062) L/h/kg (3).

Brienza et al. (28), in an animal study, showed that the total venous return decreases with PEEP. It is likely that liver plays an important role in this response, either through the development of an increase in venous resistance or an increase in the venous backpressure at the outflow end of the liver. Hepatic arterial flow is also decreased selectively by the application of PEEP, and PEEP on liver hemodynamic, decreased portal vein flow and caused an increase in the liver venous resistance, The reduction in portal venous flow was related to an increase in the backpressure in order to increase the liver venous resistance which may cause blood pooling in the splanchich compartment and a decreased venous return through the liver.

Factors in critically ill patients which may affect the drug's clearance are: patient hemodynamic status, vasopressor usage, and cardiopulmorary by-pass (29-30). Disease states in ICU patients such as burns, trauma and hyperdynamic septic shock increase drug clearance (29-35).

The severity of illness in critically ill patients in the present study was summarized in APACHE score and had no relationship with V_d and clearance of aminophylline. The mean APACHE score was 27.2 in the high and 22.9 in the low PEEP groups.

We conclude that the pharmacokinetic behavior of theophylline, which is predominantly eliminated through the liver, seems to be substantially affected by using the positive mechanical ventilation. Close therapeutic drug monitoring could minimize possible adverse reactions and toxicity of theophylline, especially for critically ill patients in the intensive care unit.

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