THE EVALUATION OF THE POSSIBLE EFFECT OF POSITIVE END EXPIRATORY PRESSURE (PEEP) ON PHARMACOKINETICS OF PHENYTOIN IN PATIENTS WITH ACUTE BRAIN INJURY UNDER MECHANICAL VENTILATION.

[1]ELHAM HADIDI, [1]MOJTABA MOJTAHEDZADEH, [2]MOHAMMAD REZA ROUINI, [3]BEHZAD EFTEKHAR, [4]MOHAMMAD ABDOLLAHI, [5]ATABAK NAJAFI, [5]MOHAMMAD REZA KHAJAVI, [6]SAEED REZAEE, [5]REZA GHAFFARI, [2]MINOO AFSHAR.

[1]Department of Clinical Pharmacy, Faculty of Pharmacy, [2]Department of Pharmaceutics, Faculty of Pharmacy, [3]Department of Neurosurgery, Sina Hospital, Faculty of Medicine, [4]Faculty of Pharmacy andd Pharmaceutical Sciences Research Center, [5]Department of Anesthesiology, Sina Hospital, Faculty of Medicine, Tehran University of Medical Sciences, [6]Department of Pharmaceutics, Faculty of Pharmacy, Ahvaz University of Medical Sciences,

ABSTRACT

Positive ventilation has shown to have an influence on pharmacokinetic and disposition of some drugs. Beacause phenytoin with a narrow therapautic range, is the most commonly used drug for prophylaxis and treatment of early seizures after acute brain injuries, in the present study the effect of short term PEEP (5-10 cm H_2O for at least 8 hours) on phenytoin serum concentration and pharmacokinetic parameters such as V_{max} and clearance in brain injured patients under mechanical ventilation was examined. Ten patients with moderate to severe acute brain injury who were placed on mechanical ventilation with an initial PEEP level of 0-5 cm H_2O were included in the study. Patients received phenytoin loading dose of 15 mg/kg followed by a maintenance daily dose of 3-7 mg/kg initiated within 12 hours of loading dose. Sampels were taken on two different occasions before and after PEEP elevation. Total phenytoin serum concentrations were determined by HPLC method. A time invarient Michaelis-Menten pharmacokinetic model was used to calculate Vmax and clearance for each patient.
Derrived variables were calculated as follows: V_{max}, 3.5-6.8 and 3.7-8.2 mg/kg/day; Clearance, 0.1-0.7 and 0.1-1.2 l/kg/day (before and after PEEP elevation, respectively). Our data have shown a wide range of variability (2.6-32.5 mg/l) in phenytoin serum concentrations. There were no statistically significant differences in the measured total concentrations ($p=0.721$) and calculated V_{max} and clearance ($p=0.285$) before and after PEEP elevation. Administration of fluid and inotropic agents, limitation in application of higher levels of PEEP and drug interactions, shall be considered as possible explanations for these findings.

Keywords: Acute brain injury, PEEP, Phenytoin, Pharmacokinetic

INTRODUCTION

Seizures are common during the early phase following a stroke and have been reported to occur with a frequency of 2.4-6% within 14 days afterward (1-4). Phenytoin is commonly and widely used anticonvulsant drug in critically ill patients (5) and is being considered as a drug of choice for prophylaxis and treatment of seizures post–brain injury (6,7).

In most patients with cerebrovascular events, significant respiratory problems do not occur but when present, they may be a marker of severe derangement. In fact respiratory arrest represents primary cause of death in the first few days after a stroke (8). The ventilatory management of patients with diffuse acute lung injury (e.g., ARDS) requires mechanical ventilation. According to a recent study, 10% of unselected stroke patients require mechanical ventilation during their hospital stay (9). In this setting, adequate arterial oxygen saturation is usually achieved by raising the inspired oxygen fraction (FiO_2) and increasing the end expiratory lung volume to recruit collapsed or flooded alveoli. This can be achieved by addition of extrinsic positive end–expiratory pressure (PEEP) (10,11).

Correspondence: Mojtaba Mojtahedzadeh, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran, E-mail:mojtahed@sina.tums.ac.ir.

PEEP is a mode of therapy which is used in conjunction with mechanical ventilation whenever in spite of administeration of 100 percent oxygen, there is still inadequate oxygenation (10). Mechanical ventilation with PEEP is a well-documented cause of reduction in cardiac output, renal flow, glomerular filtration rate and urine flow (12-14). Also, it has been shown that PEEP is associated with decrease in hepatic and/or portal blood flow as well (15-17). Therefore, it has been theorized that the pharmacokinetics of drugs that are predominantly eliminated through the liver might be substantially affected following positive ventilatory supports measures (18).

While alteration in pharmacokinetic parameters of some drugs such as lidocaine (19), amikacin (20) and aminophylline (21) by PEEP have been reported, the contribution of mechanical ventilation in alteration of phenytoin clearance is unknown and has not yet been quantified.

On the other hand, in vitro studies on oxidatively metabolized drugs such as propranolol and theophylline have shown that hypoxic conditions (Even by relatively minor reductions in oxygen supply, of a magnitude likely to be encountered in vivo) and oxygen supplementation may result in impairement or restoration of oxidative metabolism of these drugs, respectively (22-24).

Beacause phenytoin elimination performs almost entirely through hepatic oxidation (by cytochrome P450 (CYP) 2C9 and CYP2C19 as principle enzymes), it is expected that the hepatic oxidative metabolism of phenytoin should be influenced by alteration in oxygenation or conditions that alter hepatic oxygenation. This may be of special attention in regard to PEEP beacause while its use improves oxygenation and treates acute pulmonary failure, it may contribute to mesenteric ischemia due to alteration in regional blood flow.

Phenytoin has a relatively narrow therapeutic range of serum concentrations, 40-80 μmol/l (10-20 mg/l), and is known to show concentration-dependent kinetics within this therapeutic range. Because of the fact that, small changes in dose and minor alterations in hepatic metabolism of phenytoin may cause a disproportionately large effect on serum concentrations, in this study it was intended to examine whether the application of PEEP in levels usually used for brain injured patients could have influences on the pharmacokinetic profile of phenytoin in these patients? and if so, will there be a need for dosing adjustment in this setting?

METHODS

The study was conducted at trauma/neurosurgical ICU of Sina Hospital. Fifteen male or nonpregnant female patients aged 18 or older who had moderate to severe acute brain injury defined as Glasgow Coma Scale score (GCS)≤12, requiring intravenous phenytoin for treatment or prophylaxis of post injury seizures and also were required mechanical ventilation with a PEEP level of 5-10 cm H_2O due to respiratory failure and PaO2/FiO2<300 mmHg (e.g., Acute Lung Injury), were included in the study. The study protocol was approved by the ethical committee of Tehran University of Medical Sciences.

Patients were excluded if any one of the following was present:

Bradycardia, second- or third degree heart block, clinically important hypotension, laboratory evidences of preexisting hepatic or renal disease (i.e., total bilirubin>2 mg/dl, ALT>3 times of normal, serum creatinine>2 mg/dl), history of phenytoin administration and hypersensitivity to phenytoin.

The use of medications which are known to affect the phenytoin metabolism (cimetidine, corticosetroids, chloramphenicol, phenobarbital) or alter it's protein binding (warfarin, aspirin, heparin, tolbutamide, valproic acid, or a sulfonamide) were restricted throughout the study.

Drug administration and sampling:

Patients received an IV loading dose of 15 mg/kg of phenytoin sodium (50 mg/ml, Daru-Pakhsh, Iran) at a maximum rate of 50 mg/min followed by a maintenance dose of 3-7 mg/kg/day divided into three doses, administered at 8 hours intervals. Each dose was diluted in 0.9% saline and administered over 30 minutes by means of a controlled infusion pump at an infusion rate that did not exceed 50 mg/min.

Two blood samples were collected at trough levels (30 min before the next dose), first after at least 3 days (completion of 9 doses) of phenytoin administration when patients were either extubated or under mechanical ventilation with initial PEEP level of 0-5 cm H_2O, and the second, at least 8 hours after PEEP elevation to 5-10 cm H_2O. Blood samples were obtained from an induelling arterial or central venous catheters whenever possible or by venipuncture.

Measurments

The severity of the condition of each patient was globally characterized by the use of the Acute Physiology and Chronic Health Evaluation (APACHE) II score (25). This score is routinely calculated within the first 24 hrs of the patient's intensive care unit admission. In this study, the APACHE II score was also computed at each time that phenytoin serum concentrations were measured. Evidence of misadventure or seizures during phenytoin therapy was determined by

direct investigator observation and daily concurrent review of medical record. Continous monitoring of the electrocardiogram with lead II, systolic, diastolic, mean arterial pressure (MAP), heart rate, central venous pressure (CVP) and pulse oxymetry were accomplished in accordance with ICU protocol. Respiratory parameters such as arterial oxygen pressure (PaO_2), PaO_2/FiO_2, oxygen saturation (SpO_2), at each sampling time, before and after PEEP elevation were reported. Central venous pressure (CVP) was also monitored every 3 hours. Serum albumin concentrations were measured before therapy and within 24 hours of the serum phenytoin concentration measurments.

Drug assay procedure

Blood samples were allowed to clot and were centrifuged at room temperature for 15 minutes at 3000 rpm. The serum was transferred and stored at -20°C until final assay.

An HPLC method was developed for the analysis of total phenytoin serum concentrations. One hundred µl of serum samples were precipitated by addition of two fold volume of methanolic solution of phenacetin (5 µg/ml) as internal standard. Fifty µl of supernatant was injected into a Spherimage C18 column (5 µm, 250×4 mm, Knauer, Germany) through a rheodyne injector fitted by a 50 µl loop. Analysis was performed by using a high pressure pump k-1001 and k-2600 UV spectrophotometer (all from knauer, Germany). Phosphate buffer (pH=7): acetonitril: methanol (57:22:21) were used as mobile phase with flow rate of 1 ml/min and the eluent was monitored at 220 nm.

Unknown phenytoin concentrations were determined by the application of unweighted least-squares regression analysis of peak–height ratios of phenytoin to internal standard as function of the concentration of the standards ranging from 1.73 to 29.62 µg/ml (r^2= 0.999). The limit of detection for phenytoin assay was 0.05 µg/ml. The coefficient of variation for intra- and inter-day assays for total phenytoin concentrations was less than 7**%** (2.4-6.7**%**). The recovery (mean±SD) of phenytoin was 91±5**%**.

Pharmacokinetic and Statistical Analysis

A Michaelis-Menten pharmacokinetic model was used to calculate maximum rate of metabolism (V_{max}) and Clearance (Cl) of phenytoin for each sampling time. Michaelis-Menten constant (k_m) was set at 4 mg/l (26).

Winter–Tozer method (Equation I) was used to calculate adjusted total phenytoin concentration (dphET) based on the albumin concentration (Alb) (27).

$$dphET=dphT/(Alb(g/dl)\times 0.2)+0.1 \quad \text{(Equation I)}$$

Where dphT is measured total phenytoin concentration.

Results of a study on 17 neurosurgical patients (28) showed that the Sheiner–Tozer equation (26) provides an unbiased and precise clinical estimate of measured free phenytoin concentration (dphF) in patients for whom dphF is unavailable or impractical. This equation (No II) was used to estimate free phenytoin concentration (dphEF) based on (dphT) in present study.

$$dphEF= [dphT /(Alb(g/dl)/4.4)\times(0.9+0.1)] \times 0.1 \quad \text{(Equation II)}$$

Adsjusted total serum concentrations (dphET) were used for estimation of Vmax and clearance.

A non-parametric method (wilcoxon signed rank test) was used to compare pharmacokinetic and respiratory parameters before and after PEEP elevation. A p value of <0.05 was considered statistically significant. Data are represented as mean ±SE.

RESULTS

Of 15 patients, who were enrolled in the study, 10 (6 men and 4 Women) aged 55–81 years (mean 67.7) completed the study protocol. Five patients were excluded from the study: one patient was expired before completion of the study time, one patient was transferred elsewhere, two patients had early extubation and one patient was excluded due to variations in PEEP levels.

Demographic characteristics and concomitant drug therapy which potentially interfere with phenytoin disposition for each patient are listed in Table 1. Phenytoin maintenance doses, APACHE II scores at sampling times, measured total phenytoin concenrations (dphT), estimates of total (dphET) and free (dphEF) phenytoin concentrations before and after PEEP elevation are provided in Table 2.

Albumin concentrations, estimates of Vmax and Cl, initial and final levels of PEEP for each patient before and after PEEP elevation are summarized in Table 3.

There were no statistically significant differences between the measured total concentrations (dphT) before and after PEEP elevation (p=0.721). The difference observed between pre- and post-PEEP values of Vmax and Cl were not also significant (p=0.285 for both variables).

While there were no significant difference between values of PaO_2 and SpO_2, before and after PEEP elevation (125±16 versus 149±15, p=0.285 and 96±0.85 versus 98±0.64, p=0.153, respectively), a trend in increase of these parameters was observed. The PaO_2/FiO_2 ratio showed a significant improvement after PEEP elevation (p=0.021) (Figure 1). Application of

Table1. Patients Demographics and Clinical Data

Patient No.	Age (years)	gender	weight (Kg)	Admission GCS	APACHE II 1st 24h	Diagnosis	Concomitant Medications*	Outcome
1	55	F	70	8	22	ICH	Dxm (7)	Died
2	55	M	60	11	18	Ischemic Stroke		D/C
3	68	F	70	5	27	ICH,IVH	Dxm (7)	Died
4	56	M	70	4	29	MVA	Dxm (8), Chlm(2)	Died
5	78	M	75	10	26	SDH		Died
6	65	F	85	4	28	ICH,IVH	Phb**(10), Dxm(3)	Died
7	81	M	55	7	31	ICH		Died
8	81	F	60	6	26	Ischemic Stroke	Cmt (2), Phb (1)	Died
9	73	M	85	7	22	Ischemic Stroke	Phb (10), Dxm(9)	D/C
10	65	M	80	7	19	ICH,IVH	Cmt (5)	Died

GCS = Glascow Coma Score; APACHE = Acute Physiologic and Chronic Health Evaluation; ICH = intracerebral hemorrhage; intraventricular hemorrhage; SDH = subdural hemorrhage; MVA = motor vehicle accident; Dxm =dexamethasone; Chlm = chloramphenicole; Phb = phenobarbital; Cmt = cimetidine; D/C = discharged. * medications that could alter phenytoin metabolism. Number in parentheses indicates duration of therapy. ** discontinued 8 days before sampling.

Table2. Comparison of Measured and Estimated Phenytoin Concentrations Before and After PEEP Elevation

		Before PEEP Elevation				After PEEP Elevation			
Patient No.	PHT MD (mg/kg/day)	dphT	dphET	dphEF	APACHE II	dphT	dphET	dphEF	APACHE II
1	3.2	14.2	23.6	2.3	17	11.2	15.1	1.5	22
2	5.0	11.5	11.7	1.1	13	11.7	11.9	1.2	14
3	4.3	14.1	17.2	1.7	22	16.6	20.3	2.0	30
4	4.3	19.5	22.2	2.2	14	28.6	32.5	3.2	18
5	4.0	10.5	10.3	1.0	23	4.3	4.2	0.4	24
6	3.5	8.7	9.2	0.9	22	8.8	9.4	0.9	17
7	5.4	17.6	27.6	2.8	21	15.2	23.8	2.3	26
8	5.0	5.4	8.2	0.8	23	4.8	7.3	0.7	16
9	3.5	3.6	4.8	0.5	19	1.9	2.6	0.3	20
10	3.7	12.1	20.8	2.0	18	13.1	22.6	2.2	22
Mean ±SE	4.2 ±0.2	11.7 ±1.6	15.6 ±2.4	1.5 ±0.2	19.2 ±1.1	11.6 ±2.4	14.9 ±3.1	1.5 ±0.3	20.9 ±1.5

PHT MD = phenytoin maintenance dose; PEEP = positive end expiratory pressure; dphT = measured total phenytoin concentration; dphET = adjusted total phenytoin concentration; dphEF = estimated free phenytoin concentration; APACHE II = acute physiologic and chronic health evaluation II.

Table3. Comparison of Pharmacokinetic Parameters of Phenytoin Before and After PEEP Elevation

		Before PEEP Elevation			After PEEP Elevation		
Patient Number	Albumine (g/dl)	Initial PEEP (cm H2O)	Vmax* (mg/kg/day)	Cl* (L/kg/day)	Final PEEP (cm H2O)	Vmax* (mg/kg/day)	Cl* (L/kg/day)
1	2.5	0	3.5	0.1	8	3.7	0.2
2	4.4	0	6.2	0.4	5	6.1	0.4
3	3.6	3	4.9	0.2	8	4.7	0.2
4	3.9	3	4.6	0.2	8	4.4	0.1
5	4.6	5	5.1	0.3	10	7.2	0.9
6	4.2	5	4.6	0.3	10	4.6	0.3
7	2.7	3	5.7	0.2	10	5.9	0.2
8	2.8	3	6.8	0.6	10	7.1	0.6
9	3.2	5	5.9	0.7	10	8.2	1.2
10	2.4	3	4.1	0.2	10	4.1	0.1
Mean±SE	3.4±0.2	3±0.6	5.1±0.3	0.3±0.1	8.9±0.5	5.6±0.5	0.4±0.1

PEEP= positive end expiratory pressure; V_{max} = maximum rate of metabolism; Cl =clearance. * calculated based on adjusted total phenytoin concentrations (dphET) at each sampling.

PEEP was not associated with a significant alteration in APACHEII scores (19.2±1.1 versus 20.9±1.5, p=0.238). In addition no significant correlation was observed between calculated V_{max} and Cl of phenytoin and APACHE II scores at sampling times (spearman's ρ=0.066, p=0.782; spearman's ρ=-0.037, p=0.876; respectively.)

DISCUSSION

Our data indicated a wide range of variability (2.6-32.5 mg/l in dphET) that was most similar to findings of Mlynarek (28) in a study of 17 neurosurgical patients (6-34 mg/l) in which, most patients had non-traumatic brain injury. According to APACHE II scores in table 2, patients of this study have had a rapid change in physiological conditions (range=13-30), which may contribute to a great intraindividual and interindividual variability. Assuming APACHE II as a measure of the severity of the patient physiological conditions and therefore as an indirect measure of organ function, the absence of any significant change in an individual APACHE II score for each patient might be considered as a possible reason for the lack of significant alteration in phenytoin concentrations after PEEP elevation. On the other hand, our data did not show any significant correlation between the pharmacokinetic parameters of phenytoin and APACHE II scores at sampling times. These findings are contradict to the results of a study on pharmacokinetic of amikacin in septic patients which showed a significant correlation between APACHE II score and V_d of amikacin (p=0.003, r^2=0.26) (20). This can be explained by the fact that phenytoin is mainly metabolised in the liver and APACHE II is not an appropriate index of hepatic function.

The results of this study did not show any significant alterations in phenytoin concentration and metabolism which could be attributed to application of PEEP.

As far as we know, no study has described whether hemodynamic response and factors associated with a vital support measures such as positive ventilation could affect serum phenytoin clearance. However, the potential effects of PEEP on pharmacokinetic of high extraction ratio drugs and drugs which are predominantly eliminated through the liver, have been reported in several studies (18). In a study on 5 patients, lidocaine pharmacokinetic before and after weaning from mecanichal ventilation was compared and an increase in peak and steady state plasma concentrations and a decrease in clearance of patients who were subjected to mechanical ventilation was found (19). The volume of distribution however did not change significantly. Also through studying the relationship between hemodynamic measures and pharmacokinetic behaviors of amikacin in 30 critically ill septic patients, it has been demonstrated a poor but significant relationship between application of PEEP mode (about 10±6 cm H2O) and both Vd and clearance (20). The influence of controlled mechanical ventilation on the pharmacokinetic

profile of gentamicin in 23 patients after elective open-heart surgery has been also reported (29). The results suggested that controlled mechanical ventilation leads to an increase in gentamicin V_d through a decrease in urine volume and negative water clearance.

The lack of the influence of PEEP on disposition of phenytoin which was detected in this study may seem to be odd, however there are some explanations.

First, it is well established that PEEP can cause deleterious hemodynamic effects. The most obvious of these effects is a decrease in cardiac output which is induced by two mechanisms:1) increase in intrathoracic pressure, which results in a decrease in venous return to the heart (30) and 2) at higher levels of PEEP, a shift of the interventricular septum, which results in a reduced stroke volume (12,31). Consequently, it is well known that application of PEEP causes a reduction in mean arterial pressure (MAP), central venous pressure (CVP) as well as decrease in hepatic, and renal blood flow (32).

However, as demonstrated by several experimental studies the deleterious hemodynamic effects may be minimized by a reduction of airway pressure and may be alleviated at least in part by inotropic agents or fluid administration (17,33,34).

In the present study patients were appropriately hydrated and were on drugs which are known to cause an increase in blood pressure and cardiac output (e.g. dopamine and dobutamine) as required. This is evidenced by the absence of any significant reduction in either MAP (p=0.919), or CVP (p=0.721) after application of PEEP of 5-10 cm H_2O.

Secondly, we had some clinical limitations for intervening higher levels of PEEP (i.e., ≤15 cm H_2O), which probably could have more profound effects on splanchnic blood flow and consequently drug metabolism.

It is well established that there is a positive correlation between the PEEP level and the amount of splanchnic blood flow reduction (35,36). This means that application of higher levels of PEEP are associated with more profound decrease in splanchnic blood flow which could not be reversed by fluid administration and inotropic supports. This is due to the fact that the decrease in venous return could be overcome by fluid administration, but the shift of interventricular septum which occures in higher levels of PEEP seems to be resistant to therapy (31,33). For example, it has been reported that dopamine reverses the decreased portal venous blood flow that occurres in a canine model of acute lung injury in which 10-cm H_2O pressure PEEP is added (34). However, in a rat model of acute lung injury, it has been shown that under increasing levels of PEEP (from 0 up to 20 cm H_2O), administration of higher doses of dopamine and dobutamine (12.5 versus 2.5 µg/kg/min) could only partially correct the cardiac output depression. However, significant declines in cardiac output at ≥10 cm H_2O of PEEP were still sustained (37).

In another study for evaluation of the pharmacokinetic behavior of aminophylline under positive ventilation in acute lung injury patients, in which higher levels of PEEP (10-15 cm H_2O) than those that were used in present study (5-9 cm H_2O) were employed, a significant reduction in V_d and clearance in higher PEEP group versus levels of 5-9 cm H_2O was observed (21).

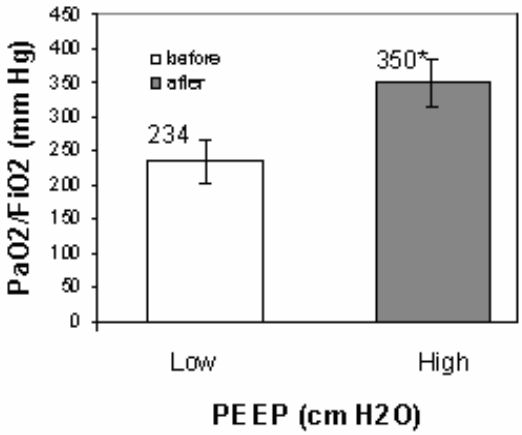

Figure 1. Comparison of PaO2/FiO2 ratios before and after PEEP elevation.

PEEP=positive end expiratory pressure; Low= peep levels of 0-5 cm H_2O; High=peep levels of 5-10 cm H_2O *p<0.05

Finally, there are some evidences that PEEP induced liver hypoperfusion and hypoxia could be compensated by some mechanisms. As it has been demonstrated, decreased organ perfusion due to PEEP effect may be compensated by an increased oxygen extraction if pulmonary gas exchange is sufficient (34). In another word, splanchnic oxygen consumption may remain unchanged due to an increase in oxygen extraction. The observation of a significant improvement in PaO_2/FiO_2 ratios from 234±33 to 350±36 (p=0.023) after application of PEEP in the present study potentiates this assumption (Figure 1).

Neverthless, to establish whether the correction or compensation of the deleterious hemodynanic and oxygenating effects of PEEP is responsible for the observed configurations, requires a simultanous advanced evaluation of more specific hemodynamic profiles such as cardiac output, portal, hepatic or mesanteric blood flow, as well

as measurment of the hepatic oxygenation. Although, the impact of concomitant medications on metabolism could not be specifically evaluated because of the small sample size, the contribution of drug interactions to the observed variability also should not be ignored.

In this study the phenytoin free level was also calculated according to Sheiner-Tozer equation. On the basis of data shown in table 2, levels of dphEF in 7 cases were subtherapeutic (considering 0.1-0.2 mg/l as therapeutic range). However, except for the patient No 9 in whom phenobarbital was added due to uncontrolled seizures, there were no reports of convulsive seizures during the study. Beacause EEG monitoring was not available in ICU setting, the possibility of ongoing nonconvulsive seizures dose exist. As a result whether these levels of phenytoin are adequate for making the patients of this population free of seizure is not clear and requires larger sample size, well controlled conditions and direct maesurment of free concentration of phenytoin to make the rational decision.

In conclusion, no inhibitory effects for these levels of PEEP were found to increase concentration and to suppress V_{max} and Cl. Although therapeutic drug monitoring is highly recommended, it seems that application of PEEP in those levels which are usually used to optimize oxygenation in brain-injured patients may not require to adjust doses.

The variabilities observed in the results and the absence of PEEP effect on our datas can be explained partially by the possible effects of fluid therapy and medications such as dopamine and dobutamine which reverse the hemodynamic compromization due to positive ventilation.

ACKNOLEDGMENT

This work was supported by a grant from Pharmaceutical Sciences Research Center, at Tehran University of Medical Sciences. The authors thank the staff of the Intensive Care Unit at Sina Hospital, specially Mrs. Homa Moallemi and Mrs. Fatemeh Mohammadzadeh for their kind assistance in patient recruitment and sample collection. Also the authors aknowledge the excellent technical support of Dr Amir H. Mohammadpoor.

REFERENCES

1. Arboix A, Garcia-Eroles L, Massons JB, Oliveres M, Comes E. Predictive factors of early seizures after acute cerebrovascular disease Stroke 1997; 28: 1590-1594.
2. Kilpatrick CJ, Davis SM, Tress BM, Rossiter SC, Hopper JL, Vandendriesen ML. Epileptic seizures in acute stroke. Arch Neurol 1990; 47:157-160.
3. Giroud M, Gras P, Fayolle H, Andre N, Soichot P, Dumas R. Early seizures after acute stroke: a study of 1640 cases. Epilepsia 1994; 35:959-964.
4. So EL, Annegers JF, Hauser WA, O'Brien PC, Whisnant JP. Population–based study of seizure disorders after cerebral infarction. Neurology 1996; 46:350-355.
5. Hernandez TD. Preventing post-traumatic epilepsy after brain injury: weighing the costs and benefits of anticonvulsant prophylaxis. Tips 1997; 18-59-62.
6. Broderick JP, Adams HP, Barsan W, Feinberg W, Feldmann E, Grotta J, Kase C, Krieger D, Meyberg M, Tilley B, Zabramski JM, Zuccarello M. Guidelines for the management of spontaneous intracerebral hemorrhage. A statement for healthcare professionals from special writinggroup of the Stroke Council, American Heart Association. Stroke 1999; 30:905-915.
7. Ferro JM, Pinto F. Poststroke epilepsy: epidemiology, pathophysiology, and management. Drugs Aging 2004; 21:639-653.
8. Demling R., Riessen R. Pulmonary dysfunction after cerebral injury. Crit Care Med 1990; 18:768-774.
9. Meyer SA, Copeland D, Bernardini GL, Boden-Albala B, Lennihan L, Kossoff S, Sacco RL. Cost and outcome of mechanical ventilation for life-threatening stroke. Stroke 2000; 31:2346–2353.
10. Moor FA, Haenel JB. Ventilatory strategies for acute respiratory failure. Am J Surg 1997; 173:53-56.
11. Esteban A, Anzueto A, Alia I, Gordo F, Apesteguia C, Palizas F, Cide D, Goldwaser R, Soto L, Bugedo G, Rodrigo C, Pimentel J, Raimondi G, Tobin MJ. How is mechanical ventilation employed in the intensive care unit? An international utilization review. Am J Respir Crit Care Med 2000; 161:1450-1458.
12. Smith PK, Tyson GS Jr, Hammon JW Jr, Olsen CO, Hopkins RA, Maier GW, Sabiston DC Jr, Rankin JS. Cardiovascular effects of ventilation with positive expiratory airway pressure. Ann Surg 1982; 195:121-130.
13. Steinhoff HH, Samodelov LF, Trampisch HL, Falk KJ. Cardiac afferents and the renal response to positive pressure ventilation in the dog. Intensive Care Med 1986; 12:147-152.

14. Berry AJ. Respiratory support and renal function. Anesthesiology 1981; 55:655-667.
15. Johnson EE, Hedley-Whyte J. Continuous positive pressure ventilation and portal blood flow in dogs with pulmonary edema. J Appl Physiol 1972; 33:385-389.
16. Winso O, Biber B, Gustavsson B, Holm C, Milsom I, Niemand D. Portal blood flow in man during graded positive end-expiratory pressure ventilation. Intensive Care Med 1986; 12:80-85.
17. Matuschak GM, Pinsky MR, Rogers RM. Effects of positive end-expiratory pressure on hepatic flow and performance. J Appl Physiol 1987; 62:1377-1383.
18. Perkins MW, Dasta JF, DeHaven B. The physiological implications of mechanical ventilation on pharmacokinetics. Drug Intel Clin Pharm 1989; 23:316-323.
19. Richard C, Berdeaux A, Delion F, Riou B, Rimailho A, Giudicelli JF, Auzepy P. Effect of mechanical ventilation on hepatic drug pharmacokinetics. Chest 1986; 90:837-841.
20. Lugo G, Castaneda-Hernandez G. Relationship between hemodynamic and vital support measures and pharmacokinetic variability of Amikacin in critically ill patients with sepsis. Crit Care Med 1997; 25:806-811.
21. Hadavand N, Mojtahedzadeh M, Sadray S, Shariat Moharreri R, Shafaghi B, Khajavi MR, Salary P. Pharmacokinetic behavior of Theophylline following PEEP in critically ill patients with acute lung injury. Ir J Pharmaceut Res 2004; l:35-40.
22. Angus PW, Morgan DJ, Smallwood RA. Hypoxia and hepatic drug metabolism-clinical implications. Aliment Pharmacol Ther 1990; 4:213-225.
23. Elliott SL, Morgan DJ, Angus PW, Ghabrial H, Watson RG, Smallwood RA. The effect of hypoxia on propranolol clearance during antegrade and retrograde flow in the isolated perfused rat liver preparation. Biochem Pharmacol 1993; 45:573-578.
24. Hickey PL, Angus PW, McLean AJ, Morgan DJ. Oxygen supplementation restores theophylline clearance to normal in cirrhotic rats. Gastroenterology 1995; 108:1504-1509.
25. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985; 13: 818-829.
26. Winter ME, Tozer TN. Chapter 25. Phenytoin. In: Evance WE, Schentag JJ, Jusko WJ, eds. Applied Pharmacokinetics. Principle of Therapeutic Drug Monitoring. 3rd ed. Vanccouver, WA: Applied Therapeutics; 1992. p.1-44.
27. Anderson G D, Pak C, Doane KW, Griffy KG, Temkin NR, Wilensky AJ, Winn HR. Reversed winter-tozer equation for normalized phenytoin concentrations in trauma and elderly patients with hypoalbuminemia. Ann Pharmacother 1997; 31:279-284.
28. Mlynarek ME, Peterson EL, Zarowitz B. Predicting unbound phenytoin concentrations in the critically ill neurosurgical patient. Ann Pharmacother 1996; 30: 219-223.
29. Triginer C, Izquierdo Y, Fernandez R, Torrent J, Benito S, Net A, Jane F. Changes in gentamicin pharmacokinetics profiles induced by mechanical ventilation. Eur J Clin Pharmacol 1991; 40:297-302.
30. Dhainaut JF, Devaux JY, Monsallier JF, Brunet F, Villemant D, Hyughebaret MF, Mechanism of decreased left ventricular preload during continuous positive pressure ventilation in ARDS. Chest 1986; 90: 74-80.
31. Jardin F, Farcot JC, Boisante L, Curien N, Margairaz A, Bourdarias JP. Influence of positive end-expiratory pressure on left ventricular performance. N Engl J Med 1981; 304:387-392.
32. Schuster HP, Hemodynamic effects of positive pressure breathing. Klin Wochenschr 1984; 62:56-64.
33. Dorinsky PM, Hamlin RL, Gadek JE. Alterations in regional blood flow during positive end-expiratory pressure ventilation. Crit Care Med 1987; 15: 106-113.
34. Johnson DJ, Johannigman JA, Branson RD, Davis K Jr, Hurst JM. The effect of low dose dopamine on gut hemodynamics during PEEP ventilation for acute lung injury. J Surg Res 1991; 50:344-349.
35. Sha M, Saito Y, Yokoyama K, Sawa T, Amaha K. Effects of continuous positive-pressure ventilation on hepatic blood flow and intrahepatic oxygen delivery in dogs. Crit Care Med 1987; 15:1040-1043.
36. Bonnet F, Richard C, Glaser P, Lafay M, Guesde R. Changes in hepatic flow induced by continuous positive pressure ventilation in critically ill patients. Crit Care Med 1982; 10:703-705
37. Lee RDH, Choe E, Flint L, Steinberg S. Neither dopamine nor dobutamine corrects mesenteric blood flow depression caused by positive end-expiratory pressure in arat model of acute lung injury. Crit Care Med 1998; 26:1875-1880.