Evaluation of Intravenous Phenobarbital Pharmacokinetics in Critically Ill Patients With Brain Injury

Seyedeh Sana Khezrnia[1], Bita Shahrami[2], Mohammad Reza Rouini[3], Atabak Najafi[4], Hamid Reza Sharifnia[4], Sima Sadrai[3], Arezoo Ahmadi[4], Aarefeh Jafarzadeh Kohneloo[1], Farhad Najmeddin[2], Mojtaba Mojtahedzadeh[1,2]

[1] Research Center for Rational Use of Drugs, Tehran University of Medical Sciences, Tehran, Iran

[2] Department of Clinical Pharmacy, School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

[3] Department of Pharmaceutics, School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

[4] Department of Anesthesiology and Intensive Care, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

Received: 11 Apr. 2021; Accepted: 02 Dec. 2021

Abstract- Phenobarbital is still one of the drugs of choice in managing patients with brain injury in the intensive care unit (ICU). However, the impact of acute physiological changes on phenobarbital pharmacokinetic parameters is not well studied. This study aimed to evaluate the pharmacokinetic parameters of parenteral phenobarbital in critically ill patients with brain injury. Patients with severe traumatic or non-traumatic brain injury at high risk of seizure were included and followed for seven days. All patients initially received phenobarbital as a loading dose of 15 mg/kg over 30-minutes infusion, followed by 2 mg/kg/day divided into three doses. Blood samples were obtained on the first and fourth day of study at 1, 2, 5, 8, and 10 hours after the end of the infusion. Serum concentrations of phenobarbital were measured by high-pressure liquid chromatography (HPLC) with an ultraviolet (UV) detector. Pharmacokinetic parameters, including the volume of distribution (Vd), half-life ($t_{1/2}$), and the drug clearance (CL), were provided by MonolixSuite 2019R1 software using stochastic approximation expectation-maximization (SAEM) algorithm and compared with previously reported parameters in healthy volunteers. Data from seventeen patients were analyzed. The mean value±standard deviation of pharmacokinetic parameters was calculated as follows: V_d: 0.81±0.15 L/kg; $t_{1/2}$: 6.16±2.66 days; CL: 4.23±1.51 ml/kg/h. CL and V_d were significantly lower and higher than the normal population with the value of 5.6 ml/kg/h (*P*=0.002) and 0.7 L/kg (*P*=0.01), respectively. Pharmacokinetic behavior of phenobarbital may change significantly in critically ill brain-injured patients. This study affirms the value of early phenobarbital therapeutic drug monitoring (TDM) to achieve therapeutic goals.

Acta Med Iran 2022;60(1):18-24.

Keywords: Phenobarbital; Pharmacokinetics; Brain injury; Critical illness; Therapeutic drug monitoring

Introduction

The story of the clinical use of phenobarbital as an anticonvulsant agent is back to 1912. It has revolutionized epilepsy treatment and is still one of the drugs of choice for status epilepticus (1). World Health Organization (WHO) recommended phenobarbital as the first line of treatment in developing countries due to high efficacy and low price; however, it is less welcome in Western medicine probably because of adverse effects profile (2,3). Despite the widespread use of this medication in intensive care units (ICUs), including prevention of early seizures after brain damage (4-7), treatment of refractory seizures (8), alcohol withdrawal (9,10), and some more specific situations like cerebral salvage following traumatic and/or hypoxic brain injury (11), the need for pharmacokinetics study in various populations could not be ruled out.

Physiological changes in critically ill conditions can significantly alter the pharmacokinetics of prescription medications (12,13). A head injury can cause physiological changes, unpleasant complications,

Corresponding Author: F. Najmeddin
Department of Clinical Pharmacy, School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 2166980467, Fax: +98 2166461178, E-mail address: farhad.najm@gmail.com

including acute and delayed changes in cardiovascular variables, hypercapnia, cerebral hypoxia, ischemia, metabolic disorders, changes in intracranial pressure (ICP), seizure, epilepsy, changes in behavior, cognitive and motor disorders, sleep problems, and so on (14,15). Systemic inflammatory response syndrome (SIRS) indicates a general inflammation beyond local involvement (16). An inflammatory response is related to the severity and complexity of the disease and may also impact on pharmacodynamics and pharmacokinetics of administered drugs (17).

The proper use of drugs requires an accurate understanding of the potential effects of these critical conditions on the processes of absorption, distribution, metabolism and drug excretion (18). Phenobarbital pharmacokinetics has been evaluated many years ago in healthy volunteers and patients with status epilepticus (19,20). Phenobarbital clearance can be affected by specific prescribed drugs for the patient, the disease condition, and the patient's age. The clearance in children aged 1 to 19 years is 0.0082±0.0031 L/kg/h, in adults aged 19 to 65 years is 0.0056±0.0026 L/kg/h and in geriatrics is described 0.0024 L/kg/h (11). One concept regarding drug clearance to keep in mind is that under-dosing leading to inadequate drug concentrations are more likely than overdosing leading to adverse drug reactions under critical conditions (16).

Up to now, several studies confirmed the alteration of pharmacokinetic behavior of different drugs administered to patients under critical conditions (21). The present study was designed regarding several brain-injured cases on phenobarbital with impaired pharmacokinetics in our center and aimed to evaluate the pharmacokinetic parameters of parenteral phenobarbital in a larger population of critically ill patients with brain injury and edema.

Materials and Methods

Study design

This descriptive pharmacokinetics study was performed at the ICUs of "Sina" Hospital, affiliated to Tehran University of Medical Sciences (TUMS).

Adults with an age range of 18 to 70 years of old with severe brain injury presented with Glasgow Coma Scale (GCS) less than 8, the consequent risk of seizure and secondary brain damage during their stay in the ICU, radiological evidence of brain edema and increased ICP, and intubated were included. Patients with unstable hemodynamics, known hypersensitivity to barbiturates, hepatic or renal impairment, history of seizure, and taking phenobarbital during the last month were excluded.

Drug dosing and blood sampling

Patients who had been on phenobarbital within 72 hours after brain injury were enrolled based on the inclusion criteria. Informed consent was obtained from all participants' guardians included in the study.

All patients initially received phenobarbital as a loading dose of 15 mg/kg of total body weight over 30-minutes intravenous (IV) infusion, and after 12 hours, the IV maintenance dose of 2 mg/kg/day was divided into three doses, which was experimentally determined as the effective dose in this particular population by intensive care specialists of our center, usually administered up to 7 days.

Blood samples were obtained on the first and fourth days of the study. Serum concentrations of phenobarbital were measured at the following times after the end of the loading dose on the first day: at 1, 2, 5, 8, and 10 hours. On the fourth day, sampling was done before administration of the ninth dose and at 1, 2, 5, and 8 hours after the end of the infusion. The samples were centrifuged, and extracted serum was stored at -70°C until the final analysis.

The serum concentration of phenobarbital was determined by High-performance liquid chromatography (Smartline HPLC Series KNAUER) equipped with a C-8 reverse-phase column with an internal diameter of 46 mm and a length of 15 cm, and a variable-wavelength UV detector set at 240 nm. The mobile phase was 10% acetonitrile and 22.5% methanol in distilled water at a flow rate of 1 ml/min.

Patients' data gathering

The clinical and demographic data and source of brain injury were documented by reference to the medical records of the patients. Routine clinical tests in ICU patients were recorded at daily visits of patients.

Population pharmacokinetic parameters estimation

Estimation of individual parameters of the volume of distribution (V_d), half-life ($t_{1/2}$), and the drug clearance (CL) were provided by MonolixSuite 2019R1 as the mean of their posterior distribution using stochastic approximation expectation-maximization (SAEM) algorithm.

Results

A total of 17 (82.4% men) brain-injured patients with a mean age of 51.88 were enrolled in the study. Patients

with severe traumatic brain injury (TBI) represented the majority of cases included (58.8%). Table 1 describes the demographic information of patients, and Table 2 shows the causes of admission to the ICU.

Table 1. Demographic parameters of patients

Demographics	Number	Mean±Std. Deviation
Gender (male/female)	14/3	-
Age	17	51.8±18.7
Total body weight	15	81.7±20.4
eGFR[a] (ml/min/1.73 m^2)	17	72.9±21.4
APACHE[b] Score*	17	18.1±4.6
SOFA[c] Score*	17	9.4±2.3
NRS[d]	16	4.5±0.9

aeGFR: estimated glomerular filtration rate; bAPACHE Score: Acute Physiology, Age, and Chronic Health Evaluation Score; cSOFA Score: Sequential Organ Failure Assessment Score; dNRS: Nutrition Risk Screening. *APACHE and SOFA scores were calculated at the admission, but the worst score was considered for NRS

Table 2. Causes of admission to ICU

Source	Frequency	Percent
Brain Tumor	1	5.9
Status epilepticus	1	5.9
Stroke	5	29.4
Traumatic Brain Injury	10	58.8
Total	17	100.0

The phenobarbital for three patients was discontinued before reaching the fourth day of study. It was due to an increase in consciousness and improvement of the general condition in one of the patients. The phenobarbital order was interrupted because of unknown reasons in another patient. The last patient was expired on the third day of the study; therefore, blood sampling in these three patients was taken only on the first day.

The mean value±standard deviation of pharmacokinetic parameters was calculated as follows: CL: 4.23±1.51 ml/kg/h; V_d: 0.81±0.15 L/kg; $t_{1/2}$: 6.16±2.66 days. The pharmacokinetic parameters of phenobarbital are pinpointed in Table 3. The correlation between detected phenobarbital concentrations and predicted ones by our model is shown in Chart 1.

The results revealed that V_d was significantly higher than the normal population, which has previously been described as 0.7 L/kg (11) (P=0.01). CL was significantly lower than the normal population with a value of 5.6 ml/kg/h (11) (P=0.002). $T_{1/2}$ was significantly higher than the normal population, which is considered to be four days (11) (P=0.004).

From the data in Table 4, despite the apparent differences in the pharmacokinetic parameters of patients with different causes of brain injury, only a significant difference was found between the V_d of the two groups due to the small sample size.

Table 3. Pharmacokinetic parameters of patients during the acute phase in comparison with normal population

Variable	Number	Mean value	SD	Standard Deviation of the Random Effects	Normal Population	*P*
CL (ml/kg/h)	17	4.23	1.51	0.451	5.6	0.002
V_d (L/kg)	17	0.81	0.15	0.198	0.7	0.01
$T_{1/2}$ (days)	17	6.16	2.66	-	4	0.004

Abbreviations: SD, standard deviation; CL, clearance; t1/2, half-life; Vd, the volume of distribution; Standard Deviation of the Random Effects was calculated by Monolix software

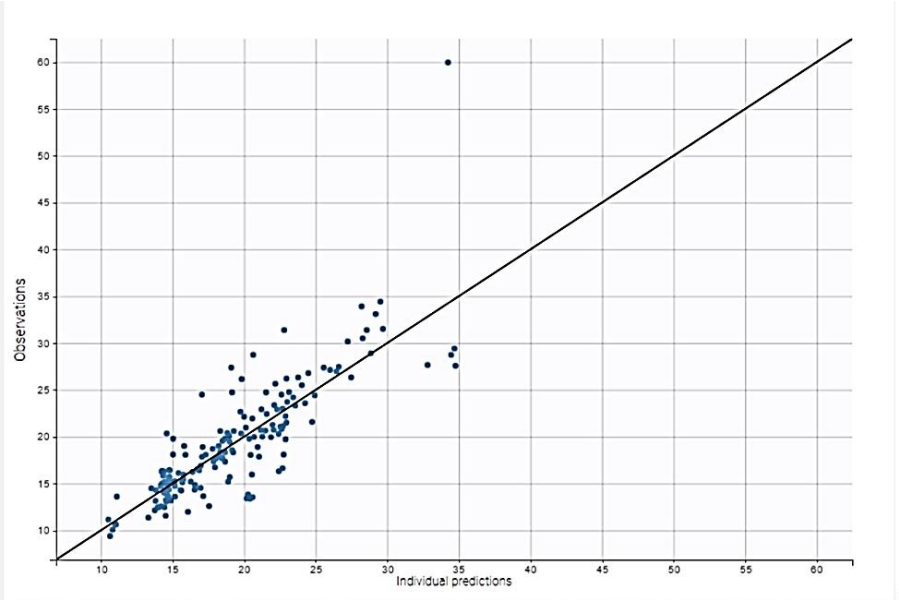

Chart 1. Correlation between observed phenobarbital concentrations and individual predictions

Table 4. Comparison of pharmacokinetic parameters in patients with stroke and TBI

	Source	Number	Mean value ± SD.
V_d (L/kg)	Stroke	5	0.7 ± 0.15
	TBI	10	0.87 ± 0.12
CL (ml/kg/h)	Stroke	5	4.14 ± 0.73
	TBI	10	4.65 ± 1.69
$t_{1/2}$ (days)	Stroke	5	5 ± 1.29
	TBI	10	6.07 ± 2.83

Abbreviations: SD, standard deviation; CL, clearance; t1/2, half-life; Vd, the volume of distribution; TBI, Traumatic Brain Injury

Discussion

Pharmacokinetic parameters of IV phenobarbital remarkably change in the acute physiologic phase of brain damage in ICU patients. Considering the range of 20 to 40 mg/L as the therapeutic goal of phenobarbital therapy (11), interestingly, a group of patients (35.3%) would experience steady-state concentrations (C_{ssmin}) ≤30 mg/L, and with the current dosing system, the rest of the patients would have C_{ssmin} >30 mg/L with an extensive variation. Patients with estimated C_{ssmin} ≤30 mg/L had CL calculated 4.8 ml/kg/h, which is significantly different from those with an estimated value >30 mg/L, and this would confirm the need for therapeutic drug monitoring (TDM). According to assessments, 25.5±4.9 mg/kg of loading dose would be needed to reach the trough level of 30 mg/L on the first day, and 2.5±1.5 mg/kg/day is desired as a maintenance dose to reach C_{ssmin} of 30 mg/L.

This study affirms the value of early phenobarbital TDM in critically brain-injured patients. To the best of our knowledge, this is the first published study that evaluates the pharmacokinetic parameters of IV phenobarbital in the acute phase of brain damage. As it seems, higher initial doses are needed for individualized dosing to achieve therapeutic goals in critically brain-injured patients, which would generally consider concentrations of 20-40 mg/L in which patient respond should guide us through proper dose adjustment. Despite a significant decrease in CL compared with the normal population, there is a wide range of CL values among the patients. In cases of refractory status epilepticus, the recommended therapeutic range is even determined by more than 70 mg/L, and for cerebral salvage from hypoxic or traumatic brain damage, this amount is considered more than 75 mg/L (11). These high concentrations may induce barbiturate coma as a therapeutic strategy. Results and risk of adverse events related to toxic blood concentrations should be considered. The effect of barbiturate coma can vary regarding various factors such as age (22). As shown in the results section, the regular dosing of phenobarbital may not result in effective concentration and desirable response in this population. Due to the low troughs on the first day and high estimated C_{ssmin} in the majority of the

patients, TDM is necessary.

Several physiological events following brain damage, including cytokine cascades, catecholamine storm, decoupling, endothelial and vascular problems, brain hypoxia, ischemia, metabolic disturbances, ICP changes, and hundreds of other cases, can affect pharmacokinetic parameters (14,15,23). All of them lead the practitioner not to be able to predict the behavior of the drug during initial therapy after brain injury, and this insists on the importance of TDM in this population, especially during the acute phase.

Despite phenobarbital CL decrease, all the measured blood concentrations were in the therapeutic range and none of the patients experienced drug toxicity due to short duration of treatment. Some studies contradict what we found. The CL of pentobarbital from the barbiturates family in TBI patients increases for several days. CL of phenytoin has also increased in the acute phase after brain injury (12). Plasma levels of pentobarbital were evaluated by Heinemeyer G *et al*., in 16 ICU patients suffering from severe brain injury who received a dose of 30 mg/kg/day. It was observed that plasma concentrations of pentobarbital decreased continuously in ten patients, while total plasma CL increased from 0.81 to 1.06 ml/kg/min (24). Our experiences also confirm the previous study of cyclosporine clinical pharmacokinetics. It was showed that cytochrome P450-mediated cyclosporin metabolism was hampered by an inflammatory response after bone-marrow transplantation. The maximum concentration of cyclosporin was correlated with interleukin 6 and C-reactive protein (biomarkers of acute inflammatory response) blood levels (17).

Another key concept is phenoconversion which considers the conversion of genotypic extensive metabolizers (EMs) into phenotypic poor metabolizers (PMs) of drugs so similar to genotypic PMs (25). Potential effects of several inflammatory conditions leading to phenoconversion were studied, for instance, human immunodeficiency virus infection, cancer, and liver disease which all of them are associated with cytokines elevation and are clinically acceptable as causes of NAT2, CYP2C19, and CYP2D6 phenoconversion. There is also clinical evidence confirming infection-induced down-regulation of CYP1A2, CYP3A4, and CYP2C9. Contrary to initial belief, this is not a rare phenomenon that affects the pharmacokinetics of the drugs and patients' clinical outcomes. phenoconversion highlights the importance of personalized medicine (25,26).

Samaras and Deitz found that the pentobarbital behavior was hyperbolized in rats treated with trypan blue, an immune system stimulating substance. They observed that pentobarbital metabolism was impaired during the inflammatory response. Many studies have shown the association between cytokines levels such as interleukin-6 and diminished drug CL consisting of theophylline, antipyrine, hexobarbital, and midazolam. The remarkable result of reviewed data is that brain edema, and inflammation does not only suppress the local cytochromes but also peripheral cytochromes can be affected (27). It is important to consider environmental factors causing a mismatch of genotypes with phenotypes through alteration of enzyme expression (28).

Another possible explanation of decreased CL could be related to liver blood flow. A severe decrease in hepatic blood flow usually occurs in shock. This is not the case with the current study; however, liver blood flow may also be affected by our patients. Macnab *et al.*, introduced six patients in shock with a significant decrease in morphine CL (29). Reduced CL becomes more important for drugs that have a narrow therapeutic index, and also, in the population with genotype PM, it can lead to negligible metabolism of drugs (27).

Considering the observed increase in V_d, we stratified the patients based on the etiology of brain damage, and we observed a significant number of patients with TBI had increased V_d. Phenobarbital is a lipophilic drug with low V_d and protein-binding (11). Therefore, the determining pharmacokinetics parameter is CL. It may be possible to justify an increase in V_d by changing liver function and the accumulation of endogenous substances (30). However, this phenomenon in patients with TBI may not be interpreted easily, and further studies are required. Changes in liver blood flow, mechanical ventilation in patients, increase in the levels of stress hormones such as cortisol, increase in acute phase proteins, damage to the hypothalamic-pituitary system, increased ICP, age, and factors related to nutrition all can affect the CL and V_d of different drugs prescribed in this population; therefore, monitoring of drug plasma concentrations is strongly suggested.

Limitations

Although the significant results from the study led us to stop it with the mentioned number of patients to prevent the waste of resources, the small sample size of this study could be one of its limitations. Also, our patients were not homogeneous; a percentage of them underwent craniotomy surgery, some of them had a hematoma, and also they had different causes of brain injury. These differences are expected to affect the

pharmacokinetic parameters of the drug. Patients in the ICU receive different drugs at the same time. They can interact with each other in terms of pharmacokinetics or pharmacodynamics, which could not be avoided in our study too. Almost all patients were on phenytoin concurrently. The onset of inducible effects of phenytoin takes time. It has been reported that concomitant use of phenytoin and phenobarbital initially decreases phenobarbital CL (31). This may have affected the results of this study. It has been shown that ICP monitoring may reduce mortality rates in operated patients, length of ICU stay, radiation exposure and brain specific interventions (32). Due to a lack of facilities and existing conditions, we were unable to measure the ICP of the patients and evaluate its relationship with pharmacokinetic parameters of phenobarbital which can be considered in later studies.

Phenobarbital pharmacokinetic parameters may change remarkably in the critically ill brain-injured patients; it is noteworthy that a significant decrease in CL is very important and affects the treatment process. Given this finding, early TDM is necessary to adjust the appropriate dose.

Acknowledgements

We would like to appreciate the ICU wards, Sina Hospital nursing staff for their effort and collaboration. We also thank Mrs. Hoda Lavasani for her valuable help in the drug assay phase of this work.

References

1. Trinka E, Kälviäinen R. 25 years of advances in the definition, classification and treatment of status epilepticus. Seizure 2017;44:65-73.
2. Yasiry Z, Shorvon SD. How phenobarbital revolutionized epilepsy therapy: the story of phenobarbital therapy in epilepsy in the last 100 years. Epilepsia 2012;53:26-39.
3. Hocker S, Clark S, Britton J. Parenteral phenobarbital in status epilepticus revisited: Mayo Clinic experience. Epilepsia 2018;59:193-7.
4. Temkin NR. Preventing and treating posttraumatic seizures: the human experience. Epilepsia 2009;50:10-3.
5. Temkin NR. Antiepileptogenesis and seizure prevention trials with antiepileptic drugs: meta- analysis of controlled trials. Epilepsia 2001;42:515-24.
6. Schierhout G, Roberts I. Antiepileptic drugs for preventing seizures following acute traumatic brain injury. Cochrane Database Syst Rev 2001;4:CD000173.
7. Gupta Y, Gupta M. Post traumatic epilepsy: a review of scientific evidence. Indian J Physiol Pharmacol 2006;50:7-16.
8. Uchida T, Takayanagi M, Kitamura T, Nishio T, Numata Y, Endo W, et al. High- dose phenobarbital with intermittent short- acting barbiturates for acute encephalitis with refractory, repetitive partial seizures. Pediatr Int 2016;58:750-3.
9. Hayner CE, Wuestefeld NL, Bolton PJ. Phenobarbital treatment in a patient with resistant alcohol withdrawal syndrome. Pharmacotherapy 2009; 29:875-8.
10. Perry EC. Inpatient management of acute alcohol withdrawal syndrome. CNS Drugs 2014;28: 401-10.
11. Murphy JE. Clinical pharmacokinetics. 6th ed. Bethesda: ASHP; 2017.
12. Boucher BA, Wood GC, Swanson JM. Pharmacokinetic changes in critical illness. Crit Care Clin 2006;22:255-71
13. Yamamoto Y, Takahashi Y, Horino A, Usui N, Nishida T, Imai K, et al. Influence of Inflammation on the Pharmacokinetics of Perampanel. Ther Drug Monit 2018;40:725-9.
14. Szaflarski JP, Nazzal Y, Dreer LE. Post-traumatic epilepsy: current and emerging treatment options. Neuropsychiatr Dis Treat 2014;10:1469-77.
15. McIntosh TK. Novel pharmacologic therapies in the treatment of experimental traumatic brain injury: a review. J Neurotrauma 1993;10:215-61.
16. Blot SI, Pea F, Lipman J. The effect of pathophysiology on pharmacokinetics in the critically ill patient—concepts appraised by the example of antimicrobial agents. Adv Drug Deliv Rev 2014;77:3-11.
17. Slaviero KA, Clarke SJ, Rivory LP. Inflammatory response: an unrecognised source of variability in the pharmacokinetics and pharmacodynamics of cancer chemotherapy. Lancet Oncol 2003;4:224-32.
18. Smith BS, Yogaratnam D, Levasseur-Franklin KE, Forni A, Fong J. Introduction to drug pharmacokinetics in the critically III patient. Chest 2012;141:1327-36.
19. Brzaković B, Pokrajac M, Dzoljić E, Lević Z, Varagić V. Cerebrospinal fluid and plasma pharmacokinetics of phenobarbital after intravenous administration to patients with status epilepticus. Clin Drug Investig 1997;14:307-13.
20. NELSON E, POWELL JR, CONRAD K, LIKES K, BYERS J, BAKER S, et al. Phenobarbital pharmacokinetics and bioavailability in adults. J Clin Pharmacol 1982;22:141-8.
21. Pokorná P, Posch L, Šíma M, Klement P, Slanar O, van den Anker J, et al. Severity of asphyxia is a covariate of phenobarbital clearance in newborns undergoing hypothermia. J Matern Fetal Neonatal Med 2019;32:2302-9.
22. Schalen W, Sonesson B, Messeter K, Nordström G,

Nordström CH. Clinical outcome and cognitive impairment in patients with severe head injuries treated with barbiturate coma. Acta Neurochir (Wien) 1992;117:153-9.

23. Boucher BA, Hanes SD. Pharmacokinetic alterations after severe head injury. Clinical pharmacokinet 1998;35:209-21.
24. Heinemeyer G, Roots I, Dennhardt R. Monitoring of pentobarbital plasma levels in critical care patients suffering from increased intracranial pressure. Ther Drug Monit 1986;8:145-50.
25. Shah RR, Smith RL. Addressing phenoconversion: the Achilles' heel of personalized medicine. Br J Clin Pharmacol 2015;79:222-40.
26. Shah RR, Smith RL. Inflammation-induced phenoconversion of polymorphic drug metabolizing enzymes: hypothesis with implications for personalized medicine. Drug Metab Dispos 2015;43:400-10.
27. Renton KW. Regulation of drug metabolism and disposition during inflammation and infection. Expert Opin Drug Metab Toxicol 2005;1:629-40.
28. Monostory K, Nagy A, Tóth K, Bűdi T, Kiss Á, Déri M, et al. Relevance of CYP2C9 Function in Valproate Therapy. Curr Neuropharmacol 2019;17: 99-106.
29. Macnab M, Macrae D, Guy E, Grant I, Feely J. Profound reduction in morphine clearance and liver blood flow in shock. Intensive Care Med 1986;12:366-9.
30. Krishnan V, Murray P. Pharmacologic issues in the critically ill. Clin Chest Med 2003;24:671-88.
31. Lambie D, Johnson R. The effects of phenytoin on phenobarbitone and primidone metabolism. J Neurol Neurosurg Psychiatry 1981;44:148-51.
32. Vora TK, Karunakaran S, Kumar A, Chiluka A, Srinivasan H, Parmar K, et al. Intracranial pressure monitoring in diffuse brain injury-why the developing world needs it more? Acta Neurochir (Wien) 2018;160:1291-9.