The Effect of Phenytoin Loading Dose to Hepatic Enzyme in Epilepsy Patients

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Abstract
Epilepsy was defined as neurologic abnormality that was characterized with tendency to cause consistent epileptic seizure and neurobiologist, cognitive, psychologist, and social consequences. According to WHO, it was proximately about 50 million people with epilepsy worldwide. Single use of antiepileptic drug (AED) became first choice in starting epilepsy treatment, because most of patients was successfully controlled by first or second single therapy of AED. Phenytoin mostly was used for focal and generalized seizure type and as second line for mixed seizure type (myoclonic and tonic-clonic). Beside its good effectiveness in controlling seizure, phenytoin also caused significant adverse effects. Such as, phenytoin could cause hepatotoxicity with a couple of days until eight weeks onset, which is characterized by elevation of aspartate aminotransferase (AST).with level range of 2-100 times from normal baseline and also elevation of alanine aminotransferase (ALT).

Keywords*: Epilepsy, Antiepileptic, Phenytoin, Adverse effects***.**

I. INTRODUCTION

Operationally, epilepsy was brain disease which characterized with symptoms or conditions, such as: at least, there was two seizures without provocation or one reflect seizure with possibility of repeated seizure and risk of no provocation seizure recurrence by 60%, that can occur until the next ten years. Reflect seizure was seizure which occurred because of induction of predisposition factors such as visual stimulation, auditory, somatosensitive and somatomotoric (Kurniawan, Suharjanti, and Pinzon, 2016). Epilepsy study club of Indonesian Neurological Association conducted study in over 18 hospitals in 15 cities in 2013 for 6 months. The study result of 2288 patients including 487 new cases and 1801 old cases. The average age of new case was 25,06 years old ± 16,9 years old, meanwhile the average age of old case was 29,2 years old ± 16,5 years old. As 77,9% patients got their medication for the first time at their neurologist, 6,8% went to general practitioner, and the rest got no medication (Oktaviana and Khosama, 2014).

Most of patients had good responses with single therapy, as 47% patients was seizure free with first line AED and 13% was seizure free with second line drugs. The usage of combination therapy could be considered when patient failed with second or third line AED (Kwan and Brodie, 2000). It has been reported that the usage of AED have hepatotoxic effects. AED with hepatotoxic effect were carbamazepine, phenytoin, and valproic acid which characterized with the elevation of hepatic enzyme (AST, ALT, ALP and GGT). Other adverse reaction that been reported were gastrointestinal disturbance (nausea, diarrhea and pancreatitis), neurologic disturbance (sedation), metabolic disturbance (elevation of ammonia) (Lacy and Charles, 2009). These case reports focus on the effect of phenytoin loading dose to hepatic enzyme (AST and ALT) in epilepsy patients.

II. CASE REPORT

The case of 6 women of 24 – 61 years old diagnosed with epilepsy. They were inpatient patients of September – November 2017 at Neurology Department of Soetomo Hospital Surabaya. The data were secondary data which taken from medical record. Among 30 patients that been taken care in the period, there were 6 cases that fulfilled epilepsy diagnostic criteria with no history of liver insufficiency. Mrs MAM 24 years old with generalized – motor – tonic clonicseizure type, and history of oral phenytoin usage 100 mg three times a day. Mrs S 52 years old with focal onset – sinister – aware – clonic – sensory seizure type and history of taking phenytoin 100 mg three times a day. Mrs EBM 22 years old with generalized – motor – tonic clonic seizure type, and no history

of taking AED. Mrs RW 61 years old with aware – focal tubilateral – tonic clonic seizure type and history of taking valproic acid 500 mg two times a day. Mrs SF 31 years old with focal onset – impaired awareness – automatism chewing, and history of taking AED unknown, however she had been taken AED for the two years. Mrs RW 61 years old with focal onset – focal tubilateral – tonic clonicdextra, and history of taking AED combination of phenytoin 100 mg three times a day and valproic acid 500 mg three times a day.

From the laboratory examination data before phenytoin loading dose administration, it was conducted hepatic enzyme AST and ALT measurement. From all six patients, ALT (16-35 µ/L) and AST (17-40 µ/L) were normal. Then, loading dose of phenytoin was administered based on table and continued to maintenance dose of phenytoin 100 mg three times a day for 3 days. After that, hepatic enzymes were measured once again and it was almost all pasien having elevation of AST. 3 patients had elevated AST, and also 2 patients had elevated ALT, and one patient had both. Laboratory profile and result was on table below.

Tabel 1. Laboratory Profile and Result

No	Name	Sex	Age	Weight (Kg)	Diagnose	Type	LD (mg)	MD (mg)	Hepatic Enzyme Measurement Result			
									Pre (µ/L)		Post (µ/L)	
									AST	ALT	AST	ALT
1	MAM	F	24	56	epilepsy	generalized - motor - tonic clonic	900	3 x 100	25	17	26	23
2	S	F	52	58	Epilepsy	focal onset - sinistra - aware - clonic - sensory seizure	1080	3 x 100	32	38	*45	42
3	EBM	F	22	60	Epilepsy	generalized - motor - tonic clonic	900	3 x 100	16	23	19	23
4	RW	F	61	60	Epilepsy bad compliance	aware - focal tubilateral - tonic clonic	900	3 x 100	17	26	16	27
5	SF	F	31	55	Epilepsy	focal onset - impaired awareness - automatism chewing	500	3 x 100	35	40	*164	*92
6	RW	F	61	60	Epilepsy bad	focal onset	900	3 x 100	23	24	*62	*61

					complian ce	focal tubilatera l - tonic clonicde xtra						

*LD: Loading Dose, MD: Maintenance Dose, *: Ubnormal Hepatic Enzyme Measurement Result*

III. DISCUSSION

All patients reported of having history of epilepsy and recurrent seizure with different type so that they have to be admitted to the ward. From a prospective randomized trial, it was reported that seizure with no provocation was considered the risk of recurrence could occur after 2 years in patient who taken no medication with range of 40-50% (Marso et al., 2005) (Kim et al., 2006). Recurrence risk can be occurred on first year after seizure and reduced as the time flies. About 80-90% patients had recurrent seizure on two years (Berg, 2008 and Hauser et al., 1998).

Clinical factors that influenced improvement of recurrence seizure risk after the first seizure with no provocation were abnormality in electroencephalography data, symptomatic factor such as brain tumor, bran malformation, head injury with loss of consciousness, central nervous system infection, that each of these factors had been connected with about 2 – 2,5 times of increasing recurrence seizure risk. The report also included patient who taken AED or not (Hauser et al., 1998, Musicco et al., 1997 and Ramos et al., 2000). There were less evidence about relation between all risks, and there was no formula to explain estimation of addictive risk (Krumholz et al., 2015).

Other factors that potentially caused recurrent seizure had investigated, however the result was still unclear. For example, patients with seizure and epileptic state or with a few seizure a day, they were likely treated with AED compared to patients with short duration and single seizure. However, the limited data reported that seizure with epileptic state with no other risk factor, did not increase the risk of recurrence seizure (Lho, 2006). For adults who had first seizure with unclear etiology, treatment with AED could reduce recurrence seizure at least 35% for the next one or two years (Leone et al., 2016). This estimation has been reported from a metaanalysis of RCT to about 1600 patients. The study conducted comparison of early and delayed AED treatment to adult patients with no provocation (Krumholz et al., 2015). However, according to other study, it shown that initiation of AED only gave small impact in long term result. In 4 and 5 years after the first seizure, these patients who taking AED as soon as after the first seizure have AED effect as good as they who have delay AED after the second seizure occurred (Musicco et al., 1997). At least one RCT reported that 20 years mortality did not have direct impact compared to patients with delay treatment (Leone et al., 2011).

Treatment for epilepsy patients was administration of antiepileptic drugs (AED) and almost 50% of them will be free of seizure with single AED (Kwan and Brodie, 2000). In selecting therapy for the patients, doctors have to consider efficacy and adverse effect of each drug. Comparison of efficacy and tolerability data was still limited. Kinds of clinical trial that conduct, did not show any significant differences yet, among all AED in term of efficacy. Therefore, doctors have to plan the treatment based on drugs combination, seizure type and other specific factors (Kwan and Brodie, 2002).

In this case, patient was administered with phenytoin loading dose after recurrence, and then continued with maintenance dose. Phenytoin firstly reported in 1930 for antiepileptic drugs and mostly was used for focal and generalized seizure type and as second line for mixed seizure type (myoclonic and tonic-clonic). The mechanism of action was almost similar to carbamazepine that is by blocking voltage-dependent neuronal sodium channels (Yaari, Selzer, Pincus, 1986). Other effect of phenytoin included reduction of synaptic transmission, limiting fluctuation of neuronal ionic gradients via sodium-potassium ATPase, and affecting second messenger systems by inhibiting calcium-calmodulin protein phosphorylation. The first step in the metabolism of phenytoin, which takes place in the liver, involves arene oxidase, which has nonlinear kinetics (20). Beside its good effectiveness in controlling seizure, phenytoin also caused significant adverse

effects. Such as, phenytoin could cause hepatotoxicity with a couple of days until eight weeks onset, which is characterized by elevation of AST with level range of 2-100 times from normal baseline and also elevation of ALT. Moreover, it occurred jaundice, lymphadenopathy, splenomegaly, cholestasis, prolonged of thrombin time, elevation of bilirubin, allergy reaction such as rash, fever, leukocytosis, and eosinophilia, gingiva hyperplasia, and gastrointestinal disturbance (Jahromi, 2011).

Hepatotoxicity that induced by phenytoin was idiosyncratic and not dose and duration dependent. Phenytoin was enzyme inducer and could cause elevation of GGT level that was asymptomatic in almost 100% patients. Aminotransferase serum level could increase a bit but sometimes it would be normal although therapy was continued (Kaplowitz,2013). This idiosyncratic effect also could be happened to patients who reported in this case. Because all six patients had history of epilepsy and taking AED, all of them were administered with phenytoin loading dose in normal dose range. Neurocritical Care Society recommendation, may give an additional dose of 5 to 10 mg/kg 10 minutes after the loading dose. Hepatotoxicity that induced by AED was suspected because of reactive metabolite production and/or immune allergy reaction induction.

Hepatic necrosis with prominent inflammatory response occurred 1-8 weeks after phenytoin administration in 1 of 1000 patients who taking phenytoin as antiepileptic drug so that it was common known as idiosyncratic reaction. Formation of phenytoin reactive metabolite that followed by covalent binding could be associated with idiosyncratic toxicity through activation of immune response. Phenytoin reactive metabolite such as oxide arene and phenytoin catechol were the substance that could form complex with protein in hepatic microsomes and then processed by macrophage as antigen (Sasaki, 2013). It would stimulate immune response activation that would cause expression of FasL and TNF-α that could mediate hepatocyte cell death. Damage or injury of hepatocyte then could lead to elevation of hepatic enzyme (Yuan and Kaplowitz, 2013). Hepatocyte was completed with many kinds of mechanism to prevent or repair any damage. In some cases, toxicity could be minimalized in short time, however recurrent incident that lead to fibrosis eventually could danger the organ.

Major cellular response to drugs that potentially toxic was illustrated in picture below, where hepatocyte damage caused by toxic exposure repeatedly. So that cell could lead to apoptosis programmed cell death) or necrosis (uncontrolled cell death). Apoptosis could be beneficial when the goal was to eliminate damage cell without damage the surrounding tissue. Blocking of apoptosis often occurred in cancer cells. If toxic exposure was so severe, cell may encounter necrosis. Necrosis could be characterized by elevation of hepatic enzyme, cellular protein denaturation, and cell membrane disturbance. Meanwhile apoptosis cells could influence surrounding tissue damage by affecting surrounding health cells (David et al., 2010).

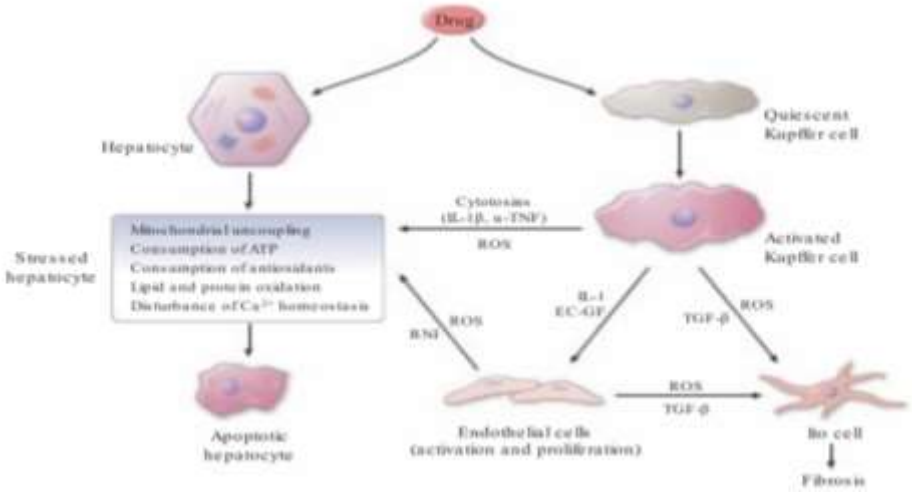

Figure 1. Hepatocyte Damage Mechanism at Subdose (David et al., 2010).

Generally, reactive metabolite formulation that followed by covalent binding could be associated with idiosyncratic toxicity through immune response mechanism. Main metabolic mechanism of

phenytoin was hydroxylation of phenytoin by CYP450 enzyme to form its phenol metabolite, that is 5-(p-hydroxyphenyl-),5-phenylhidantoin (HPPH). HPPH moreover could be oxidized to form phenytoin catechol. Phenytoin catechol was the one needed to form protein complex in hepatic microsome and forming phenytoin catechol mainly catalyzed by CYP2C19 and CYP2C9. Covalent binding formulation could be suppressed if there was antioxidants such as glutathione and cysteine in hepatic microsomes. So that based on that mechanism, it was assumed that phenytoin reactive metabolite which produced by CYP that bind covalently with hepatic protein was responsible to idiosyncratic toxicity induced by phenytoin. Liver injury that caused by covalent binding between phenytoin reactive metabolite with liver protein, moreover will stimulate the release of damage-associated molecular patterns (DAMPs), such as S100 protein and high-mobility group box 1 (HMGB1), then next will activate innate immune cell through toll-like receptors (TLRs) that will amplify or make liver injury worse. Cytokine and chemokine, followed by inflammation or infiltration of lymphocyte to hepatocyte, was involved in hepatotoxicity mediated by immune response and dominantly secreted by immune cell such as lymphocyte T and macrophage (Sasaki, 2013).

To determine maintenance dose of phenytoin, phenytoin level measurement in blood could be conducted after oral or IV administration. Based on phenytoin long half life time, serum level must be measured in five to seven days after administration of phenytoin to determine steady state of serum concentration in new maintenance dose. Like all antiepileptic drug, phenytoin dose must be guided especially for seizure and tolerability. Mostly, but not all, patient who have normal renal function and albumin serum level could be free of seizure without adverse effect with phenytoin serum concentration of 10 to 20 mcg/mL (40 to 79 micromole /L) (Caudle et al, 1986). Laboratory examination furthermore may be included liver function test and serum electrolyte urgently needed. Liver dysfunction will increase the risk of phenytoin toxicity and prolong intoxication effect by reducing metabolism rate. In patients with antiepileptic hypersensitivity syndrome, liver function test often showed elevation of aminotransferase (Engel, Mellul, Goodman, 1986). There was no significant correlation statistically between duration of phenytoin administration, phenytoin dose and serum concentration to liver enzyme conversion (Husein et al., 2013). The same result also was reported that there was no significant correlation statistically between phenytoin serum level to the risk of hepatotoxicity (Craig, 2005). On contrary (Perucca et al., 2004) concluded that hepatotoxicity was depended of phenytoin dose which induced liver enzyme. So did (Aiges et al., 1980) reported that elevation of AST and ALT temporary and there was no specific histopathology result as long as treatment with phenytoin and it did not cause hepatotoxicity, however it was more likely caused by effectiveness of induction liver enzyme. Beesmertny et al (2001) reported phenytoin hepatotoxicity as antiepileptic hypersensitivity syndrome that need termination of antiepileptic drug immediately if there was significant elevation of liver enzyme.

Other factors that also suspected causing hepatotoxicity in phenytoin usage was branded and generic product of phenytoin in the composition of phenytoin and other formulation characterization that influenced bioavailability (Soryal, 1992). The differences sometimes could cause elevation or reduction of phenytoin serum level (Mikati, Bassett, Schachte, 1992) that eventually influenced seizure recurrence or toxicity when patients used other branded product. Therefore, serum level was often measured and high clinical precaution may be needed when changing phenytoin formulation in patients with seizure that difficult to control or who insecure to adverse effect (Burkhardt, 2004).

IV. CONCLUSION

Hepatotoxicity that induced by phenytoin was idiosyncratic and no dose and duration dependent. Phenytoin was enzyme inducer and could cause conversion of liver enzyme level.

Phenytoin level measurement in blood was needed to conduct to plan the right dose of every patients to control recurrence seizure.

Liver function test before and after phenytoin administration was needed to acknowledge and plan treatment if hepatotoxicity was occurred. \

V. CONFLICT OF INTEREST

The author (s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this report.

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