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Adjustment of Phenytoin Dosage of Hypoalbuminemia Patients: A Review

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Abstract

Phenytoin is indicated for generalized tonic-clonic seizure, complex partial seizure (psychomotor, temporal lobes), and also preventing and treating the seizure that occurred during or after neurosurgery, with insignificant sedative effect and without hypnotic effect in high dose. Phenytoin acts as a sodium channel inhibitor by increasing the efflux and decreasing the influx of sodium ion that passing the membrane. Phenytoin has a high protein binding (90%), so hypoalbuminemia condition will affect the free drug amount in the body, while it is known that only drug that unbound by protein (free drug) who can pass through the membrane and reach its target. This causes an increasing plasma concentration and the risk of toxicity. Adjustment of phenytoin dosage is needed in this condition.

Keywords: Phenytoin, Dosage Adjustment, Hypoalbuminemia

1.0 INTRODUCTION

Phenytoin, diphenylhydantoin, is a selective sodium channel inhibitor (Chiosi et al., 2017), indicated for generalized tonic-clonic seizure, complex partial seizure (psychomotor, temporal lobes), and has approved by US Food and Drug Administration as the prevention and treatment for a seizure that occurred during or after neurosurgery (Brodie & Dichter, 1996; Perucca, 2005). Phenytoin is considered as a great antiepileptic drug with an insignificant sedative effect. Moreover, in a high dose, phenytoin does not induce any hypnotic effect (Vardanyan & Hruby, 2006).

Phenytoin had been used as an epilepsy treatment since the late 1930s, and still considered as one of the most prescribed antiepileptic drug, worldwide (Dale & Federman, 2007). Over time, the phenytoin is less preferred due to the competition from new antiepileptic drugs (Shanmugarajah et al., 2018). In 1985, besides of phenytoin, carbamazepine also appeared as first-line therapy in the USA. However, in Europe, carbamazepine is more preferred than phenytoin, whilst in the USA phenytoin is the preferable treatment for partial seizures and generalized tonic-clonic seizures (Wilder, 1995). On the other hand, some case studies had reported phenytoin related toxicity in patients, particularly the patients with hypoalbuminemia condition (Lindow & Wijdicks, 1994).

2.0 RESEARCH DISCUSSION

2.1 Phenytoin Mechanism of Action

Phenytoin is included as the first generation of antiepileptic drug with some mechanisms of action, such as sodium channel inhibitor (Dale & Federman, 2007; Cook & Bansalem-Owen, 2011). Phenytoin stabilizes the neuron membrane and reduces the seizure activity by increasing the efflux and decreasing the influx of sodium ion that passes through the cell membrane in the motoric cortex during neuronal impulse generation (Lacy et al., 2009). Phenytoin is expected to facilitating the sodium ion secretion from neuronal cells, that reduces the neuron stimulation. This, in turn, prevents the activation of neurons after receiving impulses from epileptogenic centres (Vardanyan & Hruby, 2006), extending the effective refractory period and suppressing the ventricular pacemaker automatically, and shortening the potential action in the heart (Lacy et al., 2009).

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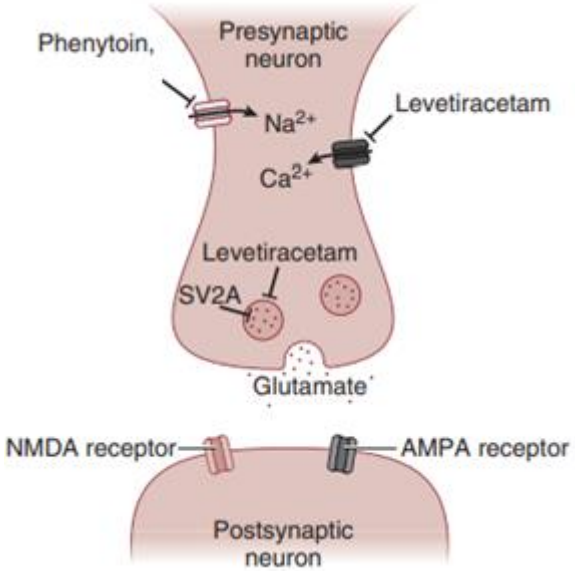

Figure I. Mechanis of action phenytoin inhibit presynaptic voltage-gated sodium channels (Goodman & Gilman, 2010)

2.2 Phenytoin Pharmacokinetics

Phenytoin (diphenylhydantoin) is a weak acid and has an erratic GI absorption (Miller, 2018). Phenytoin is usually administered as sodium salt or acid. The microcrystalline sodium salt is well absorbed. This form is more soluble than acid (Pryka et al., 1991). Phenytoin can be administered orally or intravenous (IV) or infusion for patients who cannot take an oral drug and/or patients who need rapid drug effect. Phenytoin absorption varies after intramuscular (IM) administration, so this administration (IM) is not allowed (Routledge & Hutchings, 2013).

Almost all drug administered orally are absorbed and most of them are metabolized in the liver. Phenytoin has a narrow therapeutic index and the relationship between the dose and serum concentration of phenytoin is non-linear (BNF, 2017). A little increased dose can produce a bigger plasma concentration proportionally, even within the plasma concentration therapeutic range. The half-life is varied and depended on its dose. Phenytoin is a strong enzyme inducer, has an interaction with the other drugs by increasing their clearance (Routledge & Hutchings, 2013).

Phenytoin therapeutic range is 10–20 mg/L (10-20 µg/ml) with the biggest potential toxic concentration is >20 mg/L (>20 µg/ml) (Routledge & Hutchings, 2013; BNF, 2017; Aldaz et al., 2011). Phenytoin absorption varies, with T_{max} ranges from 2 up to 12 hours (Dale & Federman, 2007). The therapeutic plasma concentration is achieved after 1-week treatment, while IV administration will reach its therapeutic plasma concentration after 1-2 hours (McEvoy & Snow, 2011).

The bioavailability of phenytoin is more than 90% with half-life ranges from 10 up to 60 hours dan is depended by its concentration. Phenytoin has a high protein binding proportion, up to 95%. Phenytoin can pass through the placenta and can be distributed in the breastmilk (McEvoy & Snow, 2011). So its administration in patients who are breastfeeding or pregnant needs to be reconsidered.

Phenytoin is metabolized by cytochrome P-450 system before being excreted in the urine and faeces (Dale & Federman, 2007). Phenytoin is transformed into its inactive metabolite, 5-(-p-hydroxyphenyl)-5-phenyl hydantoin (HPPH). This metabolism is a saturated process. Therefore, a small increase in phenytoin dose can produce a substantial increase in its plasma concentration. At the time of drug elimination, 5-(p-hydroxyphenyl)-5-phenyl hydantoin (HPPH) is excreted in the urine, mainly as glucuronide, around 60-75% of the daily dose (McEvoy & Snow, 2011).

2.3 Pharmacokinetic Changes in Hypoalbuminemia Condition

Hypoalbuminemia condition is a common problem of patients with an acute or chronic medical condition, defined as albumin serum level below 3.5 mg/dl. The reference range of albumin in the serum

is 3.5 – 5 mg/dl (Ganong, 2003). Albumin molecular weight is about 66 kDa and its half-life is 21 days. Albumin is exclusively synthesized by liver, from pre-proalbumin to proalbumin, that transformed into albumin in the Golgi apparatus, the final form that released from hepatocytes (Lenitt & MD, 2016).

Albumin acts as a protein binder and transporter of some substance, including drugs (Busher, 1990). Based on its binding to the protein, drugs in plasma are bound and unbound. The concentration of the unbound drug in steady conditions will determine the pharmacological effects both efficacy and toxicity because only drugs that are unbound to protein can penetrate the membrane and reach the target (Goodman & Gilman, 2010). In the hypoalbuminemia condition, the fraction of unbounded drugs will generally increase.

Phenytoin is a drug that is known to have high protein binding. So, patients with hypoalbuminemia condition will affect the amount of drug unbound to protein (the number of free drugs) in the body. For example, a change in drug-protein binding from 90 to 98% will double the free drug concentration, allowing faster clearance and broader distribution (Roberts et al., 2013). Moreover, phenytoin dosage adjustment is important since the therapeutic concentration of phenytoin is close to its toxic concentration (narrow therapeutic index) (Routledge & Hutchings, 2013).

A case study of critically ill patients with hypoalbuminemia condition (Kemper et al., 2007) reported that two patients, 35 and 60 years old, with albumin level <25 g/L had severe neurologic adverse events during phenytoin treatment without any dosage adjustment. A 35 years old patient admitted with spina bifida, a ventriculoperitoneal drain due to hydrocephalus, recurrent urinary tract infection, and the history of status epilepticus. This patient was experiencing disorientation, myoclonia, hallucinations and drowsiness during phenytoin treatment. And the other patient, 65 years old, suffered from diabetic ketoacidosis complicated by epileptic convulsions, received phenytoin treatment after coma. The toxic levels of free phenytoin were found: 4 and 8 mg/l, respectively, while the therapeutic range is 0.5-2 mg/l. The first patient recovered after the phenytoin treatment was stopped, and she was placed on a lower dose; the second patient died.

2.4 Adjustment of Phenytoin Dosage in Hypoalbuminemia Condition

The big amount of phenytoin protein binding with albumin requires the need to adjust the dose of the drug in patients with hypoalbuminemia condition. Phenytoin that is bounded to protein can not pass through the blood-brain barrier, only free active phenytoin can. Therefore phenytoin level needs to be corrected based on albumin level (Wu & Lim, 2013).

The adjustment of phenytoin dosage can use the equation below to correct the total phenytoin level based on albumin level compared to its target concentration range (10-20 mg/L) (Allison & Coulson, 2016; Glasgow & Clyde, 2019):

$$Corrected\ Phenytoin\ Level\ (mg/L) = \frac{\text{Reported level (mg/L)}}{(0.9 \text{ x serum albumin (g/L)}/42) + 0.1}$$

While hypoalbuminemia patients (<35 g/L) with reduced renal function (CrCl <20 ml/minutes) need dosage adjustment using this equation:

$$Corrected\ Phenytoin\ Level\ (mg/L) = \frac{\text{Reported level (mg/L)}}{(0.01 \text{ x serum albumin (g/L)}/42) + 0.1}$$

An error in the calculation should be noted due to the usage of the wrong unit for albumin. The laboratory often reports the value in g/L instead (g/dL = g/L x 0.1).

Beside dosage adjustment, there is a drug therapy monitoring study that tried to monitor the drug dose in the blood through measurement or prediction of free drug concentration in the body. But, it is hard to be applied due to the difficult technique and the high cost of this method. The monitoring of free phenytoin level in a critically ill patient with hypoalbuminemia condition had studied by Jayadi et al., using a method to calculate the free drug concentration but this calculation couldn't predict the accurate free phenytoin concentration in all patients, particularly in older patients. So Jayadi et al., concluded that not only drug therapy monitoring, drug dosage adjustment is important to the patients with hypoalbuminemia condition (Javadi et al., 2018).

It must be considered that the amount of phenytoin dose after the adjustment, in some patients may not reach its recommended reference range to achieve free seizure condition in the patients, but for other patients, it may show some adverse event related to its concentration (Wu & Lim, 2013). So, the clinicians who manage the patients need to pay more attention. It is not recommended to increase the dose of phenytoin in seizure-free patients even with low therapy levels. Instead, the dose must be reduced in patients who exhibit symptoms of phenytoin toxicity with "therapeutic" levels. This explains the importance of building individual therapy concentrations for different patients (Wu & Lim, 2013).

3.0 CONCLUSION

Adjustment of phenytoin dosage in hypoalbuminemia condition is an important step. This is due to the narrow therapeutic index of phenytoin; a small increase can produce toxicity. The dose of phenytoin in hypoalbuminemia conditions is estimated to be lower, but remains with the aim of seizure-free, while other patients may show side effects associated with that concentration.

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