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MONITORING OF ANTIEPILETIC DRUG'S (AED) ADVERSE EVENTS ON BONE

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ABSTRACT

Background: Epilepsy is still a major problem in pediatric neurology cases because epilepsy is a neurologic condition that related to social stigma, psychiatry comorbidities, and high cost. Antiepileptic treatment is a long term medication which often requiresa combination of some antiepileptic drugs (AED), so the adverse events of each AED need to be monitored. Recently, many clinicians concern about AED's adverse event on Vitamin D deficiency. Vitamin D has many roles in the human body, particularly on calcium and bone metabolism. **Results:** One of the AED's adverse events is affecting bone metabolism and potentially increase the risk of bone fracture. Based on WHO adverse drug reaction classification, this effect is included in type C category. **Conclusion:** Adverse drug events (ADE) is the main factor that contributes to the failure of the antiepileptic drug (AED) treatment.

KEYWORDS: Epilepsy, Antiepileptic drugs (AED), Drug's Adverse Effects, Bone.

INTRODUCTION

Epilepsy is still a major problem in pediatric neurology cases because epilepsy is a neurologic condition that related to social stigma, psychiatry comorbidities, and high cost.[1] Based on ILAE, epilepsy is a brain disorder characterized by enduring predisposition to generate epileptic seizure, with the neurobiological, cognitive, psychological, and social consequences of this condition, which consists of more than one epileptic seizure[2] Based on WHO, epilepsy is a neurologic disorder due to an abnormal and excessive neuronal electrical discharges.[3]

WHO reported that more than 50 million people worldwide have epilepsy. Globally, the incidence of epilepsy is estimated at up to 2.4 million people each year.[3] The incidences of epilepsy in children from different countries have shown a wide variation, approximately 4-6 of 1000 children, based on the study design and population's age. In Indonesia, there are 700.000 – 1.400.000 epilepsy cases with 70.000 new cases each year. It is estimated that 40 – 50% cases found in children.[4]

Antiepileptic treatment is a long term medication which often requires a combination of some antiepileptic drugs (AED), so the adverse events of each AED need to be monitored. Recently, many clinicians concern about AED's adverse event on Vitamin D deficiency. Vitamin D has many roles in the human body, particularly on calcium and bone metabolism. Besides, vitamin D deficiency also increases the risk of some diseases including cancer, autoimmune disease, hypertension, and infection. The prevalence of vitamin D deficiency in children has increased annually, particularly in epilepsy patients.[5]

DISCUSSION

The Pathophysiology of Epilepsy

The pathophysiology of epilepsy is diverse based on seizure disorder types. Generally, epilepsy arises from excitatory (through glutamatergic signaling) and inhibitory (through GABAergic signaling) imbalance in the synaptic level that generate epileptic seizure activity. An excessive spontaneous and synchronized neuronal excitation triggers epileptic seizure that produces the activation of general and focal motoric, sensory, autonom (saliva), or a complex cognitive function.[6]

A phenomenon that triggers the epileptic seizure is a paroxysmal depolarization shift due to Ca^{2+}-channel activation. An activity surge happens due to prolonged neuronal membrane depolarization. The opening of non-specific cation channel allow the influx of extracellular calcium (Ca^{2+}) that result in excessive depolarization which opens the sodium (Na^{+}) voltage-dependent channel, the influx of Na^{+}, generate many potential actions, and last, open the activated Ca^{2+} channel and K^{+}-Cl^{-} channel. This event is followed by hyperpolarization and mediated by γ-aminobutyric acid receptor (GABA) or Kalium (K^{+}) channel, based on the cell types (figure 1). An epileptic seizure occurs when there are enough excitated neurons to produce seizure.[6,7] In normal condition, synaptic excitation activity is strictly regulated by interneuron inhibitor. But, genetic mutation, trauma, and abnormal development can disturb this physiologic condition and resulting hyperexcitation of cortical tissue.[8]

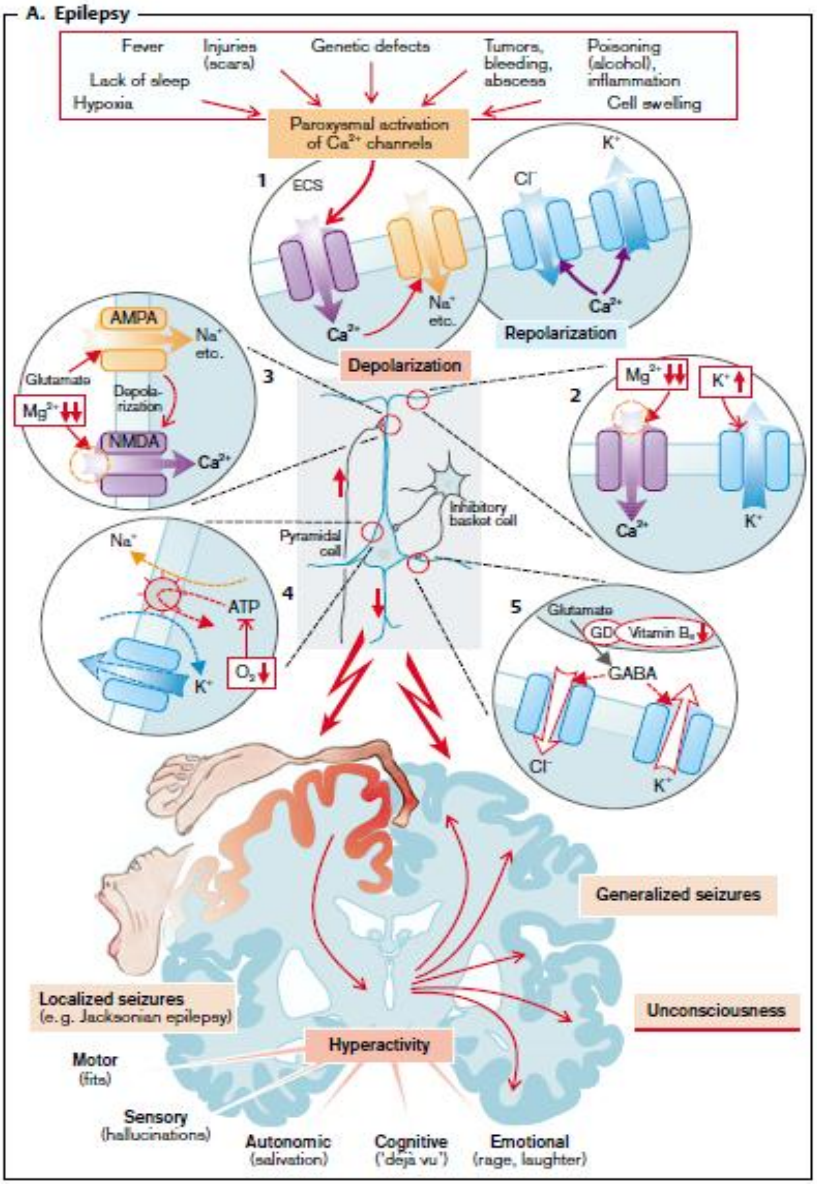

Figure 1: The pathophysiology of epilepsy.[6]

Management

Epileptic management consists of acute phase therapy called epileptic seizure medication and epilepsy treatment. The goals of acute phase management are maintaining adequate oxygenation in the brain, early termination of the convulsion, prevent recurrent convulsion, and investigate the risk factors.[9] The main objective of epilepsy treatment is optimizing the quality of life so the patient can live normally, without epileptic attack and with minimum adverse event.[10]

Generally, there are two treatment options for epileptic seizure, pharmacological and non-pharmacological treatment. Pharmacological treatment is the first line therapy to manage

epileptic seizure. In Indonesia, phenytoin, carbamazepine, phenobarbital, and valproic acid groups are the first line of antiepileptic drugs (AED).[10] The patients need to routinely take those drugs to prevent an epileptic seizure effectively. Despite epileptic seizure absence, AED should be continued if there isn't any sign of a severe adverse event or drug intoxication.[9]

Principally, AED start to be given as a monotherapy, in their lowest dosage that can manage convulsion. This initial dosage is gradually titrated until reaching the effective dosage or inducing adverse events. If the maximum dosage of the first AED failed to manage seizure, switch to another AED. This can be done while the first AED had reached its therapeutic level. The dosage of the first AED is tapered off. If there is a seizure when tapering off the first AED, give the second AED. If there is no adequate response, switch to another AED. Adding the third AED couldn't be done except if the previous maximum dosage AED combination failed to reach optimal response.[11,10,9]

Non-pharmacological therapies for epilepsy patients are surgery, vagal nerve stimulation, Deep Brain Stimulation, ketogenic diet, behavioral cognitive therapy, and biofeedback.[10] Surgery intervention is addressed to focal convulsion disorder that well located in non-critical brain area.[8] Meanwhile, vagal nerve stimulation is an adjuvant therapy to reduce seizure frequency in refractory epilepsy patients, both adult and children, that couldn't be operated. Vagal nerve stimulation is suitable for both focal and generalized seizure.[10]

Nutritional therapy with a ketogenic diet can be used for epileptic children who resistance to AED. Although anti-convulsion effects from a ketogenic diet haven't fully understood, stable ketosis can manage and control the convulsion.[12] A literature review by Seo et al demonstrated some promising yet limited ketogenic diet usage in epilepsy.[13] To optimally manage the convulsion, nutritional therapy should be combined with AED.[12]

Antiepileptic Drugs

In Indonesia, carbamazepine (CBZ), clobazam (CLB), clonazepam (CZP), phenobarbital (PB), phenytoin (PHT), and valproic acid (VPA) are the first line of antiepileptic drugs (AED).[14] How many times the patients should take these drug is depends on their half-life in plasma, and should be maintained as low as possible to achieve patient's adherence. AED are usually taken twice a day at their common dose. Phenobarbital and phenytoin have a long half-life, so they were given once a day at night. But if the AED need to be given in a higher

dose, they can be split three times a day to avoid any adverse event related to a high drug concentration in plasma.[10] When monotherapy failed to fulfill the patient need, the AED can be given as a combination therapy after considering the higher toxicity and possibility of any drug interaction.[15]

Table 1: AED choice based on seizure types.[10]

AED	Focal seizure	Secondary generalized seizure	Tonic-clonic seizure	Absence seizure	Myoclonic seizure
Phenytoin	+(A)	+(A)	+(C)	-	-
Carbamazepine	+(A)	+(A)	+(C)	-	-
Valproic acid	+(B)	+(B)	+(C)	+(A)	+ (D)
Phenobarbital	+(C)	+(C)	+(C)	0	?+
Gabapentin	+(C)	+(C)	?+(D)	0	?-
Lamotrigine	+(C)	+(C)	+(C)	+(A)	+-
Topiramat	+(C)	+(C)	+(C)	?	?+(D)
Zonisamide	+(A)	+(A)	?+	?+	?+
Levetiracetam	+(A)	+(A)	?+(D)	?+	?+
Oxcarbamazepine	+(C)	+(C)	+(C)	-	-
Clonazepam	+(C)	-	-	-	-

Level of evidence

A: effective as monotherapy; B: probably effective as monotherapy; C: possibly effective as monotherapy; D: potentially effective as monotherapy.

AED's Mechanism of Action

Some AEDs, including phenytoin, carbamazepine, lamotrigine, and oxcarbazepine, mainly act on sodium channels, to stabilizing their inactive state (figure 2). Recently, there are newer drugs, lacosamide, and eslicarbazepine acetate, that also gradually act on inactive sodium channel.[16]

These AED can be given as a combination therapy.[17] But, this combination potentially increases their adverse events such as lightheadedness, headache, fatigue, nausea, vomiting, diplopia, ataxia, and drowsiness. If this condition happened, the dosage of phenytoin, carbamazepine, oxcarbazepine, or lamotigrine should be reduced to manage convulsion with better tolerability.[16]

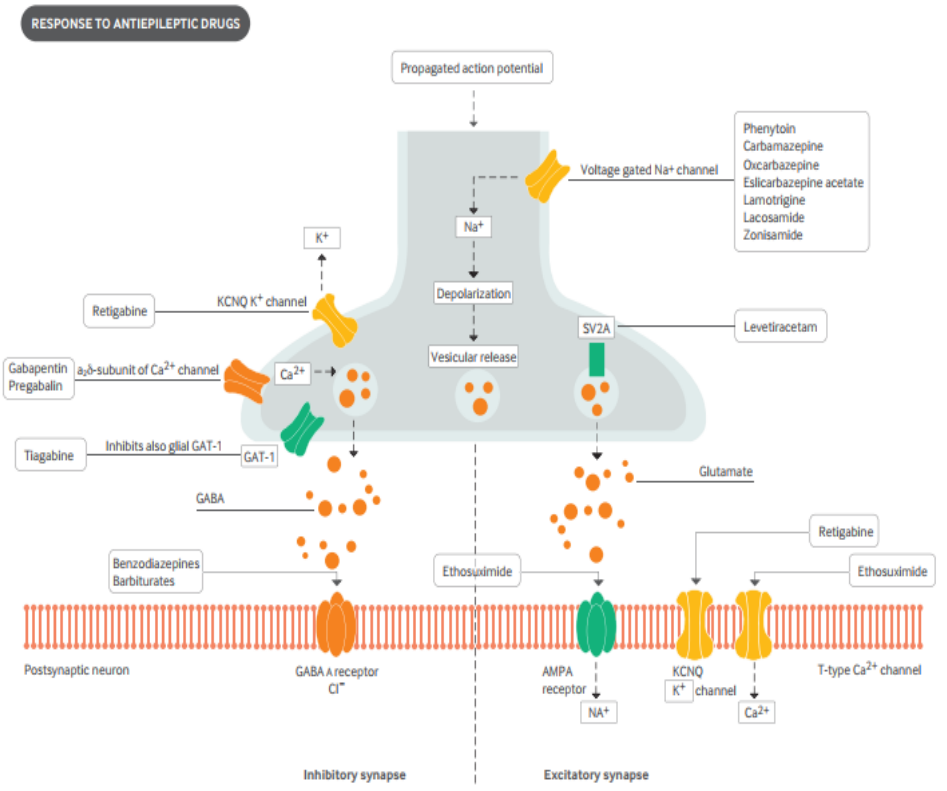

Fig 4|Mechanisms of action of antiepileptic drugs, which act by diverse mechanisms, mainly involving modulation of voltage activated ion channels, potentiation of GABA, and inhibition of glutamate.[27 30] Approved antiepileptic drugs have effects on inhibitory (left hand side) and excitatory (right hand side) nerve terminals. The antiepileptic efficacy in trials of most of these drugs as initial add-on does not differ greatly, indicating that seemingly similar antiseizure activity can be obtained by mechanisms aimed at diverse targets. However, putative mechanisms of action were determined only after discovering the antiseizure effects; mechanism driven drug discovery has been largely ignored.[9] Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; GABA, γ-aminobutyric acid; GAT-1, sodium dependent and chloride dependent GABA transporter 1; SV2A, synaptic vesicle glycoprotein 2A. Modified, with permission, from *Nature Reviews Neurology*.[28]

Figure 2: Antiepileptic drug's mechanism of action.[16]

Gabapentin and pregabalin shared the same action in inhibiting calcium channel, but pregabalin is absorbed easier and its pharmacological effect is better. These drugs can be used to treat neuropathic pain, restlessness, and also epilepsy patients with comorbidities.[18]

AED's Adverse Event on Bone

Adverse drug events (ADE) is the main factor that contributes to the failure of the antiepileptic drug (AED) treatment. 25% patients dropped out of therapy due to ADE. ADE also contribute to the patient's low adherence. Besides, ADE have a negative impact on patient's health and quality of life, and tend to cause some significant disabilities, morbidities, or mortalities.[19]

Furthermore, a and psychologic factor also play a role in ADE. Unstructured information and education delivering make the patients unaware of AED's adverse events so the rate of ADE tends to increase. Other factors which potentially affect ADE's reporting are the patient's background, comorbidity, and demographic character.[19] WHO classified adverse drug

reaction into five groups: type A (acute); type B (bizarre); type C (chronic); type D (delayed); and type E (secondary due to drugs interaction).

Based on WHO adverse drug reaction classification, AED's adverse event on bone metabolism and potentially increase the risk of bone fracture, are included in type C category. But, some diseases affecting epilepsy, in the corresponding amount and severity, can increase the risk of bone fracture.

In the refractory cases, ketogenic diet (KD) which is high in fat, low in carbohydrates and protein, can be used. The ketogenic diet was thought can reduce convulsion frequency because it changed compound composition in the brain. But, this therapeutic strategy isn't recommended for adult patients with a history of diabetes or cardiovascular disease. The bone health can be assessed by measuring: bone density (particularly calcified matrix density), bone growth and size, and biochemical dimension from bone turnover and calcitropic hormones.[20]

Mechanism of AED's Adverse Event on Bone

Previously, AED was thought can affect bone health by inhibiting vitamin D metabolism. But, non-inducer AED was shown to has the same effect causing the bone disorder. It is found that there is no significant association between the risk of fracture and vitamin D metabolite level. Some studies revealed how AED affecting the bone: decreasing bone density through a direct effect on bone signaling (for example in phenytoin), or indirect effect through liver enzyme induction by some AED.[18]

Liver enzyme induction can increase vitamin D degradation, resulting in functional vitamin D deficiency and secondary hyperparathyroidism. Carbamazepine can affect bone metabolism through liver enzyme induction, it potentially alters vitamin D metabolism resulting in low vitamin D level. Phenytoin has both a direct toxic effect on bone and decreasing vitamin D level via liver enzyme induction.[18]

The main target of some AED are ion channels expressed by osteoblast and osteocyte, including some voltage-gated ion channels. Ion channels are involved in bone stress and strain transmission. Although osteocyte is considered as a major bone binder, osteoblast also plays a role in responding to mechanical stress. Osteoblast has many ion channels, including hyperpolarization and osmolarity, 6 voltage-gated sodium channels (NaV).[21]

Monitoring the Adverse Events

Before prescribing any drug, the adverse event profile should be adjusted to the patient's individual characteristic. After choosing the most suitable drugs, there are some steps to prevent and minimize complication. At the initial therapy and dosage escalation, clinical monitoring to identifyany adverse event potential needs to be routinely conducted. If there is any adverse event, the physician should solve it.

To achieve successful therapy, the physician and the patient need to collaborate in some treatment aspects, start from choosing the suitable AED until early identify any intoxication sign. To avoid new-onset symptoms or symptoms that arise from conscious or unconscious advice from a physician, it should be noted that epilepsy patients are stressed and susceptible to any misconception due to literal interpretation, ambiguity, or unclear communication.[19]

Prevention strategy to Minimize Adverse Drug Event

After choosing the most suitable AED, start them with the lowest dose, titrate gradually, reach the lowest effective therapeutic dosage, and apply dosage scheme appropriately to minimize adverse drug event.[10] For the patients with low adherence, the physician needsan additional strategy to reduce pessimism and minimize intoxication risk of AED, including the assurance of tolerability and new treatment safety. Start with a low dose and titrate with lower speed than usual.

Prevention strategies to minimize adverse drug event are start the therapy with a low dose and titrate gradually, choose the most suitable drug formulation[10], inform and educate the patients about the appropriate treatment, monitor the drug plasma level and dose-depended adverse event, particularly for drug with narrow therapeutic index and/or non-linear kinetics such as phenytoin or carbamazepine. Early identification of drug interaction can save a life. And the most important thing is to inform the patients and their family about the adverse drug event and report it if there is any of them to the doctor or pharmacist.[19]

CONCLUSION

Adverse drug events (ADE) is the main factor that contributes to the failure of the antiepileptic drug (AED) treatment. But, this problem can be minimized by starting the therapy with a low dose and titrate gradually, choosing the most suitable drug formulation, monitoring the drug plasma level, then informing and educating the patients and their family about the adverse drug event and report it if there is any of them to the doctor or pharmacist.

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