Seizures, Antiepileptic Drugs, and CKD

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There are 2 major categories of patients with seizures and chronic kidney disease (CKD): patients who develop acute symptomatic seizures in the setting of CKD and patients with epilepsy who at some point develop CKD. The incidence of uremic seizures with kidney failure is ~10%. These seizures are often nonconvulsive and may mimic uremic encephalopathy. Recognition and management of such situations may be challenging for treating physicians who are non-neurologists. Furthermore, practitioners caring for patients with seizures with or without an established diagnosis of epilepsy in the setting of CKD frequently encounter challenges in the selection, loading, titration, and maintenance of antiepileptic drugs (AEDs) due to potentially altered pharmacokinetics of the AEDs. We review the pathophysiology of uremia, uremic seizures, and other neurologic complications of kidney failure; management approaches to the treatment of such complications; the relevant mechanisms of action and pharmacokinetics of AEDs with their use in CKD; and in particular, the management of AEDs in patients requiring hemodialysis therapy.

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Case Vignette: *A 65-year-old man with end-stage kidney disease on hemodialysis (HD) therapy is brought to the emergency department with confusion, lethargy, perseverative speech, and myoclonic jerking of his extremities. He had missed dialysis the previous week. Examination reveals a disheveled, thin, and lethargic man. He occasionally scratches himself. He is oriented only to self. Heart rate and rhythm are regular, and he is breathing comfortably. There is irregular, subtle, but excessive eyelid movement, more pronounced on the left. His limbs have mildly increased tone and brisk reflexes throughout, with intermittent irregular myoclonic jerks of all 4 extremities. His plantar response is extensor. The patient's serum urea nitrogen level is 80 mg/dL, and serum creatinine level is 5.1 mg/dL. He is found to have periodic triphasic waves on electroencephalography, raising concern for possible status epilepticus.*

Introduction

With a growing elderly population and worsening vascular disease, kidney disease has become a serious health problem in the United States and throughout the world. This condition may lead to diverse neurologic manifestations, such as myoclonus (sudden involuntary jerky movements resulting from brief bursts of muscle activity), asterixis (ie, "negative myoclonus," which results from brief involuntary loss of muscle contraction), chorea (brief, random, flowing irregular movements from one body part to another), uremic encephalopathy, and ultimately seizures. In addition, patients with an established diagnosis of epilepsy and chronic kidney disease (CKD) can encounter challenges in the loading, titration, and maintenance of their antiepileptic drugs (AEDs) due to altered pharmacokinetics, including rapid decreases in serum drug levels after HD. These issues can also lead to breakthrough seizures.

There are 2 major categories of patients with seizures and CKD: patients who develop acute symptomatic seizures in the setting of CKD and patients with epilepsy who at some point develop kidney disease. In this review, we discuss both categories of patients, as well as the relevant pathophysiology and AED pharmacokinetics, mechanisms of action, and management.

Epilepsy

Epilepsy was conceptually defined as a brain disorder in which there is an ongoing predisposition to generate unprovoked seizures.[1] The most recent definition by the International League Against Epilepsy (ILAE) in 2014 added a practical definition requiring: (1) occurrence of at least 2 unprovoked epileptic seizures more than 24 hours apart, or (2) occurrence of 1 unprovoked seizure and a likelihood of additional seizures in the subsequent 10 years that is comparable to the general risk for recurrence (≥60%) following 2 unprovoked seizures, or (3) diagnosis of an epilepsy syndrome.[2]

An epileptic seizure (henceforth referred to as "seizure") is a "transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain."[2(p 476)] In the past decade, there has been much debate about the classification of seizures. Briefly, according to the most recent ILAE classification, seizures can be generalized or focal in origin. Generalized seizures can be absence, myoclonic, atonic, tonic, and tonic-clonic. Focal seizures include focal aware seizures (previously known as simple partial seizures), focal impaired awareness seizures (previously known as complex partial seizures), focal motor or nonmotor seizures, and focal to bilateral tonic-clonic seizures.[3]

For the purposes of this review, the cause of epilepsy may have relevance insofar as particular AED therapy may be affected by decreased kidney function. In brief, there are multiple causes, including genetic,[3] structural due to irreversible changes in brain cells,[4,5] infectious,[6] metabolic, and

autoimmune causes (due to autoantibodies in the central nervous system as in encephalitides associated with NMDA (N-methyl-D-aspartate),[7,8] gamma-aminobutyric acid class A ($GABA_A$)[9] or class B ($GABA_B$) receptors,[10] and leucine-rich glioma inactivated 1 (LGI1), a protein associated with voltage-gated potassium channels[11]).

Acute Symptomatic (Provoked) Seizures in CKD

The prevalence of epilepsy is ~1% worldwide,[12] and the lifetime prevalence of a single unprovoked seizure is 9%.[13] The prevalence of CKD stages 1 to 5 is ~15% (stage 3 being most common).[14] It is unknown whether the prevalence of epilepsy is higher in patients with CKD in comparison to the general population; however, the incidence of seizures with chronic kidney failure is ~10%.[15] Notably, about one-third of patients with uremic encephalopathy develop acute symptomatic, that is, provoked, seizures.[13,16]

In this light, a crucial distinction must be made. A provoked seizure, such as one caused by uremia, is defined as a "reactive seizure" or "acute symptomatic seizure" when due to a transient factor that acts on an otherwise normal brain to cause the seizure threshold to be temporarily decreased. Such a seizure does not meet criteria for a diagnosis of epilepsy.[2] Examples of agents or conditions that can cause an acute symptomatic seizure include alcohol, barbiturate, or benzodiazepine withdrawal; metabolic changes such as acute uremia; hyponatremia; hypoglycemia; concussion; fever; sepsis; and drugs of abuse.

The phenotype of uremic seizures can be variable: myoclonic, simple focal motor and nonmotor seizures with impaired awareness, absence seizures, and in late stages, generalized tonic-clonic seizures.[17] Myoclonic seizures must be distinguished from intermittent uremic myoclonus by myoclonic contractions of the limbs with accompanying electroencephalogram epileptiform discharges. Status epilepticus, whether convulsive or nonconvulsive (absence or focal), is frequent,[16] although its exact incidence has not been reported. Nonconvulsive status epilepticus is particularly difficult to discern clinically (see the case vignette). Therefore, one must maintain a low clinical threshold for bedside electroencephalography, brain imaging, and neurologic consultation for uremic patients with acute persistent severe encephalopathy.

There are multiple potential causes of seizures in the setting of kidney disease and in particular uremia. Kidney failure leads to accumulation of uremic toxins that are known to cause neurologic complications, including encephalopathy, myoclonus, and eventually seizures. No one isolated uremic compound (or at any given concentration) is recognized to be a singular cause of seizures, but rather a combination of toxins, especially when their accumulation is rapid. Of the identified organic compounds responsible for uremic encephalopathy, the metabolites of creatinine (guanidino compounds) are thought to be particularly proconvulsant due to their putative inhibition of GABA receptors and stimulation of excitatory NMDA receptors in the brain. This action leads to the influx of calcium into neurons.[18-20] Parathyroid hormone has also been implicated in its role of facilitating calcium influx.[17,20] The resultant imbalance of excitatory (AMPA [α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid] and NMDA) and inhibitory (GABA) tone causes enhanced cortical excitability.[21]

Electrolyte disturbances are expected in CKD and are also important in the pathophysiology of uremic seizures. In particular, dysglycemia, hyponatremia, hypernatremia, hypomagnesemia, hypocalcemia, and acid-base disturbances are associated with seizures in uremic encephalopathy.[16,22] Studies in rat models done in the 1980s showed the importance of the potassium ion in epileptic seizure initiation. It was found that by increasing the extracellular content of potassium, neuronal hyperpolarization decreased.[23,24] Lowering the extracellular concentration of calcium or magnesium caused depolarization of neuronal membranes and epileptiform activity.[25,26] Overall, changes in extracellular ionic concentrations have an important influence on voltage-gated ion channels, potentially contributing to the genesis of seizures.[23,25,26] Rarely, acute seizures may occur in the setting of dialysis disequilibrium syndrome, which is characterized by transient encephalopathy, usually precipitated by rapid dialysis or after a skipped dialysis session. According to the reverse urea hypothesis, it is thought to be caused by relatively more rapid clearance of urea from plasma compared to the brain, although the exact cause is not known.[19,22,27] Fortunately, this syndrome is rare today due to improved dialysis techniques.[19,22] Air embolism is another rare but serious complication of HD that may also cause acute seizures.[28]

Posterior reversible encephalopathy syndrome (PRES) is another important and likely under-recognized cause of acute symptomatic seizures in CKD.[22,29] It may develop in the setting of uncontrolled hypertension or immunosuppressant use, as well as other factors. PRES is accompanied by seizures in 60% to 75% of patients[22] and often includes lethargy and cortical visual disturbances. It is thought to occur due to failure of vascular autoregulation that results in extravasation and vasogenic edema in the posterior cerebral circulation.[23] Poor adherence to diet recommendations and excessive fluid intake are common predisposing factors because they can lead to uncontrolled hypertension. Immunosuppressants (tacrolimus and cyclosporine) used by kidney transplant recipients can predispose them to the development of PRES with accompanying seizures.[23,30,31] These seizures usually resolve with adequate control of blood pressure, but may require acute management with phenytoin or levetiracetam.

There are important comorbid conditions of kidney disease that should be considered. Treatment of anemia with recombinant human erythropoietin was once believed to be a risk factor for seizures[32]; however, this

Table 1. Pharmacokinetics of Major Antiepileptic Drugs

Drug	Protein Binding	Metabolism	Major AED Interactions	Urinary Excretion[a]	Reported Nephrotoxicities	Reference Range, mg/L[b]
Brivaracetam	Weak	Hydrolysis	Slightly ↓ carbamazepine; ↑ carbamazepine-10,11 epoxide, phenytoin	>95%	None reported	—[c]
Carbamazepine	70%-80%	Hepatic (CYP450); has autoinducer abilities	↓ carbamazepine, clobazam, ethosuximide, lamotrigine, felbamate, lacosamide, levetiracetam, oxcarbazepine, primidone, pregabalin, topiramate valproic acid, phenytoin, perampanel, zonisamide	—[d]	AHS w/ interstitial nephritis; hyponatremia	4-12
Clobazam	86%	Hepatic (CYP3A4)	↑/↓ phenytoin	94%	None reported	0.03-0.3
Ethosuximide	0%	Hepatic (CYP3A4)	↓ valproic acid, phenobarbital, phenytoin, primidone; ↑ primidone; increased by valproic acid	20%-25%	Drug-induced SLE, including renal involvement consistent w/ LN	40-100
Felbamate	25%	Hepatic (CYP3A4)	↑ carbamazepine-10,11 epoxide, clonazepam, lamotrigine, phenobarbital, phenytoin, valproic acid; ↓ carbamazepine, vigabatrin	40%-50%	Kidney stones are rarely reported	30-60
Eslicarbazepine	40% (active MHD metabolite *S*-licarbazepine)	Hydrolysis	↓ lamotrigine, topiramate, valproic acid; ↑ phenytoin	92%	Hyponatremia	3-35
Gabapentin	0%	None	↓ pregabalin; ↑ felbamate	80%-95%	Peripheral edema; toxicity may mimic uremic symptoms	2-20
Lacosamide	<15%	Hepatic (CYP450)	↓ 10-hydroxycarbozepine	40%	Single reported case of nephritis	10-20
Lamotrigine	50%-55%	Hepatic	↓ clonazepam, levetiracetam, valproic acid; increased by valproic acid	10%	AHS w/ interstitial nephritis	2.5-15
Levetiracetam	<10%	Hydrolysis	None	66%	Hypokalemia; hypomagnesemia	12-46
Oxcarbazepine	40% (active MHD metabolite)	Hepatic	↓ carbamazepine, lamotrigine, levetiracetam, rufinamide, topiramate; Increases phenobarbital, phenytoin	50%	Hyponatremia	3-35[e]
Perampanel	95%	Hepatic (CYP3A4)	↓ carbamazepine, clobazam, midazolam, lamotrigine, valproic acid; ↑/↓ oxcarbazepine	2%	None reported	0.05-0.4 (50-400 μ/L)
Phenobarbital	55%	Hepatic (CYP450)	↓ carbamazepine, clobazam, ethosuximide, lamotrigine, felbamate, lacosamide, levetiracetam, oxcarbazepine, primidone, pregabalin, topiramate, valproic acid, phenytoin, zonisamide	25%[f]	AHS w/ interstitial nephritis; anemia; hypovitaminosis D	10-40
Phenytoin	90%; binding decreases in uremia	Hepatic (CYP450)	↓ carbamazepine, clobazam, ethosuximide, lamotrigine, felbamate, lacosamide, levetiracetam, oxcarbazepine, primidone, pregabalin, topiramate, valproic acid, zonisamide; ↑ phenobarbital	<5%	AHS w/ interstitial nephritis; Inhibitor of ADH release	10-20
Pregabalin	0%	None	↓ tiagabine	>95%	Peripheral edema; toxicity may mimic uremic symptoms	—[c]
Rufinamide	34%	Hydrolysis	↓ carbamazepine, lamotrigine; ↑ phenobarbital, phenytoin	4%	None reported	10-40

(Continued)

Table 1 (Cont'd). Pharmacokinetics of Major Antiepileptic Drugs

Drug	Protein Binding	Metabolism	Major AED Interactions	Urinary Excretion[a]	Reported Nephrotoxicities	Reference Range, mg/L[b]
Topiramate	20%	Variable[g]	↓ valproic acid; ↑ phenytoin	60%-70%	Renal tubular (metabolic) acidosis; nephrolithiasis ($CaPO_4$)	5-20
Valproic acid	90%; Binding decreases in uremia	Hepatic (CYP450)	↓ topiramate; ↑ free fraction phenytoin, diazepam, carbamazepine-10,11 epoxide, felbamate, lamotrigine, lorazepam, midazolam, phenobarbital, rufinamide, ethosuximide; increased by felbamate; decreased by ethosuximide, AED inducers	1%-3%	Tubulointerstitial nephritis; Fanconi syndrome; hyponatremia	50-100
Vigabatrin	0%	Not metabolized	↓/↑ carbamazepine; ↓ phenytoin, rufinamide	70%-80%	None reported	0.8-36
Zonisamide	40%-60%	Hepatic (CYP450)	↑ carbamazepine-10,11 epoxide	30%-35%	Renal tubular (metabolic) acidosis; nephrolithiasis ($CaPO_4$)	10-40

Note: Content based on information in Bansal et al (2015),[12] Asconapé (2014),[41] Israni et al (2006),[45] Diaz et al (2012),[13] Patsalos et al (2008),[48] and Patsalos and Bourgeois (2013).[104]

Abbreviations: ADH, antidiuretic hormone; AED, antiepileptic drug; AHS, antiepileptic hypersensitivity syndrome; CYP450, cytochrome P450; LN, lupus nephritis; MHD, monohydroxy derivative; SLE, systemic lupus erythematosus.

[a]Urinary excretion refers to excretion of unchanged drug.

[b]These values are only an estimate of a range at which the majority of patients showed an optimal response in studies (see Patsalos et al, 2008[48]).

[c]Not established.

[d]Negligible.

[e]Pharmacokinetic parameters, reference range, and conversion factor refer to the active MHD metabolite.

[f]Wide variability.

[g]May depend on coadministration of other AEDs.

association has been questioned.[33] Sepsis predisposes patients to the development of acute seizures due to disruption and increased permeability of the blood-brain barrier,[34] as well as long-term seizures after hospital discharge.[35] Because of their potential to cause cortical irritability, certain antibiotics used in the treatment of sepsis, such as penicillins, cephalosporins, carbapenems, and quinolones, may also generate seizures in kidney failure.[23] Cefepime in particular has recently been implicated in neurotoxicity and seizures, including when undergoing renal dosing.[36]

Last, vascular causes of seizures in patients with CKD deserve attention. In CKD, there is a higher incidence of stroke,[37] which may cause acute symptomatic seizures.[38] Subdural hematomas, which are a significant risk factor for acute seizures, have a much greater incidence in long-term dialysis patients compared to the general population. Subdural hematomas can be caused by coagulopathy during HD, as well as uremic platelet dysfunction and decreased subdural cavity pressure during HD.[39,40]

The management of acute uremic seizures consists of reversal of the pathogenic process when possible, which would often be by HD treatment. The decision to start treatment with an AED after a single provoked seizure depends on whether the patient has a high risk for seizure recurrence. In the context of CKD and its complications, the risk for recurrence may be increased short term, and AED treatment initiation is warranted. However, a neurologist should advise as to whether the risk for seizure recurrence in an individual patient is sufficiently high to continue long-term AED management. The choice of AED coverage for acute symptomatic seizures may vary based on the underlying cause, comorbid conditions, and other contributing factors. There is no single AED that would be considered first-line therapy for every patient; however, levetiracetam, phenytoin, valproic acid, and lacosamide are typically good options for initial monotherapy with appropriate dosing adjustments as needed, as discussed later. For example, in our case vignette, the patient was found to have severe encephalopathy that ultimately evolved into status epilepticus. After 2 brief courses of treatment with valproic acid and subsequent readmissions for nonconvulsive seizures, the patient was ultimately started on long-term levetiracetam therapy with good seizure control.

AEDs in Patients With Epilepsy and CKD

Overview

In patients with epilepsy and CKD, it is very important to have a good understanding of the pharmacokinetics and properties of each drug and its metabolites, particularly because most of the new AEDs undergo renal clearance. In terms of day-to-day management, a few key concepts must be recognized.

First, dose reduction may be required when a parent drug or active metabolite is excreted at least 30% unchanged in urine. Additionally, clearance of the drugs by HD may require post-HD dosing because the dialyzability of a drug depends on its protein-binding properties and molecular size. These issues are discussed next, as well as in Tables 1 and 2.

Second, the apparent volume of distribution of highly protein-bound drugs may increase depending on the protein-binding level, which is decreased in uremia. There are a number of suspected causes of this phenomenon, primarily the common hypoalbuminemic state, but also accumulation of inhibitors in serum, alteration of the albumin molecule, and other possible contributing factors.[41] Regardless of the cause, it is advisable to monitor free serum levels for highly protein-bound drugs such as phenytoin and valproic acid because their total serum concentration may be low, whereas the unbound fraction concentration is essentially unchanged.[41]

Third, uremic toxins may downregulate cytochrome P450 (CYP450) systems, which may affect AED metabolism.[13] However, this effect may rarely be of clinical significance due to a large hepatic reserve capacity.[41] Of more importance are the interactions between certain AEDs due to their metabolism by the CYP450 systems. These interactions are addressed in Table 1 and in the following text.

Phenytoin (Dilantin)

Phenytoin has been used for the treatment of generalized and focal seizures for more than 80 years. It has been falling out of favor due to its long-term side effects, such as osteoporosis and adverse lipid profile.[42,43] However, it is still a first-line AED for status epilepticus. Phenytoin's primary mechanism of action is voltage- and use-dependent inhibition of voltage-gated sodium channels resulting in stabilization of the channels' inactivated state, ultimately leading to a decrease in glutamate release and enhancement of GABA release.[44] It is metabolized by the CYP450 system and is a well-known enzyme inducer that may decrease levels of other hepatically metabolized drugs. The major metabolite of phenytoin is 5-(*p*-hydroxyphenyl)-5-phenylhydantoin glucuronide, which accumulates in kidney failure. However, it is inactive and of no clinical significance.[41] Of note, phenytoin has been associated with interstitial nephritis, sometimes with antiepileptic hypersensitivity syndrome.[12,45] Phenytoin has nonlinear elimination, which may lead to rapid increases in serum levels to higher than the therapeutic range when dosing is increased too rapidly. Less than 5% of phenytoin is excreted in urine; therefore, there is no need to adjust the dose in CKD. However, post-HD seizures may require supplementation.[12] In serum, 90% of phenytoin normally binds to albumin and thus only 10% is free and biologically active. However, in kidney disease, the unbound fraction may be as high as 30%, although without an actual absolute increase in free level.[41] Therefore, only the free level of phenytoin should be used to guide treatment in CKD because total levels may be lower than expected.

Fosphenytoin is a water-soluble prodrug of phenytoin and may be used in the acute setting instead of phenytoin because it has lower risk for phlebitis and potential cardiotoxicity. One notable property of fosphenytoin is that one of its metabolites can accumulate in kidney failure and cause a falsely elevated phenytoin level due to cross-reactivity in laboratory assays.[46]

Phenobarbital

Phenobarbital is used to treat focal and generalized seizures. It is a very effective drug and was a staple AED for decades before the release of newer medications. Its major drawback is sedation and high potential for withdrawal seizures. The mechanism of action is positive allosteric regulation of the barbiturate-binding site of the $GABA_A$ receptor.[47] It is metabolized mainly in the liver by the CYP450 system to inactive metabolites and is itself an inducer. About 55% is protein bound and ~25% is excreted through the kidney; therefore, it may require dose adjustment at a glomerular filtration rate (GFR) < 10 mL/min/1.73 m^2.[12,48,49] In patients undergoing HD or peritoneal dialysis, one may consider supplemental dosing. However, there is no consensus on precise supplementation values because there is considerable variability in renal excretion within the range of 20% to 50%.[45,48] Therefore, it is best to monitor serum levels and dose accordingly (Table 1).

Primidone (Mysoline)

Primidone is indicated in focal and generalized seizures. It is partially protein bound at <10% to 30%[41,49] and is metabolized by the liver to phenobarbital and another less active metabolite phenylethylmalonamide.[49] Primidone provides similar efficacy to phenobarbital and therefore has been used in the treatment of epilepsy; however, its use as an AED has declined markedly in recent years. Decreased kidney function can cause significant accumulation of primidone because 15% to 40% is excreted unchanged by the kidney.[41] HD removes about 20% to 50% of the drug, and a 30% supplemental dose should be given before HD or a full dose after HD.[50,51]

Carbamazepine (Tegretol)

Carbamazepine is one of the oldest AEDs used to treat focal and secondarily generalized seizures, as well as trigeminal neuralgia, neuropathic pain, and bipolar disorder. Its mechanism of action is similar to that of phenytoin. It is 70% to 80% protein bound and metabolized in the liver by CYP450 3A4 (CYP3A4) to an active epoxide metabolite, which is further metabolized to inactive metabolites and excreted into urine. About 1% of carbamazepine is excreted through the kidney; therefore, no adjustment is needed for HD patients.[12] In cases of carbamazepine toxicity, HD may reduce the drug's serum level by 22% to 50%.[41] However, carbamazepine normally has relatively

Table 2. Dose Adjustments for AEDs in Kidney Disease

AED	GFR > 60	GFR 30-59	GFR 15-29	GFR < 15	Hemodialysis
Brivaracetam	50-100 mg 2×/d	No adjustment needed	No adjustment needed	No adjustment needed	No adjustment needed
Carbamazepine	200-800 mg 2×/d	No adjustment needed	No adjustment needed	No adjustment needed	Supplemental dose not needed
Clobazam	20-40 mg daily	No adjustment needed	No adjustment needed	No adjustment needed	Supplemental dose not needed
Eslicarbazepine	800-1,600 mg daily	No adjustment needed	600 mg daily max	600 mg daily max	Not established; may need supplemental dose
Felbamate	1,200-3,600 mg	50% dose reduction	Insufficient data, reduce dose by 50%; use w/ caution	Insufficient data, reduce dose by 50%; use w/ caution	Insufficient data, avoid
Gabapentin	300-1,200 mg 3×/d	200-700 mg 2×/d	200-700 mg daily	100-300 mg daily; use w/ caution	100%-200% daily dose post-HD
Lacosamide	50-200 mg 2×/d	No adjustment needed	Slow titration; max 300 mg daily	Slow titration; max 300 mg daily	50% daily dose as post-HD supplement
Lamotrigine	50-250 mg 2×/d	Dose reduction may be needed; use w/ caution	Dose reduction may be needed; use w/ caution	Dose reduction may be needed; use w/ caution	Consider post-HD supplemental dose
Levetiracetam	500-1,500 mg 2×/d	50% dose reduction	50% dose reduction	50% dose reduction	500-1,000 mg daily & 50% daily dose as post-HD supplement
Oxcarbazepine	300-1,200 mg 2×/d	No adjustment needed	Initiate at 1/2 of usual daily dose	Initiate at 1/2 of usual daily dose	Insufficient data; may monitor levels[a]; proceed w/ caution
Perampanel	4-12 mg daily	Not established; likely no adjustment needed	Not established; likely no adjustment needed	Not established; likely no adjustment needed	Not established; supplementation likely not needed
Phenobarbital	60-100 mg 2×/d or 3×/d	Use w/ caution; dose reduction may be needed	Use w/ caution; dose reduction may be needed	Use w/ caution; dose reduction may be needed	Consider 50% of daily dose in PD & as post-HD supplement
Phenytoin	150-200 mg 2×/d or 3×/d	Oral loading dose not needed; otherwise no change	Oral loading dose not needed; otherwise no change	Oral loading dose not needed; otherwise no change	Oral loading dose not needed; otherwise no change
Pregabalin	600 mg max daily	50% dose reduction	25-150 mg daily	25-75 mg daily	Replacement dose 25-150 mg post-HD
Rufinamide	200-1,600 mg 2×/d based on weight	No adjustment needed	No adjustment needed	No adjustment needed	30% supplemental dose post-HD
Tiagabine	32-56 mg	No adjustment needed	No adjustment needed	No adjustment needed	Supplemental dose not needed
Topiramate	100-200 mg 2×/d	50% dose reduction	50% dose reduction	50% dose reduction	50% daily dose as post-HD supplement
Valproic acid	30-60 mg/kg/d 2×/d to 3×/d	No adjustment needed	No adjustment needed	No adjustment needed	Supplementation usually not given; high-flux dialysis may remove the drug
Vigabatrin	1,000-3,000 mg daily	25% dose reduction	50% dose reduction	75% dose reduction	50% supplemental dose post-HD
Zonisamide	100-600 mg daily	No adjustment needed	Unclear, use w/ caution	Unclear, use w/ caution	Give daily after HD; 50% supplemental dose may be needed for post-HD seizures

Note: Adapted with permission of the copyright holder, Wiley Periodicals, from Bansal et al 2015.[12] Additional content based on information in Israni et al (2006)[45] and Diaz et al (2012).[13]

Abbreviations: AED, antiepileptic drug; GFR, glomerular filtration rate (in mL/min/1.73 m^2); HD, hemodialysis; max, maximum; MHD, monohydroxy derivative; PD, peritoneal dialysis.

[a]Pharmacokinetic parameters, reference range, and conversion factor refer to the active MHD metabolite.

low extractability, and there is no need for supplemental dosing. Carbamazepine is an autoinducer and therefore can enhance its own metabolism, as well as that of warfarin, oral contraceptives, digoxin, corticosteroids, tacrolimus, and cyclosporine.[52] Common hepatic inhibitors such as macrolides and valproic acid increase its levels, potentially leading to toxicity.[52] Similar to other hepatic inducers, it worsens lipid levels.[42,43] Carbamazepine is associated with interstitial nephritis and hyponatremia. The mechanism of the latter is still unclear but thought to be due to syndrome of inappropriate antidiuretic hormone secretion, enhanced sensitivity of the collecting duct to vasopressin, or a reset osmostat.[12] Sodium concentration should be monitored at the start of treatment and after 3 months in patients with severely decreased kidney function, the elderly, or those who take medications that alter sodium concentrations.[45] There are also reports of acute granulomatous interstitial nephritis and tubulointerstitial nephritis.[12]

Oxcarbazepine (Trileptal)

Oxcarbazepine is structurally similar to carbamazepine and is used primarily to treat focal seizures. It is metabolized in the liver and is pharmacologically active through its monohydroxy metabolites (MHD), R- and S-licarbazepine, with the latter having a mechanism of action that is similar to carbamazepine's but with a much superior adverse-effect profile.[53]

About 40% of the MHD metabolite is protein bound, and ~50% is excreted in urine. Consequently, a 50% dose reduction is recommended with GFRs < 30 mL/min/1.73 m^2 (Table 2).[41] This medication is a much weaker CYP450 inducer compared to carbamazepine, but it is also a weak inhibitor of CYP2A9, which may increase phenytoin levels. There is a smaller risk for interstitial nephritis compared to carbamazepine; however, there is increased likelihood of hyponatremia, which is typically asymptomatic.[45,54,55]

Eslicarbazepine (Aptiom)

Ninety-five percent of eslicarbazepine acetate is rapidly and extensively metabolized to the S-enantiomer S-licarbazepine, which is also the metabolite of oxcarbazepine. Its plasma protein binding is ~40% and it is eliminated primarily by renal excretion.[56] Therefore, a reduced dose is needed with GFRs < 50 mL/min/1.73 m^2 (Table 2). Because this medication is effectively removed by HD, supplementation with a full dose has been recommended.[13]

Valproic Acid (Depakote)

Valproic acid is one of the oldest AEDs used to treat focal and generalized seizures (particularly status epilepticus and genetic generalized epilepsy) and bipolar disorder and is also used as a prophylactic medication for migraine. Blockade of voltage-gated sodium and calcium channels and enhancement of GABAergic systems are among its mechanisms of action.[12] It is metabolized by the liver, is 90% protein bound, and has increased free serum levels in uremia. Less than 3% is excreted in urine; therefore, no dose adjustment is required with reduced kidney function. Interestingly, some valproic acid is removed during HD; however, this effect on the available drug level is relatively brief because valproic acid redistributes back into the blood from tissues, and plasma levels increase again in a few hours.[57] Valproic acid has been shown to lead to tubulointerstitial nephritis, Fanconi syndrome, hyponatremia, hepatic failure, and hyperammonemic encephalopathy.[12]

Levetiracetam (Keppra)

Levetiracetam is used for treatment of focal and generalized seizures. During the past few years, it has become one of the most popular first-line AEDs due to its efficacy and tolerability. It binds to synaptic vesicle protein SV2A (synaptic vesicle glycoprotein 2A), which is a component of the neurotransmitter-containing secretory vesicle membrane involved in controlling its exocytosis[58,59] by rendering primed synaptic vesicles fully calcium responsive.[60] Levetiracetam's interaction with SV2A is considered to be the basic mechanism of its antiepileptic action.[61] It has also been shown to mediate cellular calcium homeostasis by blocking ryanodine- and IP3- (inositol trisphosphate) receptor–dependent calcium release from endoplasmic reticulum[62] and inhibit calcium entry by blocking L (long-lasting)–type[63] and N (non-L)–type voltage-gated calcium channels.[64] Last, levetiracetam modulates AMPA receptors,[65] which may also result in an antiepileptic effect.

Levetiracetam has minimal hepatic metabolism, is not dependent on the CYP450 system, and has minimal protein binding. About two-thirds of it is excreted unchanged in urine. Because its half-life increases from 7 to 25 hours if GFR is <15 mL/min/1.73 m^2, dose adjustment is vital. During HD, ~50% of levetiracetam is removed, thereby requiring a supplemental dose after HD[12] (Table 2).

Brivaracetam (Briviact)

Brivaracetam is used in the treatment of focal and generalized seizures. The main mechanism of action is the same as that of levetiracetam, but with 15- to 30-fold higher affinity for the SV2A protein. Brivaracetam's inhibition of voltage-dependent sodium channels was found in experimental studies[66]; however, it was shown to be ineffective at reducing neuronal firing, rendering this activity clinically irrelevant.[67] Brivaracetam showed faster entry into the brain than levetiracetam, which correlated with quicker activity against seizures in audiogenic susceptible mice.[68]

Brivaracetam has low protein binding of ~17.5% and is metabolized by the liver to inactive metabolites, which are primarily excreted through the kidney; only 5% to 8% of the drug is excreted unchanged.[69] It has very weak CYP3A4 activity and therefore does not need renal dosing or a supplemental dose after HD.[13,69]

Topiramate (Topamax)

Topiramate is used in the treatment of focal and generalized seizures. Mechanisms of action include inhibition of kainate/AMPA-type glutamate receptors, and voltage-gated sodium channels to limit sustained repetitive firing, enhancement of GABA-mediated chloride flux at $GABA_A$ receptors, and reduction of high threshold voltage-gated calcium currents. It also weakly inhibits carbonic anhydrase isoenzyme II and IV, enzymes that may modulate pH-dependent activation of voltage and receptor-gated ion channels.[70]

Topiramate undergoes hepatic metabolism affected by the presence of other drugs that interact with hepatic enzymes. Only ~20% of topiramate is protein bound and 40% to 80% of the drug is excreted unchanged, depending on whether it is given as monotherapy or together with enzyme-inducing AEDs. HD decreases the topiramate concentration by 50% and supplemental dosing is recommended at 50% of the daily dose.[12,45] Topiramate causes nephrolithiasis and mild metabolic acidosis due to inhibition of carbonic anhydrase. Some studies showed that topiramate-related nephrolithiasis was due to inadequate urinary acidification, with pH > 6.10, and hypocitraturia, which has been shown to increase the risk for calcium stone formation.[71,72] These patients may benefit from citrate supplementation.[73]

Zonisamide (Zonegran)

Zonisamide is a sulfonamide derivative used for treating focal and generalized seizures. It blocks repetitive firing of voltage-gated sodium channels, which leads to a reduction of T-type calcium channel currents. It has also been reported as a neuroprotective agent.[74,75] It is metabolized by the CYP450 system to form an inactive metabolite. It does not interact with other AEDs. Zonisamide is 40% to 60% protein bound, with higher affinity for erythrocytes. About 30% is excreted in urine unchanged[41]; therefore, no adjustments are needed for patients with mild to moderate kidney failure. However, there are limited studies on the clearance of zonisamide.[12,75] After HD, a 50% reduction in serum concentration has been reported, and supplementation may be needed[12,76] (Table 2). Zonisamide is a weak carbonic anhydrase inhibitor, similar to topiramate, and can also cause nephrolithiasis.[75]

Lacosamide (Vimpat)

Lacosamide is a popular AED used in the treatment of partial and generalized seizures. It acts by inactivation of slow voltage-gated sodium channels and does not interfere with fast inactivation,[77,78] although this has been recently questioned with a finding that it binds to inactivated states of fast sodium channels in a manner similar to other AEDs, but with slower kinetics.[79] It is metabolized by the CYP450 system and ~40% is excreted in urine. At GFRs < 30 mL/min/1.73 m^2, the dose should be adjusted with a limit of 300 mg daily. HD removes ~50% of the serum concentration, and a 50% dose supplementation is recommended[12,41,80] (Table 2).

Lamotrigine (Lamictal)

Lamotrigine is used in the treatment of partial and generalized seizures, as well as bipolar disorder. The primary mechanism of action is similar to that of phenytoin and carbamazepine. It also produces dose-dependent inhibition of high-voltage-gated calcium currents possibly through inhibition of presynaptic N-, P (Purkinje)-, and Q-type calcium channels.[81] It is metabolized in the liver to an inactive metabolite and is ~55% protein bound. Ten percent is excreted in urine unchanged,[41,82] and HD removes 17% to 20%.[12,83] Caution needs to be used when coadministering other hepatically cleared AEDs (Table 1). The literature is inconsistent regarding renally adjusted dosing or post-HD supplementation[12,41,45,83,84]; therefore, therapeutic drug monitoring has been recommended, as well as consideration of dose adjustment and post-HD supplementation.[85,86] Because lamotrigine is partially dialyzable, although the range of its clearance is variable, it would be prudent to monitor levels and adjust doses accordingly (Table 1).

Gabapentin (Neurontin) and Pregabalin (Lyrica)

Gabapentin is used in the treatment of focal and generalized seizures. The mechanism of action is due to the inhibition of P-, Q-, and N-type voltage-gated calcium channels at the presynaptic membrane.[87] It has minimal protein binding, a low volume of distribution, and is excreted entirely by the kidney; therefore, gabapentin clearance during dialysis is high, and supplemental dosing is required[12] (Table 2). In CKD, gabapentin level increases quickly given the exclusive renal excretion, which can lead to side effects that mimic uremic encephalopathy, such as myoclonus and somnolence; hence the need for adjusted dosing (Table 2). Gabapentin is also known to cause peripheral edema.[12,41]

Pregabalin's pharmacology is very similar to that of gabapentin because both have high renal excretion, low or negligible protein binding, and low volume of distribution.[12] It also requires dose adjustment in kidney disease, as well as post-HD supplementation[12,41] (Table 2).

Felbamate (Felbatol)

Felbamate is rarely used today and almost exclusively in severe refractory epilepsy due to potentially serious adverse effects, including aplastic anemia and hepatic failure. The primary mechanism of action is believed to be open channel blockade of the NMDA receptors and to an associated strychnine-insensitive glycine receptor, which inhibits sodium and calcium excitatory currents.[88-90] Felbamate is metabolized by the CYP450 system to weakly active and inactive metabolites. It is ~20% protein bound, and 50% is excreted in urine unchanged. Clearance decreases with low GFRs[91] and therefore initial and maintenance dosing should be decreased by ~50% in

CKD,[45] with a caveat that there is insufficient data to guide precise adjustments. Monitoring serum levels is prudent (Table 1). Of note, urolithiasis has been reported with this drug.[92]

Ethosuximide (Zarontin)

Ethosuximide is only used for treating absence seizures. Its mechanism of action is to reduce low-threshold T-type calcium current in thalamic neurons.[93] It is metabolized by the liver to an inactive metabolite. Ethosuximide is not protein bound and about 20% is excreted into urine unchanged; therefore, an adjustment may be needed in patients with GFRs < 30 mL/min/1.73 m^2, guided by monitoring of serum levels.[41] Ethosuximide can be removed by peritoneal dialysis and HD,[94,95] which prompts 50% dose supplementation.

Tiagabine (Gabitril)

Tiagabine is used as an adjunctive therapy in focal seizures but has minimal current use. The mechanism of action is GABA reuptake inhibition.[96] It is extensively metabolized by the CYP450 system and is a highly protein-bound molecule. Only ~1% is excreted in urine; therefore, dose adjustments in patients with CKD are not necessary.[45]

Vigabatrin (Sabril)

Vigabatrin is used in the treatment of refractory focal seizures and as monotherapy in infantile spasms. The mechanism of action is by irreversible inhibiting of GABA transaminase.[97] Vigabatrin is not significantly metabolized or protein bound and is 70% to 80% eliminated by the kidneys as unchanged drug.[13,98,99] The dose should be adjusted based on the patient's creatinine clearance.[97,100] HD can remove up to 60% of the drug; therefore, a 50% supplemental dose should be administered after HD[13,97] (Table 2).

Rufinamide (Banzel)

Rufinamide is used in the treatment of focal seizures and the drop attacks of Lennox-Gastaut syndrome. The main mechanism of action is believed to be inhibition of voltage-gated sodium channels by stabilizing the inactive state.[101] It is ~34% protein bound and is extensively metabolized by hydrolysis to a renally excreted inactive metabolite. In HD, ~30% of rufinamide is removed, and a 20% to 30% supplemental dose should be given.[13]

Perampanel (Fycompa)

Perampanel is used in the treatment of focal and generalized seizures. It is a highly selective noncompetitive AMPA-type glutamate receptor antagonist,[102,103] which makes it a unique AED presumably limiting excitatory drive in neurons. It is primarily metabolized by the CYP3A4 system and ~95% is bound to plasma proteins. Approximately 2% of the dose is renally excreted unchanged; therefore, HD does not require supplementation.[104]

Benzodiazepines (Clonazepam, Diazepam, Lorazepam, Midazolam)

1,4-Benzodiazepines are used for treatment of many types of seizures, primarily status epilepticus. They all bind to the benzodiazepine site of the $GABA_A$ receptor and increase its opening frequency, thus increasing GABA currents and promoting inhibition of neurons.[105] They are primarily metabolized by the liver and are highly protein bound. Their metabolites are renally excreted, and only a small percentage of the administered dose is excreted unchanged. Therefore, patients with kidney disease do not require a dosing adjustment. Note that is made of active metabolites of diazepam, which may accumulate in kidney disease, but the effect does not seem to be clinically significant.[41,105,106]

Clobazam (Onfi)

Clobazam can be used for the treatment of many types of seizures and is approved in the United States for the treatment of Lennox-Gastaut syndrome. It is a long-acting 1,5-benzodiazepine that differs structurally from the classic 1,4-benzodiazepines,[107] such as those listed above, and is slightly less sedating. Clobazam is metabolized by the CYP450 pathway and is ~90% protein bound. The main metabolite is N-desmethylclobazam, which is also active and is also metabolized by the liver. It has been shown that there is no accumulation of clobazam in kidney disease, and no supplementation is needed.[13]

Case Review and Conclusions

Patients with end-stage kidney disease may develop seizures and other neurologic manifestations as described in our case vignette. There should be a low clinical threshold for suspecting a seizure in an acutely encephalopathic patient receiving HD regardless of whether the patient has a history of epilepsy. The choice of an AED depends on seizure type, pharmacokinetics, degree of kidney disease, other comorbid conditions, and the clinician's comfort level with a particular drug. The patient in our case vignette serves as an example of a situation in which long-term AED management was ultimately needed for recurrent nonconvulsive seizures, initially with valproic acid and then with levetiracetam.

In management of established patients with epilepsy and end-stage kidney disease receiving HD, particular vigilance is required with regard to AED renal clearances, as well as drug interactions, activity of metabolites, and potential for AED renal toxicity.

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