

## Treating Seizures in Renal and Hepatic Failure

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### ABSTRACT

**Introduction:** Renal and hepatic diseases cause seizures and patients with epilepsy may suffer from such diseases which change antiepileptic drugs (AEDs) metabolism. **Objectives:** To revise how seizures may be caused by metabolic disturbances due to renal or hepatic diseases, by their treatment or by comorbidities and how AEDs choice might be influenced by these conditions. **Results:** Seizures arise in renal failure due to toxins accumulation and to complications like sepsis, hemorrhage, malignant hypertension, pH and hydroelectrolytic disturbances. Hemodialysis leads to acute dysequilibrium syndrome and to dementia. Peritoneal dialysis may cause hyperosmolar non-ketotic coma. Post-renal transplant immunosuppression is neurotoxic and cause posterior leukoencephalopathy, cerebral lymphoma and infections. Some antibiotics decrease convulsive thresholds, risking status epilepticus. Most commonly used AEDs in uremia are benzodiazepines, ethosuximide, phenytoin and phenobarbital. When treating epilepsy in renal failure, the choice of AED remains linked to seizure type, but doses should be adjusted especially in the case of hydrosoluble, low-molecular-weight, low-protein-bound, low apparent distribution volume AEDs. Hepatic failure leads to encephalopathy and seizures treated by ammonium levels and intestinal bacterial activity reductions, reversal of cerebral edema and intracranial hypertension. Phenytoin and benzodiazepines are usually ineffective. Seizures caused by post-hepatic immunosuppression can be treated by phenytoin or levetiracetam. Seizures in Wilson's disease may result from D-penicillamine dependent piridoxine deficiency. Porphyria seizures may be treated with gabapentin, oxcarbazepine and levetiracetam. Hepatic disease changes AEDs pharmacokinetics and needs doses readjustments. Little liver-metabolized AEDs as gabapentin, oxcarbazepine and levetiracetam are theoretically more adequate. **Conclusions:** Efficient seizures treatment in renal and hepatic diseases requires adequate diagnosis of these disturbances and their comorbidities besides good knowledge on AEDs metabolism, their pharmacokinetic changes in such diseases, careful use of concomitant medications and AEDs serum levels monitoring.

**Key words:** Seizures, antiepileptic drugs, pharmacokinetics, renal failure, hepatic failure, hemodialysis, immunosuppression.

### RESUMO

#### *Tratamento de crises epilépticas na insuficiência renal e na insuficiência hepática*

**Introdução:** Doenças renais e hepáticas causam crises epilépticas e pacientes com epilepsia podem sofrer doenças renais e hepáticas modificadoras do metabolismo das drogas antiepilépticas (DAEs). **Objetivos:** Rever como crises epilépticas podem ser causadas pelas alterações metabólicas próprias às doenças renais e hepáticas, pelo tratamento das mesmas e de suas comorbidades e de que forma a escolha das DAEs é influenciada por estas condições. **Resultados:** Crises surgem na insuficiência renal associadas ao acúmulo de toxinas e complicações como sepse, hemorragias, hipertensão maligna, distúrbios de pH e hidroletrolíticos. A hemodíalise associa-se a síndrome do desequilíbrio agudo e a demência. A diálise peritoneal pode conduzir ao coma hiperosmolar não-cetótico. A imunossupressão pós-transplante renal é neurotóxica e predispõe a leucoencefalopatia posterior, linfoma cerebral e infecções. Alguns antibióticos baixam o limiar convulsivante, com risco de estado epiléptico. As DAEs mais utilizadas na uremia incluem benzodiazepínicos, etossuximida, fenitoína e fenobarbital. Ao tratar-se epilepsia na insuficiência renal, a escolha da DAE permanece função do tipo de crise, mas as doses devem ser ajustadas, sobretudo no que tange às DAEs hidrosolúveis, de baixo peso molecular, pouco ligadas a proteínas e de baixo volume de distribuição aparente. A insuficiência hepática conduz a quadros de encefalopatia que geram crises, tratados pela redução dos níveis de amônia e da atividade bacteriana intestinal, reversão de edema cerebral e de hipertensão intracraniana. DAEs como fenitoína e benzodiazepínicos são quase sempre ineficazes. Imunossupressores pós transplante hepático causam crises tratadas sobretudo com fenitoína ou levetiracetam. Crises na doença de Wilson resultam de deficiência de piridoxina dependente de D-penicilamina. Pacientes com porfiria podem se beneficiar de gabapentina, oxcarbazepina ou levetiracetam. A doença hepática altera a farmacocinética das DAEs, demandando reajuste de suas doses. DAEs pouco metabolizadas pelo fígado como gabapentina, vigabatrina e levetiracetam são em teoria mais adequadas aqui. **Conclusão:** O tratamento eficaz das crises epilépticas nas doenças renais e hepáticas requer adequado diagnóstico destes distúrbios e de suas comorbidades, além de conhecimento do metabolismo das DAEs, de suas alterações farmacocinéticas nestes contextos, uso cauteloso de medicamentos concomitantes e monitoramento dos níveis séricos das DAEs.

**Unitermos:** Crises, drogas antiepilépticas, farmacocinética, insuficiência renal, insuficiência hepática, hemodíalise.

Renal and hepatic failure are known to be associated with seizures caused either by these disturbances themselves and their complications or by their treatment and treatment of comorbidities.<sup>3,27,33,42</sup> Furthermore, patients suffering from epilepsy may develop renal or hepatic diseases.<sup>44</sup> In this case, choice of antiepileptic drugs (AEDs) is still primarily guided by seizure type, but attention should be paid to changes in pharmacokinetics which diminish drug elimination, as well as to seizure aggravation by certain drugs in these particular conditions.<sup>3,8,21,27,28,32</sup>

### TREATING SEIZURES CAUSED BY RENAL FAILURE

One third of patients presenting with uremic encephalopathy shows various types of seizures – myoclonic, simple partial motor (including epilepsia partialis continua), complex partial, absence and generalized tonic-clonic seizures. Convulsive and non-convulsive (absence or partial complex) status epilepticus are not infrequent.<sup>3,11,33</sup> Seizures derive from accumulation of toxic organic acids and from uremic complications such as malignant hypertension, subdural and intracranial hemorrhage due to clotting defects, sepsis, glucose, hydroelectrolytic and acid-basic disturbances, that should be promptly recognized and corrected.<sup>3,42</sup> Another cause of seizures is reversible posterior leukoencephalopathy syndrome, also characterized by headache, clouding of sensorium and visual disturbances.<sup>23</sup> Patients with renal disease, hypertensive disturbances, malignancy and those submitted to transplantation (see below) are particularly prone to this condition. Adequate renal failure management, including hypertension control, volume control and renal replacement therapy should be started.<sup>23</sup>

### TREATING SEIZURES CAUSED BY RENAL REPLACEMENT TREATMENT

Hemodialysis may be associated to seizures produced by dialysis disequilibrium syndrome. This is due to a more rapid clearance of medium molecules from the blood than from the cerebrospinal fluid (CSF), giving rise to an osmotic gradient and brain edema. Modern dialysis methods have made this rare. Chronic dialysis encephalopathy or dementia may also produce seizures. This was linked to the use of aluminum in the dialysis fluids. Ceasing the use of aluminum has also made this condition rare.<sup>3,33,42</sup>

Peritoneal dialysis is related to seizures in the particular context of non-ketotic hyperosmolar coma arising from glucose fast exchanges and are easily avoided by monitoring the dialysis glucose content.<sup>3,33,42</sup>

Renal transplantation is followed by immunosuppression with cyclosporine, prednisone, OKT3 or tacrolimus. As a consequence, these patients are prone to developing primary cerebral lymphoma, posterior leukoencephalopathy, bacterial,

mycobacterial and fungal infections.<sup>13,33</sup> No prophylactic antiepileptic drug is recommended for cerebral lymphoma. Treatment comprises methotrexate, corticosteroids and radiotherapy.<sup>13</sup> Posterior leukoencephalopathy improves with immunosuppressants ceasing.<sup>23</sup> Infections of course will be treated by specific pharmacological agents. In all these instances, AEDs should be introduced for seizure control. Direct neurotoxic effects are most common with cyclosporin and are dose-dependent.<sup>8</sup> Use of enzyme-inductor AEDs may diminish immunosuppressant levels and cause rejection.<sup>8,26,29,34,43</sup>

Bacterial infections treated by antibiotics like penicillins, cefepime and the quinolones lead to seizures and are associated to convulsive and non-convulsive status epilepticus in the renal patient as these agents decrease the convulsive threshold. Beta-lactam antibiotics, for instance, are known to have molecular structures similar to biccuculine, which is a gabaergic antagonist. Moreover, the active transport of antibiotics from the CSF to blood is competitively inhibited by accumulated organic acids, causing increased antibiotics concentrations in the CSF.<sup>1,30,40</sup>

In clinical practice, AEDs most often used when treating seizures related to uremia are: benzodiazepines for myoclonic seizures, convulsive and non-convulsive partial complex or absence status epilepticus, ethosuximide, for absence status epilepticus, phenytoin and phenobarbital, for convulsive status epilepticus.<sup>24</sup> On the other hand, some AEDs should be employed with caution. Gabapentin was shown to worsen myoclonic seizures in terminal stage renal disease.<sup>46</sup> There are reports on acute tubular necrosis following sodium valproate use and Fanconi's syndrome<sup>2,25</sup> so that urinary sediment monitoring is advised. Topiramate should be used with caution in patients with previous history of nephrolithiasis.<sup>5,17,18</sup> Phenytoin may require dose adjustment, for accumulation of phenytoin to toxic levels generates paradoxical seizures. If severe hypoalbuminemia is present (either in renal or hepatic disease), a possible approach is to calculate the corrected phenytoin level, according to the formula  $PHT_{corrected} = PHT_{measured} / [(albumin * 0.2) + 1]$ . Charcoal hemoperfusion, high-flux dialysis and molecular adsorbents recirculating system (MARS) have been reported to correct phenytoin intoxication in hypoalbuminemic settings.<sup>14,37</sup>

### TREATING EPILEPSY IN PATIENTS WITH CONCOMITANT RENAL FAILURE

As in other situations, choice of AED lays primarily on the type of seizure to be treated. Nevertheless, renal insufficiency disturbs the pharmacokinetics of AEDs extensively eliminated by the kidneys, therefore leading to increased half-lives and drug accumulation. Albuminuria and metabolic acidosis decrease albumin serum levels as well as its binding affinity, increasing the drug free level,

but also its apparent volume of distribution (Vd) and plasmatic clearance.<sup>19,27</sup> On the other hand, gastroparesis delays maximum serum levels of AEDs and intestinal edema diminishes their absorption. Decreased intestinal cytochrome P450 metabolism and glycoprotein active transport result in more AEDs entering the portal circulation.<sup>19,28</sup> The different degrees of impact of each one of these processes leads to a non-linear difficult-to-predict drug accumulation, that is to say, creatinine clearance can not surely predict what the new AEDs half-lives will be. Thus, therapeutic levels are obtained through a loading dose followed by decreased doses or larger interval of administration.<sup>19</sup> AEDs extensively eliminated by the kidneys are hydrosoluble, of low molecular weight, low Vd and little protein-bound molecules, such as gabapentin, topiramate, ethosuximide, vigabatrin and levetiracetam.<sup>16</sup> These accumulate in renal disease. They are also easily removed by hemodialysis and need post-hemodialysis administration.<sup>16,45</sup> More lipophilic high protein bound AEDs like carbamazepine, phenytoin, lamotrigine, benzodiazepines and valproate are little affected by renal disease.<sup>12,16,19,45</sup> Hemodialysis have little impact on carbamazepine, phenytoin and valproate levels, whereas it has unpredictable effects on either benzodiazepines or on the oxcarbazepine monohydroxi derivative. A four-hour hemodialysis session decreases lamotrigine serum levels by about 20%.<sup>8,45</sup> Peritoneal dialysis bears variable effects upon AEDs serum levels, free levels being needed for drug adjustment.<sup>12,19,45</sup> Table 1 summarizes main changes in pharmacokinetics and effect of hemodialysis on AEDs.

**Table 1.** Antiepileptic drugs, pharmacokinetics and regimen changes, and hemodialysis.

AED	PK and Regimen changes	HD
Phenytoin	↓1/2 life, administer q8h	0
Phenobarbital	↑1/2 life, ↓dose, ↑interval	Largely removed. Supplement after HD.
Valproate	↓dose if levels ↑ >10%	? Monitor levels.
Carbamazepine	0	0
Oxcarbazepine	0?	Effect on monohydroxi?
Lamotrigin	0	↓levels by 20% in 4h
Gabapentin	↑1/2 life, ↓dose, ↑interval	Largely removed. Supplement after HD.
Topiramate	↑1/2 life, ↓dose, ↑interval	Largely removed. Supplement after HD.
Vigabatrin	↑1/2 life, ↓dose, ↑interval	Largely removed. Supplement after HD.
Levetiracetam	↑1/2 life, ↓dose, ↑interval	Largely removed. Supplement after HD.
Ethosuximide	0	Largely removed. Supplement after HD.
Benzodiazepines	0	0

## TREATING SEIZURES CAUSED BY HEPATIC FAILURE

Acute or chronic hepatic failure leads to encephalopathy progressing from euphoria and depression (stage I) to coma (stage IV). Generalized tonic-clonic or non-convulsive seizures and satus usually develop in stages III to IV.<sup>15</sup> Theories explaining hepatic encephalopathy comprise on one hand an increase in cerebral ammonium levels which are not converted to urea due to hepatocytes disease or to the existence of a porto-caval shunt and, on the other hand, the presence of excitatory neurotransmitters deriving from intestinal amines and by-passing the liver. Treatment of seizures in this condition consists of reducing ammonium levels and intestinal bacteria activity through low protein diet and administration of lactulose or neomycin per os.<sup>3,26,42</sup> If cerebral edema and intracranial hypertension develop, hyperventilation should be undertaken up to attaining a blood PCO<sub>2</sub> between 32 and 40 mmHg,<sup>31</sup> and mannitol administrated in order to maintain osmolality under 320 mOsm.<sup>27,38</sup> If these measures fail, barbiturate sedation and hypothermia can be employed.<sup>38</sup> Use of AEDs such as phenytoin or benzodiazepines is usually ineffective. One controlled study looked at the effect of prophylactic phenytoin in patients suffering acute hepatic failure versus those not receiving this treatment. No benefit was verified among patients receiving phenytoin and seizures were seen in equal proportions in both groups, often preceding death.<sup>7</sup> One must bear in mind that the sedative effect of benzodiazepines and phenobarbital may itself precipitate encephalopathy. Patients submitted to hepatic transplantation are prone to seizures caused by immunosuppressants toxicity.<sup>8,26,29</sup> In such cases, phenytoin appears as the most used AED. Levetiracetam may be successful when phenytoin fails.<sup>9,35,36</sup>

Wilson's disease rarely causes seizures. More often, these are precipitated by D-penicillamine-dependent pyridoxine deficiency. Pyridoxine reposition in a rate of 25 mg/d is indicated and the use of another copper chelator may be needed, such as triethylene tetramine or ammonium tetrathiomolybdate. Zinc blocks intestinal absorption of copper and can also be used. Hepatic transplantation can be successful in treating Wilson's disease with severe neurological impairment.<sup>26,41</sup>

Treating seizures occurring in porphyrias is very defying, as many AEDs induce hepatic metabolism and increase heme synthesis. Weak enzyme-inductors such as oxcarbazepine and non-inductors, like gabapentin or levetiracetam may be helpful. Porphyria attacks are treated by infusions of heme and glucose. Diazepam sometimes contributes to initial seizure control, then becoming soon ineffective.<sup>10,20,27</sup>

HELLP syndrome (hemolysis, elevated liver enzyme levels, low platelet count) and eclampsia belong to a

spectrum of pregnancy diseases with microangiopathic hemolytic anemia, hepatic necrosis, thrombocytopenia and seizures. Termination of pregnancy and use of magnesium sulfate to prevent seizures are indicated.<sup>39</sup>

### TREATING EPILEPSY IN PATIENTS WITH CONCOMITANT HEPATIC FAILURE

AEDs metabolism is impaired in hepatic disease either due to hepatocyte loss or to liver blood flow rupture. Decreased metabolism by cytochrome P450 enzymes and glucuroniltransferases, hypoalbuminemia and low albumin binding affinity tend to increase AEDs serum levels.<sup>4,38</sup> Hepatic enzymes are differently affected according to the type of liver disease, for instance CYP3A4 is mostly affected in hepatocellular dysfunction, whereas CYP2E1 is affected in cholestasis.<sup>4</sup> It is therefore important to know the inductor/inhibitor profile of each AED. AEDs like phenobarbital, phenytoin and carbamazepine induce a wide variety of isoenzymes. Valproate is a wide-spectrum isoenzyme inhibitor and increases its own serum level and that of other drugs sometimes causing toxicity. Valproate can lead to hepatotoxicity and Rey's syndrome as idiosyncratic effects.<sup>4,22,42</sup> Newer generation AEDs have a more restricted effect on liver isoenzymes. Topiramate and oxcarbazepine induce CYP3A4 and inhibit CYP2C19. Oxcarbazepine also induces the UDP-glucuronosyltransferases UGTs. Clonazepam induces the CYP2B family. Lamotrigine induces the (UGTs). Ethosuximide, levetiracetam, gabapentin, tiagabine and zonisamide are not known to have significant enzymatic activity.<sup>4</sup>

Hepatic function is difficult to quantify making it rather unlikely to predict dose adjustments on its grounds. Intrinsic hepatic clearance varies with the type and duration of liver disease. Thus, the effects of changes in protein binding of AEDs are not straightforward. When hepatic disease lowers binding without changing intrinsic clearance, total drug concentration will fall because its metabolism depends on the free fraction. On the other hand, if intrinsic clearance is reduced, drug concentrations tend to increase with higher effect or toxicity.<sup>8</sup> Light to moderate dysfunctions rarely need AEDs adjustments. Severe dysfunctions ask for frequent serum level determination to guide AEDs adjustments. Preferred AEDs should have little hepatic metabolism and be weakly protein-bound. Theoretically, gabapentin, vigabatrin and levetiracetam should be more adequate in this context, but there are little data to assure their efficacy as monotherapy.<sup>5,28,29</sup> Lamotrigine is extensively metabolized by the liver and should be used with caution.<sup>6</sup>

### CONCLUSIONS

Effective treatment of seizures in renal and hepatic diseases requires that these disorders and their complications

be promptly recognized, so that specific treatment may be started soon. Moreover, attention should be paid to the extension of renal and hepatic metabolism end elimination of each AED, as well as to changes in AEDs pharmacokinetics in such cases. Care when prescribing concomitant drugs can not be overemphasised. Monitoring serum levels of AEDs is often helpful and necessary in avoiding either toxicity or inefficacy.

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