World Journal of Nephrology

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World J Nephrol 2020 June 30; 9(1): 1-8

DOI: 10.5527/wjn.v9.i1.1

ISSN 2220-6124 (online)

MINIREVIEWS

Renal transplant recipient seizure practical management

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Author contributions: Sawhney H was involved in writing the original draft, read and approved the final manuscript; and Gill SS was involved in writing the original draft, read and approved the final manuscript.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

Manuscript source: Invited manuscript

Received: December 2, 2019
Peer-review started: December 2, 2019
First decision: December 11, 2019
Revised: May 23, 2020
Accepted: June 10, 2020
Article in press: June 10, 2020
Published online: June 30, 2020

P-Reviewer: Al-Haggar M, Gonzalez FM, Kakaei F
S-Editor: Ma YJ
L-Editor: A

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Abstract

Seizures are not uncommon in renal transplant patients. The common aetiologies are metabolic disturbance associated with renal failure, immunosuppression and associated complications and infections. Their management can be challenging because of altered pharmacokinetics of antiepileptic drugs (AEDs) and their removal by dialysis. A practical approach to the management of seizure in renal transplant patients is discussed. This review highlights the guidelines for use of various AEDs in renal transplants.

Key words: Seizures; Renal transplant; Haemodialysis; Uraemia; Antiepileptic drugs

Core tip: For selection of an antiepileptic drug (AED) in renal transplant patients: it should be a non-enzyme inducer; its metabolism and excretion should not be affected by renal failure; there are minimal dose adjustments with haemodialysis; the loading dose of most AED remain the same in renal impairment; and, sodium valproate is a good choice for an antiepileptic drug in renal transplant patients.

Citation: Sawhney H, Gill SS. Renal transplant recipient seizure practical management. *World J Nephrol* 2020; 9(1): 1-8
URL: https://www.wjgnet.com/2220-6124/full/v9/i1/1.htm
DOI: https://dx.doi.org/10.5527/wjn.v9.i1.1

INTRODUCTION

Seizures occur in 6%-36% of transplant patients[1]. Renal transplant patients may suffer

E-Editor: Wu YXJ

from seizures because of immunosuppression, infections or pre-existing epilepsy. With deteriorating renal transplant function renal failure and dialysis disequilibrium can also cause seizures. Seizures may be a reflection of metabolic derangement, drug toxicity or associated with life threatening central nervous system pathology. Though generalised tonic clonic seizures are easily recognised in these patients, confirming the diagnosis can be a challenge because of motor symptoms mimicking seizures in uraemic patients and non-convulsive status epilepticus.

The experience of using anti-epileptic drugs (AEDs) along with immunosuppression in transplant patients is quite rich in renal transplants; it being the oldest and most common transplant procedure. However, there are no double blind, controlled randomised clinical trials for the use of AEDs in this cohort. The literature for the use of newer AEDs is scarce.

This review gives a practical approach to manage seizures in renal transplant patients based on review of literature and current guidelines.

Pre-renal transplantation phase

Patients intending to be a recipient of a renal transplant are well evaluated. When they are on the waiting list to receive the transplant, they are in steady state. Any convulsive crisis cannot be attributed to uremic encephalopathy or dialysis disequilibrium syndrome that affect acute new patients requiring renal replacement therapy.

Co-existing epilepsy: It is not uncommon to see patients with renal failure with co-existing unrelated cerebral pathology resulting in epileptic seizures. There are uncommon syndromes, which may present with renal failure and neurological dysfunction. "Action myoclonus – renal failure syndrome" is a distinctive form of progressive myoclonus epilepsy associated with renal failure. Before the dialysis and renal transplant era, it was not recognised, as patients succumbed to rapidly progressive renal failure. It is an autosomal recessive disorder and may present with renal or neurological features. The neurological presentation includes progressive action myoclonus, tremors, cerebellar ataxia and infrequent generalised tonic clonic seizures. Proteinuria is detected in all cases at an early stage, progressing to renal failure. Renal biopsies demonstrate a severe variant form of focal glomerulosclerosis, a collapsing glomerulopathy. Renal dialysis and transplantation are effective for renal function only, the neurological features continue to progress in spite of normal renal function[2].

Peri-renal transplantation phases

Renal transplant patients require sedatives, anaesthetics and narcotics for surgery and pre-surgical evaluation. Many drugs used for this may cause seizures. Central anticholinergic syndrome is associated with blockage of the central cholinergic transmission and presents with seizures, agitation, hallucinations, stupor and respiratory depression.

Seizures can be a side effect of immunosuppressive therapy. High dose methyl-prednisolone given concurrently with cyclosporine can trigger seizures[3]. Calcineurin inhibitors such as tacrolimus and cyclosporine have been associated with posterior reversible encephalopathy syndrome (PRES). PRES is a syndrome which is associated with headaches, confusion, seizures and visual loss. Adverse neurological effects after mycophenolate mofetil (MMF) are uncommon. However, concomitant use of MMF with corticosteroids and cyclosporine may cause encephalopathy and seizures . Also, a case report of a generalised tonic-clonic seizure has been noted when aciclovir was used while the patient was on MMF[4].

Immunosuppression increases the risk of opportunistic infections, which may present with symptomatic seizures. The treatment of these infections may be associated with seizures because of its toxicity. Imipenem, a commonly used drug for bacterial infections in immunosuppressed patients, has been associated with seizures[5,6].

Post-renal transplantation phase

In the post renal transplantation phase, in the context of a failing graft, with acutely worsening renal function, seizures are commonly associated with uraemic encephalopathy or disequilibrium syndrome caused by haemodialysis (Table 1). Aluminium encephalopathy in children and dialysis encephalopathy are not seen with modern dialysis procedures.

Seizures in renal insufficiency can be due to electrolyte imbalance (hyponatraemia, hypocalcemia, hypomagnesemia), hypertensive encephalopathy, intracranial haemorrhage (particularly subdural haematoma) or drug intoxication[7].

Seizures are common in acute renal transplant failure. These usually occur in the

Table 1 Causes of seizures in renal transplant

Encephalopathy
Uraemic encephalopathy
Dialysis disequilibrium syndrome
Aluminium encephalopathy
Reversible posterior encephalopathy syndrome
Metabolic derangement
Hyponatremia
Hypocalcemia
Hypomagnesemia
Immunosuppression neurotoxicity
Tacrolimus (FK-506)
Cyclosporin
High dose corticosteroids
CNS infections
Meningitis
Encephalitis
Abscess
Drug toxicity
Quinolone antibiotics (*e.g.*, Ciprofloxacin)
Beta Lactams (*e.g.*, Penicillin, Mezlocillin, Cephalosporins)
Antidepressants
Bupropion HCL
Cerebrovascular disease
Subdural haematoma
Cerebral infarct
Intracerebral haemorrhage
Co-existing epilepsy
Primary CNS lymphoma
Action myoclonus – renal failure syndrome

early couple of weeks of renal failure when patient is oliguric or anuric. Seizures are relatively uncommon in chronic renal transplant failure and are seen at a pre-terminal state when significant uraemic encephalopathy is present.

Uraemic encephalopathy: It is characterised by altered mental status, sluggishness, seizures, movement disorders and ataxia. The coexistence of features of neural depression commonly seen in a metabolic encephalopathy along with neural excitation are typical of uraemic encephalopathy. Early movement disorders include muscle cramps, tremors and asterixis. A culmination of asterixis and myoclonus has been labelled as uraemic twitching and seen in severe uraemic encephalopathy[8]. Chorea and athetosis are seen rarely. These movement disorders can be confused with seizures. Video electroencephalography (EEG) is helpful in differentiating these movement disorders from epileptic seizures as there is no corresponding epileptic activity in for former.

Dialysis disequilibrium syndrome: It is an increasingly rare syndrome characterised by headache, nausea, restlessness, hypertension, blurred vision, seizures, muscular twitching, asterixis and confusion. It usually presents during or immediately after haemodialysis or during the initiation of continuous renal replacement therapy[9,10]. Rapid clearance of urea from plasma than brain leads to cerebral oedema.

Co-existing epilepsy: It is not uncommon to see patients with renal failure with co-existing unrelated cerebral pathology resulting in epileptic seizures. There are uncommon syndromes, which may present with renal failure and neurological dysfunction. Action myoclonus – renal failure syndrome is a distinctive form of progressive myoclonus epilepsy associated with renal failure. It was not recognised prior to dialysis and renal transplant era as patients succumbed to rapidly progressive renal failure. It is an autosomal recessive disorder and may present with renal or neurological features. The neurological presentation includes progressive action

myoclonus, tremors, cerebellar ataxia and infrequent generalised tonic clonic seizures. Proteinuria is detected in all cases at an early stage, progressing to renal failure. Renal biopsies show collapsing glomerulopathy, a severe variant of focal glomerulosclerosis. Dialysis and renal transplantation are effective for renal function only, the neurological features continue to progress in spite of normal renal function[11]. In other rare multisystemic conditions such as Tuberous Sclerosis patients also develop renal impairment and neurological dysfunction.

A PRACTICAL APPROACH TO SEIZURE MANAGEMENT

The seizures in a renal transplant recipient patient can be acute symptomatic seizures. These seizures are triggered by metabolic disturbance and do not reoccur if the provocative factor is eliminated or adequately treated. Patients need a fast acting anti-epileptic for short duration and long-term prophylactic anti-epileptic treatment is not required. The underlying provocative factor, for example, metabolic disturbance should be rectified. In case of dialysis disequilibrium syndrome, dialysis should be immediately stopped if patient develops seizures or obtundation. Some studies suggest that severe dialysis disequilibrium syndrome can be reversed by more rapidly with either 5 mL of 23% saline or 12.5 mg of Mannitol. However both measures may remain ineffective[12].

On the contrary, symptomatic seizures relate to structural brain lesions, for example, infective focus or an infarct, carry a high risk of recurrence and need long-term prophylactic treatment. Long standing epileptic seizures not associated with renal disease should be treated on their own merit.

Pharmacokinetics of AEDS in renal disease

It is important to understand the pharmacokinetics of AED in the setting of renal disease. The plasma drug levels of AEDs can be affected by renal failure, haemodialysis and peritoneal dialysis. The 2002 Renal-Disease-Outcome-Quality-Initiative developed guidelines which classify chronic renal disease (CKD) into five stages. CKD stage 5 is defined as a "glomerular filtration rate (GFR) of < 15 mL/min per 1.73 m²" and in this stage renal replacement therapy in the form of dialysis or transplantation has to be considered to sustain life[13].

Protein binding, GFR and drug solubility, determine AEDs renal clearance. Unlike lipid soluble drugs, water-soluble drugs are excreted in urine. Most drug metabolites (for example, epoxides) are more water-soluble than the parent drug. Hence most drug metabolites are excreted in the urine. A number of patients with CKD and nephrotic syndrome are hypoalbuminemic. This affects the pharmacokinetics of protein bound AEDs. As protein binding is decreased due to low albumin, a larger amount of free drug is available for clinical effect. Patients may have side effects of the drug even though total plasma levels of the drug are in the therapeutic range because of increased free drug levels. It is worth emphasising that loading dose of AEDs is independent of renal clearance. Therefore this usually does not require adjustment in renal failure. It is the amount of drug available in the body compared to plasma concentration. The loading dose is used to achieve faster steady state and therapeutic effects.

Haemodialysis: AEDs are cleared from blood circulation by haemodialysis into the dialysate through the filter membrane. This depends upon the molecular size of the drug, water solubility protein binding, volume distribution and dialysis condition. The haemodialysis related factors, which affect AED clearances include type of membrane, surface area, blood flow rates, dialysis frequency and duration. Modern high efficiency dialysis with larger surface area of dialysis membrane and large pore size can dialyze more drugs compared to low efficiency dialysis of the past. A number of recommendations made in literature are based on old studies.

Some AEDs are readily removed by haemodialysis. These are ones that have a combination of having a small volume distribution, not highly protein bound and are water soluble. On the other hand, AEDs with high lipid solubility and protein binding as well as high volume distribution are difficult to remove by haemodialysis.

Peritoneal dialysis: It utilises peritoneal membrane as the dialyzing membrane, which is less effective for AED clearance compared to haemodialysis. However, in the setting of associated peritonitis, significant amount of drug binds to proteins and is removed in the peritoneal effluent, increased drug clearance may occur.

Home haemodialysis: This involves short daily treatments for 2-3 h, 5-6 times per week or night time dialysis when the patient sleeps with longer hours 3-6 nights per

week. The longer dialysis time in these patients may increase the AED clearance.

Continuous renal replacement therapy: This modality is often used in critically ill patients. Membranes used are usually of larger pore size, which allow larger drug molecules to be filtered. There is continuous ultrafiltration of plasma water. These factors may lead to an increase in drug clearance compared to haemodialysis.

Choice of anti-epileptic drugs

Treating seizures in renal transplant patients is a challenge. The drug should be effective for particular seizure type. For example, phenytoin, carbamazepine and levetiracetam are effective for generalised tonic clonic or focal seizures. Sodium valproate is a good choice for myoclonic seizures. Carbamazepine can make myoclonic seizures worse and should be avoided in such a setting. AED should be fast acting in acute symptomatic seizures to avoid further recurrences. Benzodiazepines are first line drug for terminating such a seizure. We recommend Lorazepam 2-4 mg IV in such a setting. In the absence of an IV line as in a community based setting, buccal midazolam is an alternative. An algorithm for the management of acute onset generalised tonic clonic seizure is given in Table 2[14].

Renal transplant patients are treated with immunosuppressive agents, which are metabolised in the liver. The AEDs, which induce hepatic enzyme system CYP450 *e.g.*, carbamazepine and phenytoin, should be avoided. These drugs increase the metabolism of immunosuppressive drugs metabolised in the liver and make them ineffective with their standard dose.

AEDs may need dose adjustment in patients with renal failure, especially if these patients are dialysed. The dose adjustment for various AEDs in various stages of renal failure and haemodialysis is summarised in Table 3[15,16]. The commonly used drugs in renal transplant patients are:

Sodium valproate: Renal disease has little effect on valproate metabolism as it is almost entirely eliminated by hepatic metabolism. It is 85%–95% protein bound and protein binding is affected by renal disease. The total plasma concentration falls, but free Valproate levels remain unchanged. Valproate is poorly soluble in water and has a small volume of distribution. It is highly protein bound. Less than 20% of Valproate is removed by haemodialysis[17]. No dose adjustment is necessary in renal failure, and there may be a need for small supplement dose in high flux haemodialysis. It is hepatic enzyme inhibitor and may enhance immunosuppression. It also is effective for almost all seizure types, including myoclonic seizures and can be given intravenous to treat acute symptomatic seizures. These characteristics make it a drug of choice in renal transplant patients.

Phenytoin: Renal failure has a significant effect on phenytoin's pharmacokinetics. Although kidneys only clear upto 5% of phenytoin. There is an increase in the free fraction of phenytoin because of decreased protein binding in renal failure. If dosing is based on total Phenytoin plasma concentration, it can lead to over-dosing and toxicity. Phenytoin's water solubility is poor. Phenytoin has a volume of distribution that is modest, being 90% bound to protein. There is very minor loss in haemodialysis or peritoneal dialysis[18,19]. In plasmapheresis, 10% of total phenytoin is removed with each treatment. Though it is a commonly used drug in renal transplants with acute onset of recurrent seizures, it should be avoided as it is a hepatic enzyme inducer and decreases plasma levels of immunosuppressive drugs.

Levetiracetam: Approximately two-thirds of levetiracetam is cleared by the renal. Its clearance decreases in proportion to decrease in GFR and its dose decreases accordingly (Table 3). It is water soluble, has low volume distribution and protein binding. This makes it highly dialyzable. Approximately, half of drug body pool is removed during a four hour session of haemodialysis. Levetiracetam can be used as an intravenous loading dose in acute onset seizures, as it has a fast mechanism of action. It is a non-enzyme inducer and does not interact with drugs used for immunosuppression. However, there is a need to adjust the dose in renal failure and dialysis.

Newer anti-epileptic drugs: There has been a rapid growth of new AEDs in the last 10 to 15 years. For many of these drugs specific data for use in renal disease is lacking. However, a good understanding of AED and its pharmacokinetics in renal disease can allow its rational use in renal transplant patients. Brivaracetam appears to be promising drug in patients with renal disease. It is a non-enzyme inducer, broad spectrum AED, which crosses the blood brain barrier fast and effective in acute onset recurrent seizures. Its pharmacokinetic is unaltered in renal failure and no dose adjustment is required in haemodialysis[20].

Table 2 A practical approach to generalised tonic clonic seizure in renal transplant patients (modified from Chabolla *et al*[14], 2006)

Acute onset generalised tonic clonic seizure	
Monitor ABC	
IV Lorazepam 2 mg	
Post seizure	Persistent seizure or recurrent seizures without regaining consciousness follow status epilepticus protocol
Eliminate or correct identified provocative factors	
Neurologic examination, EEG, MRI brain	
If all negative, monitor without AED	
If any positive (Neurologic examination abnormal or EEG – Epileptic activity or MR structural lesion) OR spontaneous recurrence when monitoring without AED -> then Initiate AED	

EEG: Electroencephalography; MRI: Magnetic resonance imaging; AED: Antiepileptic drug.

CONCLUSION

Key points for selection of an AED in renal transplant patients: (1) It should be a non-enzyme inducer; (2) Its metabolism and excretion should not be affected by renal failure; (3) There are minimal dose adjustments with haemodialysis; (4) The loading dose of most AED remain the same in renal impairment; and (5) Sodium valproate is a good choice for an antiepileptic drug in renal transplant patients.

Table 3 Dose adjustment for antiepileptic drugs in patients with renal impairment

GFR (mL/min)	60-90	30-60	15-30	< 15	Haemodialysis
Levetiracetam	500-1000 mg BD	250-750 mg BD	250-500 mg BD	500-1000 mg OD	Plus 250-500 mg/d
Toparimate	50% decrease	50% decrease	50% decrease		50-100 mg after HD
Zonisamide	100-400 mg	100-400 mg			
Oxcarbazepine	300-600 mg BD	300-600 mg BD	300 mg/d starting dose	NA	NA
Esclicarbazepine	None	400-600 mg OD	400-600 mg OD		
Clobazam	None	None	None	NA	None
Pregabalin	None	50% decrease	25-125 mg/d	25-75 mg /d	25-150 mg after HD
Lacosamide	None	None	300 mg/d		Plus < 50% after HD
Rufinamide	None	None	None	NA	Plus 30% after HD
Vigabatrin	25% decrease	50% decrease	75% decrease	NA	NA
Tiagabine	None	None	None	None	None
Lamotrigine	None	None	None	None	NA
Phenytoin	None	None	None	None	May need in high flux HD
Carbamazepine	None	NA	NA	75% dose	Plus 75% after HD
Valproate	None	None	None	None	May need in high flux HD
Perampanel	None	None	NA	NA	NA
Brivaracetam	None	None	NA	NA	None

This table is modified from Glynn *et al*[9], Diaz *et al*[15] Lexicomp online drug information[16]. NA: Not available.

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