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Epilepsy (E Waterhouse, Section Editor)

Managing Antiepileptic Medication in Dialysis Patients

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Abstract

Purpose of review The purpose of this review is to summarize and discuss available information on the management of epilepsy patients on renal replacement therapy. Older and newer antiepileptic drugs (AEDs) pharmacology will be reviewed, as well as the need to supplement dosages during or after hemodialysis, peritoneal dialysis, and continuous renal replacement treatment.
Recent findings The great majority of anticonvulsants have been studied in patients with renal failure. Many of them have also been assessed during renal replacement therapy. For some, data are scant, and choice of management must be decided through information on pharmacology. Trials have been conducted in patients with hemodialysis and results have been extrapolated to other types of dialysis. Furthermore, decision on dose supplementation for some of the newer AEDs involves a combination of analysis of the clinical situation and physician expertise. In this paper, we discuss the basis of renal failure and renal replacement therapy as well as antiepileptic pharmacology and the options for dosage replacement during dialysis.
Summary Based on pharmacology of each AED, a dosage supplementation is required in cases where there is sufficient clearance of the drug by the method of dialysis chosen. This depends greatly on physicochemical characteristics of the drug: lipophilicity, volume of distribution, protein binding, and molecular weight; and on characteristics of dialysis membrane, mechanism of clearance and blood or dialysate flow. There are studies done for most AEDs in hemodialysis, but more trials are needed in peritoneal dialysis and continuous replacement therapies. There is insufficient information for the newest AEDs, and for some, the recommendation is to simply avoid them in renal failure and dialysis. More studies are necessary in the topic.

Introduction

The use of antiepileptic drugs (AEDs) in patients with renal failure is complex [1]. Renal failure, its direct consequences, as well as renal support therapy, modify the neurologist's treatment choices qualitatively (choice of drug) and quantitatively (drug dosage) [2•]. In particular, the use of AEDs in patients undergoing dialysis presents unique challenges.

Chronic kidney disease

Chronic kidney disease (CKD) is marked by a progressive deterioration of renal function, classified in five stages according to glomerular filtration rate (GFR). Dialysis is required at stage 5 of renal disease, typically referred as end-stage renal disease (ESRD) [2•, 3]. These categories are shown in Table 1.

Pharmacological principles of renal impairment

Kidney dysfunction alters pharmacodynamics and pharmacokinetics of any pharmacologic compound. Drug absorption, blood distribution, metabolism, and elimination, described by the word pharmacokinetics, are influenced by renal impairment in many ways [4, 5].

Absorption

Absorption decrease is influenced directly by nausea and vomiting and indirectly by the alkalinizing effect of salivary urea, reduction of the time of contact with GI mucosa, interstitial edema, and, for drugs with significant first-pass metabolism, drop in cardiac output. Erratic absorption is also a problem in diabetic nephropathy and coexisting GI neuropathy [1, 2•, 5, 6]. Interstitial edema similarly alters absorption of drugs administered concomitantly with AEDs [3].

Volume of distribution

AEDs, like other drugs, exist in two forms: free form and protein bound. The unbound fraction of the drug produces the pharmacologic effects [1, 5]. Protein binding is affected by physicochemical properties, concentration of the drug, and protein concentration [7••]. Drug affinity and displacement from the protein receptors by a second drug increases the unbound active drug [8]. Activity and distribution to tissues is affected by properties of the drug itself, including the capacity to bind to proteins, its water solubility, and by the concentration of proteins in plasma and tissues [3].

Fluid overload, marked by edema and ascites in renal failure, produces an increase in the volume of distribution of the drug as well as accumulation of endogenous substances and abnormal tissue binding [1]. This is particularly true for water-soluble drugs. The presence of these competitive substances, along with the hypoalbuminemic state in kidney disease and a conformational change of the albumin molecule, produces a decrease of the concentration of protein-bound drug, especially acidic drugs [3, 9]. Basic drugs are usually not affected as α-1-acid glycoprotein, as acute phase reactant, can be increased in renal failure. Muscle wasting and volume depletion decrease the volume of distribution [3].

Metabolism

Metabolism is the major mechanism for the elimination of drugs from the body. Non-renal clearance part of drug metabolism, i.e., hepatic metabolism, can change in renal

Table 1. Stages of chronic kidney disease (CKD) according to glomerular filtration rate (GFR)

Stage	Renal function	GFR (mL min – 1 per 1.73 m–2)
1	Normal	> 80
2	Mild renal impairment	50–80
3	Moderate renal impairment	30–50
4	Severe renal impairment	< 30
5	ESRD	Requires dialysis

Original table created from information extracted from Expert Rev. Neurother. 12 (1), 99105 (2012)

disease. The activity and uptake of efflux transporters, in the small intestine, kidney, and liver is altered in different ways, and many drug-metabolizing enzymes are found both in liver and kidney. Decreased metabolism of intestinal cytochrome P450 and glycoprotein active transport incites more drugs to enter the portal circulation [6]. Metabolic enzyme and transporter activity are interdependent, significantly affecting systemic exposure of drugs cleared through non-renal mechanisms. Thus, drugs that are metabolized solely by non-renal metabolism can also accumulate in kidney disease and need dosage adjustment. Decrease in hepatic enzyme activity and accumulation of uremic toxins is also related, usually during phase I or glucuronidation phase [3, 6].

All these phenomena lead to a difficult to predict non-linear drug accumulation and to a change in the anticonvulsant half-lives [6].

Elimination

Glomerular filtration, tubular secretion, and tubular reabsorption contribute to renal clearance of a drug. Plasma proteins, as large molecules, are not normally filtered in the kidney, leaving unbound fraction to be excreted through the glomerulus. The loss of excretory function varies in the diseased kidney and is usually proportional to the glomerular filtration rate [3].

Drugs that are hydrosoluble, of low-molecular weight, low VD, and modestly bound to proteins are extensively eliminated by the kidneys. Dysfunction of the kidneys alters renal excretion of the unchanged drug and its metabolites and modifies distribution, transport, and biotransformation of the drug. These drugs are also heavily removed by hemodialysis and need dose replacement [6].

In terms of pharmacodynamics, renal impairment also modifies the action of AEDs in the brain. Interactions between different anticonvulsants also increase or decrease activity of the drug.

About therapeutic drug monitoring

It is extremely important to identify and monitor patients with renal failure to assure control of epilepsy, many times requiring strict therapeutic drug monitoring [1, 10, 11]. A correlation between the concentration of the AED and its therapeutic and toxic effect is frequently found, and reliable studies have established therapeutic ranges for older and some of the newer drugs. However, as more research is completed, evidence demonstrates a variation of the previously defined therapeutic values to achieve seizure control for old and new AEDs [10, 12].

Usually, the drug dose needs to be adjusted in renal failure to avoid accumulation of drug or metabolites, which could increase the amount and severity of adverse effects [3, 8, 13]. This maintains the same average unbound drug concentration steady and can be done by either reducing the maintenance dose or prolonging the interval between doses. The specific dose reduction should be done taking into consideration the estimation of the renal function by GFR. Usually, a dose change is not necessary until GFR decreases to less than 30 mL/min [5]. Renal function can be over or underestimated if it is rapidly changing with a consequent over- or underdosing. Other aspects to consider when calculating doses are presence of metabolites with an active component of more than 25–59% and a narrow therapeutic window [5].

To reach a steady-state concentration with a maintenance dose, approximately five half-lives are needed. If there is urgency to achieve therapeutic concentrations, a loading dose should be given. The loading dose should generally not be modified in renal impairment, although lowering the dose could be considered in drugs with narrow therapeutic window and increasing it should be done in fluid overloaded or septic patients for some medications. In renal failure, therapeutic levels can be obtained through an unchanged loading dose, followed by decreased doses or a larger interval between doses [8].

Dialysis mechanisms and their effect on drug pharmacokinetics

Chronic renal failure causes a pathologic accumulation of toxins and water. Dialysis is the artificial process through which physicians attempt to supply normal kidney function and remove toxic waste products, drugs, and active metabolites from the blood. The basic principle of dialysis involves the movement or diffusion of solute particles across a semipermeable membrane [11, 12].

The characteristics of the substance, such as molecular weight, protein binding and volume of distribution, the properties and geometry of the dialysis system (membrane type, surface area, thickness and countercurrent, or concurrent blood and dialysate flow respectively) are responsible for the effectiveness in removing drugs [4, 14].

In general terms, larger pores in a dialysis membrane, smaller drug molecules, low degree of protein binding (more free drug), uremia (decrease in protein binding), decreased protein concentration, a small volume of distribution, and medications with higher water solubility and lower lipid solubility as well as high blood flow rate during hemodialysis and faster dialysate flow rates will

increase the clearance of a compound by dialysis [1, 15, 16]. How the clearance of a drug increases or decreases according to its physicochemical properties is depicted in Fig. 1.

Adjustments of medications can be done by replacing the amount of drug lost in the dialysate during the treatment period. Different studies about drug clearance have been done with variable subtypes of renal replacement therapy (RRT), which are difficult to compare. In the clinical setting, supplemental doses are rarely given unless more than 30% of the drug is cleared or there is a narrow therapeutic index. If the drug has multiple dosages per day, at least one dose needs to be given soon after dialysis [5].

Different methods to calculate ideal dose are available, such as nomograms, tables, and computerized calculations. These tactics are helpful but not always reliable and, given the intricacy of kidney disease, an individualized approach to every clinical scenario and evolution in time are a must.

There are three main modalities of RRT: intermittent hemodialysis (IHD), peritoneal dialysis (PD), and continuous renal replacement therapies (CRRT) [17].

In hemodialysis, waste is removed by an external filter that contains a semipermeable membrane called dialyzer. A concentration gradient between the blood and the dialysate drives the clearance of solutes. This procedure can be associated with faster clearance of medium molecules from the blood compared to CSF. The subsequent osmotic gradient and brain edema cause a dialysis disequilibrium syndrome that may produce seizures [4, 6]. In general, intermittent dialysis (IHD) is prescribed for 3 to 6 h per treatment. In chronic patients, it is performed three times per week. Most drugs are cleared during hemodialysis and should be supplemented [2•, 18•, 19].

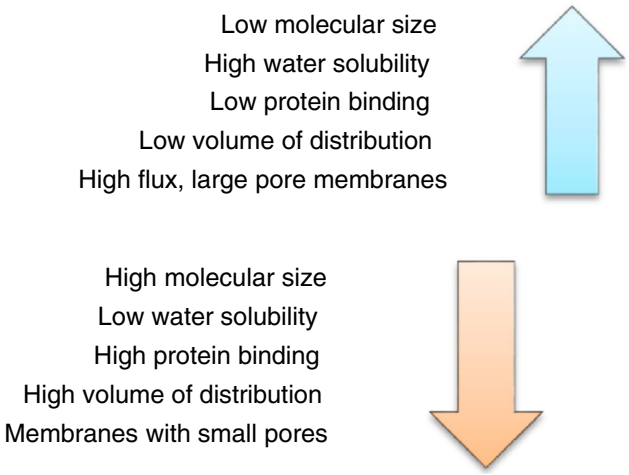

Fig. 1. Clearance modification according to physicochemical properties of a drug. original figure.

Home hemodialysis and nocturnal hemodialysis are treatments done by the patients at home. They can be daily and short (2 to 3 h, 5 or 6 times per week), or nightly long treatments (3 to 6 times per week, during sleep hours). Indications are individualized to every patient and follow the same rules as regular hemodialysis [2•]. Slow efficiency daily dialysis (SLEDD) or extended daily dialysis (EDD) is a variant of IHD where the duration of dialysis is extended between 8 and 12 h, the blood flow is lowered, fluid removal is more gradual, and solute clearance is slower [17].

In peritoneal dialysis, the peritoneum is used as a natural semipermeable membrane, taking water and waste into the dialysate. Continuous ambulatory peritoneal dialysis (CAPD) is generally less efficient than hemodialysis, but with variable effects on different drugs; serum levels and free levels are needed for drug adjustment. Drugs usually cleared by this type of procedure have a very low volume of distribution and low protein binding or a high concentration gradient between blood and dialysate. Other reasons for increased clearance are peritonitis or high peritoneal dialysate flow rates [1, 5]. It is related to seizures especially in non-ketotic hyperosmolar coma that arises from glucose fast exchanges. Monitoring dialysis glucose is recommended to avoid this. As a general rule, this method provides a low drug clearance during any exchange, but the cumulative drug removal may require dosage supplementation [15].

CRRT has a duration of 24 h and it is applied usually in the intensive care unit (ICU). In comparison with intermittent therapies, it has slower, but more efficient clearance. The removal of waste products can be accomplished by diffusion (hemodialysis), convection (hemofiltration), or both (hemodiafiltration) [2•, 5]. It relies heavily in continuous ultrafiltration of plasma water, removing a large amount of drug from the plasma. Its membranes have larger pore sizes and the transport of solute is through convection. Drugs that are not easily cleared usually have a large volume of distribution and are highly protein bound. However, many guidelines are extrapolated from experience from chronic hemodialysis or from theoretical data based on general principles of dug removal. Molecular weight of a drug has less influence in dialysability in this modality because high flux permits passage of bigger molecules through the

dialytic membrane. Higher rates of ultrafiltration can remove more drugs and produce the need of more frequent replacement doses. The concentration of drug in the effluent can also be measured to determine how much drug is removed [5].

Several factors are involved in modality choice: availability, cost, physician expertise and preference, hemodynamic stability, and the primary purpose of the procedure (fluid removal vs. solute clearance) [17].

Effect of dialysis on individual AEDs

The effects of dialysis on specific anticonvulsants will be explained in the following section and a review is presented in Table 2 at the end of the text.

Barbiturates (phenobarbital and primidone)

Phenobarbital (PB) is an old AED approved for focal and generalized seizures. It is a long-acting barbiturate with hypnotic and anticonvulsant properties [20]. It is absorbed easily and rapidly, can bind to proteins from 40 to 60%, and its elimination is mainly hepatic, except for 25% that is excreted in urine without changes [7••, 21]. Its narrow therapeutic range and interpatient variability in absorption, metabolism, and drug clearance make it reasonable to strictly observe its plasmatic concentrations. Recommendations on management in patients with dialysis are very variable. Conventional dialysis, high-flux and peritoneal dialysis enhance plasma clearance by at least 30%, and supplemental doses may be necessary [6]; however, data demonstrate a variable rate of elimination, from slightly up to five times reduction [5, 7••, 15, 21, 22]. Most recommend drug level monitoring to define dose supplementation [7••].

Primidone (PRM) is indicated in the treatment of generalized and focal seizures. It metabolizes to phenobarbital and another active compound. It is rapidly and nearly completely absorbed following oral administration. Its pharmacokinetics and behavior in dialysis are like PB. About 20 to 50% of a dose is removed by hemodialysis. On dialysis days, a supplementation of one third of the usual dose is recommended [8, 21].

Benzodiazepines

These are drugs employed as sedatives anxiolytics and anticonvulsants. Used in the treatment of focal or generalized seizures and first line in the treatment of status epilepticus. They are notably lipophilic and highly protein bound, are metabolized widely by the liver to active and inactive metabolites, and are mainly excreted by the kidney. Benzodiazepines do not demonstrate elimination by conventional hemodialysis and a dose supplementation is not necessary [6]. There are no studies on benzodiazepine clearance by high permeability hemodialysis and peritoneal dialysis elimination seems unlikely based on physicochemical characteristics of the drug [14, 15].

Clobazam

CLB is the first and only 1–5 benzodiazepine (as opposed to 1–4) for the treatment of epilepsy. It is approved as first-line treatment for seizures associated with Lennox-Gastaut syndrome [20]. It is rapidly and completely absorbed by mouth, being highly lipophilic, and 90% protein bound. The liver metabolizes this drug extensively to various metabolites, some active. Mild and moderate renal failure do not affect significantly protein binding and hemodialysis has little to no effect in plasma concentration of the drug or its metabolites. Dosage adjustment during dialysis is not necessary [8].

Valproate

VPA is a broad-spectrum anticonvulsant, effective in generalized and focal seizures, especially useful in the treatment of primary (genetic) generalized epilepsies [20]. It is significantly protein bound, about 90%, and less than 3% is excreted in urine [21]. Valproic acid is an inhibitor of multiple CYP enzymes, causing drug-drug interactions, with drugs such as carbamazepine, felbamate, lamotrigine, phenobarbital, and phenytoin [11]. Hemodialysis has a transient effect on plasma levels of VPA with a posterior rebound of levels; a supplemental dose is not necessary [7••]. High-flux and peritoneal dialysis have been used for intoxications, however there are mixed results on valproate concentrations [4, 7••, 8, 15].

Phenytoin

AED approved for focal epilepsies and is used widely [20]. Phenytoin's absorption is erratic in renal disease; it has a saturable metabolism, non-linear pharmacokinetics, and extensive protein binding [11, 21].

Table 2. Behavior of drugs in dialysis and dose replacement

AED	HD	PD	CRRT	Supplemental dose required after HD
Phenobarbital	Clears at least 30%			Yes (supplement 30% of daily dose)
Primidone	Clears at least 30%			Yes (supplement 30% of daily dose)
Benzodiazepines	None	No data	No data	No
Clobazam	None	No data	No data	No
Valproate	Low	Low	No data	No
Phenytoin	Low	Low	Yes	No
Carbamazepine	Low	Low	Yes	No
Ethosuximide	High (at least 50% in 6 h)	No data	High*	Yes (supplement one extra dose)
Felbamate	No data	No data	No data	Unknown (see text)
Tiagabine	None	None	None*	No
Vigabatrin	At least 60%	No data	At least 60%*	Yes (supplement 50% of daily dose)
Oxcarbazepine	Yes	Yes	Yes	Calculate dose according to patient, drug level, and method of dialysis
Lamotrigine	Low (close to 20% in 4 h)	Probably not	No data	Consider dose supplementation according to clinical scenario
Gabapentin and pregabalin	Yes	No data	Yes*	Yes (after each session, supplement GBP: 200 to 300 mg or PGB 25 to 150 mg according to usual dose (see text))
Topiramate	Yes (50% of the drug removed)	No data	Yes	Yes (supplement 50% of the daily dose after each session)
Levetiracetam	Yes (50% in 4 h)	No data	Yes 100%	Yes (load with 1.5 times the daily dose, give 30% of maintenance dose and supplement 30–50% of usual daily dose after dialysis)
Lacosamide	Yes (about 57%)	Unlikely	No data	Yes (supplement 50% of daily dose after each session)
Eslicarbazepine	Yes (effectively reduced after two dialysis)	No data	No data	No clear recommendation. Consider according to clinical scenario
Perampanel	No data	No data	No data	Not recommended for use in severe CKD or RRT
Brivaracetam	No data	No data	No data	Not recommended for use in CKD or RRT
Rufinamide	Yes	Unlikely	Yes	Yes (supplement 30% of daily dose after each session)
Zonisamide	Yes	No data	No data	Yes (one extra dose of 200 to 400 mg after each session)
Cannabidiol	No data	No data	No data	Unknown (see text)

Table made from recollected data for this article. *Data extrapolated from studies in hemodialysis patients. Decisions on supplemental dose should be made in conjunction with clinical judgment

Increased levels of free PHT are seen in neonates, patients with hypoalbuminemia and uremia due to renal failure. In such cases, it is recommended to calculate the corrected phenytoin level (PHT corrected = PHT measured/[(albumin*2) + 1] [11]. Less than 5% is excreted in urine. [7••] Hemodialysis and peritoneal dialysis have little impact on its clearance and additional doses are not recommended. Charcoal hemoperfusion and high-flux dialysis may clear the drug from plasma [4, 6–8, 15].

Carbamazepine

CBZ is an AED indicated in focal epilepsies [20]. It is more lipophilic high protein bound, and less affected by renal disease. This AED is a potent enzyme inducer and should be monitored for drug interactions and adverse effects. Less than 1% is excreted in urine [7••]. Peritoneal dialysis and hemodialysis have little impact on the drug's concentration and extra doses are generally not needed [6, 7••, 23]; however, high-flux methods can be effective in clearing plasma from carbamazepine [4, 8].

Ethosuximide

Anticonvulsant used in the treatment of absence epilepsy. This hydrosoluble, low-molecular weight drug has a low volume of distribution, and low protein-bound molecules. An extra dose after hemodialysis is recommended due to high clearance by this method [6]; 50% can be eliminated in 6 h of hemodialysis [7••, 16]. Extrapolating data from conventional dialysis studies, high-flux dialysis can also have a significant effect in removal of the drug. There is no data on peritoneal dialysis efficiency in clearing ethosuximide from the blood [15].

Felbamate

FBM is not a first-line AED; it is recommended only as alternative treatment of refractory focal seizures and focal or generalized seizures associated with LGS [20]. Felbamate has a high oral bioavailability (90%), very low water solubility, is modestly bound to proteins (25%), and has linear dose proportional pharmacokinetics [21]. FBM and its inactive and weakly active metabolites (40%) are eliminated almost completely by the kidney. Its dialysability is unknown [4, 15, 24, 25]. Given that 75% of FMB remains unbound to proteins, clearance by dialysis is possible; however, since multiple factors influence clearance, such as molecular weight, dialysis flux, and membrane pore size, a clear recommendation cannot be given and decisions should be done according to clinical scenario.

Tiagabine

TGB is used for focal epilepsy [25]. It has a good oral bioavailability, with fast absorption of the drug. It is 96% bound to proteins and has a linear pharmacokinetics; however, relationship between plasma concentration and clinical response has not been elucidated. It is metabolized extensively in the liver and only 2% is excreted unchanged, 25% in urine, and 64% in feces, mainly as metabolites. Consequently, kinetics is not changed by renal disease or conventional hemodialysis. Dose adjustment is unnecessary [4, 21]. Based on drug's properties, it is unlikely that high-flux hemodialysis or peritoneal dialysis can clear the drug from plasma [8, 15, 26, 27].

Vigabatrin

Vigabatrin is indicated for infantile spasms in children and as adjunct treatment in refractory focal epilepsy [20, 25]. It is a highly hydrosoluble, low-molecular weight substance, it binds to protein modestly and undergoes mayor renal excretion (70% of the initial dose) [8]. Ease of clearance of at least 60% of the drugs' enantiomers in hemodialysis harvests a need for a post-hemodialysis dose of at least half the dose. Data on this type of dialysis could be extrapolated to high-permeability systems. There is no data on peritoneal dialysis [15]. If given daily, the dose should be given after dialysis instead of supplementing an additional one.

Oxcarbazepine

OXC is approved for focal epilepsy [25]. It is 40% protein bound, undergoes hepatic metabolism to an active metabolite, and 50% of the drug is excreted in urine as CBZ or its metabolite [21]. The oxcarbazepine monohydroxy derivative is affected by hemodialysis (conventional or high permeability) or peritoneal dialysis in unpredictable ways [4, 6]. Decisions on dose

supplementation should be tailored to patient, drug levels, and method of dialysis.

Lamotrigine

Lamotrigine is a broad-spectrum anticonvulsant that is indicated for the treatment of juvenile myoclonic epilepsy, LGS and focal epilepsy [20]. Given its lipophilic and high protein-bound characteristics, it has low renal excretion as well as very low effect on hepatic enzymes [25]. Evidence suggests that a 4-h session of conventional hemodialysis can decrease plasma concentration by approximately 20% (low clearance) [4, 6, 7••]. There is inconsistency on recommendations about dose replacement; however, since there are reports on drug overdose treatment with dialysis, a supplementation should be considered according to clinical scenario [7••]. There are no data on high-flux hemodialysis and it is unlikely, based on the properties of the drug, that it could be cleared by peritoneal dialysis.

Gabapentin and pregabalin

Indicated in the treatment of focal epilepsy. Both medications are hydrosoluble, of low-molecular weight, with a high and rapid oral absorption, and low protein binding. Excretion is almost completely renal, and accumulation causes CNS adverse effects such as somnolence, lethargy, dizziness, and ataxia. Gabapentin can worsen myoclonic seizures in end-stage renal disease. Both medications can be easily cleared by conventional dialysis and most likely with a high permeability membrane [4–6, 7••]. Typically, 200–300 mg of GBP is given after HD [7••, 21]. For PGB, a supplemental dose should be administered after dialysis: in patients with 25 mg daily, supplement 25 to 50 mg. In patients with 25 to 50 mg, supplement 50 to 75 mg, and patients with 50 to 75 mg should be supplemented with 75 to 100 mg of the drug. There is no information on clearance by peritoneal dialysis [8, 15, 25].

Topiramate

Indicated in the treatment of focal epilepsy and primary (genetic) generalized epilepsy [25]. Low-molecular weight drug with low protein-bound molecules and very hydrosoluble. Renal excretion is noteworthy. Caution is advised in patients with a history of nephrolithiasis. The plasma concentration of TPM decreases about 50% during hemodialysis [21]. In conventional and high-flux hemodialysis patients, at least half-extra dose should be supplied after each session [4, 6, 7••]. Data on peritoneal dialysis is not known [7••, 8, 15].

Levetiracetam

LEV is an AED approved for use in focal and primary (generalized) epilepsy [25]. It is almost completely (> 95%) absorbed after oral ingestion, is weakly bound to proteins, has a low metabolism, and linear time-independent kinetics. LEV and its primarily inactive metabolite are almost completely (> 90%) excreted in urine and mild to moderate impairment of renal function can increase half-life significantly and double its plasma concentrations. Hemodialysis (conventional and extrapolating, high flux) seems to clear the drug entirely [6]; 50% seems to be removed during a 4-h treatment [7••, 21]. Patients on hemodialysis should receive an initial loading dose of 1.5 times the daily maintenance dose, a daily maintenance dose of 30% of the healthy subjects, and, on dialysis days, supplement 30 to 50% the daily dose after dialysis [4, 6, 9, 28]. There are no data on peritoneal dialysis.

Lacosamide

This is a functionalized amino acid indicated for focal epilepsy [7••] Characterized by rapid absorption, complete absolute oral bioavailability (100%), high water solubility, and low plasma protein binding. It has no first-pass metabolism and it is metabolized by three CYP isozymes, which causes less interactions. About 99% of its elimination takes place in the kidney and it has been proven to have a linear pharmacokinetic profile, which is important in terms of predictability of response and adverse effects [10].

Conventional hemodialysis extracts about 57% of LCM; up to 50% of the divided daily dose should be supplemented directly after the end of hemodialysis [7••]. In cases of drug overdose, hemodialysis can be implemented to clear 50% of the systemic concentration of LCM in 4 h [2•, 10]. There is no information on pharmacologic behavior with other renal support therapies, but it is unlikely to be cleared in peritoneal dialysis [15].

Eslicarbazepine acetate

Eslicarbazepine is indicated for focal epilepsy [29]. ESL acetate undergoes a rapid and extensive first-pass

metabolism, changing into its major metabolite ESL, responsible for the pharmacologic effect on voltage-gated sodium channels (VGSC). It has no relevant induction or inhibition of hepatic metabolism, has low protein binding (40%), and is cleared primarily by renal excretion (90%). Phase I studies show that mean plasma concentration of metabolites can be effectively reduced after two dialysis [29]. However, patients with dialysis were excluded from phase III studies and a consensus on management has not been made [30, 31•]. There are no data on peritoneal dialysis clearance [11, 22].

Perampanel

PER, indicated for focal and primary (genetic) generalized epilepsy, has a complete and rapid oral absorption, it is 95% bound to proteins, has extensive hepatic metabolism, and about 22% of it is recovered in urine, being primarily eliminated by fecal excretion. It is not advised in severe renal impairment or hemodialysis. Studies relating pharmacokinetics in severe renal disease and renal replacement therapy have not been done [32, 33].

Brivaracetam

Brivaracetam is indicated for focal epilepsy. It belongs to the same family of levetiracetam. This compound has a high oral bioavailability, is weakly protein bound, and has a rapid and complete tissue distribution. Pharmacokinetics is linear and time-independent. Its way of elimination is metabolism to three inactive compounds by liver and renal excretion of 95% of the dose. There is no data on pharmacokinetics or pharmacodynamics in patients undergoing dialysis; BRV is not recommended in this population [34, 35].

Rufinamide

Rufinamide is indicated as adjunctive treatment of seizures in the Lennox-Gastaut syndrome [36]. This medication is well-absorbed (85%) after oral administration, has a low protein binding (34%), and a high volume of distribution. Main elimination is through extensive hepatic metabolism to an inactive metabolite. The remaining fraction (2%) along to the metabolite is then excreted in urine. This does not change radically in renal failure. However, given its low binding to proteins, it is likely to be removed by hemodialysis (conventional and high permeability) and an adjustment of dose would be necessary. A supplement of 30% of the daily dose should be administered, in addition to the usual dose, after each dialysis session [2•, 36]. It is unlikely to be cleared by peritoneal dialysis given the physicochemical characteristics of the drug [15].

Zonisamide

Indications of ZNS include focal and primary (genetic) generalized epilepsy [25]. C-zonisamide is rapidly metabolized to its metabolite (ZNS) and is excreted in urine as the glucuronide of a metabolite in approximately 62%. ZNS is modestly bound to proteins, and conventional dialysis can clear drug from plasma at an unknown level. A Japanese study describes a 50% reduction in plasma levels of ZNS after a standard session of HS [7••]. A supplemental dose of 200 to 400 mg may be necessary after treatments [5, 7••, 8, 21]. There is no documentation found on high-flux hemodialysis or peritoneal dialysis.

Cannabidiol

Cannabidiol is the main non-psychoactive component of the Cannabis plant. This drug has shown antiepileptic properties and has being studied in certain types of treatment-resistant epilepsy with or without intellectual or developmental disability [37]. The Food and Drug Administration has recently approved CBD for the treatment of Lennox-Gastaut syndrome (LCS) and Dravet syndrome (DS). CBD was found to be rapidly absorbed and later shows a high interindividual pharmacokinetic variability. Oral bioavailability is low (6–10%) due to an extensive first-pass metabolism but increases fivefold when co-administered with food. It distributes extensively into tissues, from which it releases slowly, resulting in a late-phase terminal half-life of 24 h [38]. Studies suggest in vitro protein binding is higher than 94%. CBD is metabolized in the gut and in the liver by cytochrome P450 to active and inactive metabolites. It is excreted in feces and has minor renal clearance. There is insufficient information on the use of CBD in the setting of hemodialysis and peritoneal dialysis [37–39]. Considering, the drug is highly bound to proteins, dialysis would have a little effect on its clearance, and an extra dose would probably not be required. However, studies are needed in patients with CKD and dialysis to confirm this behavior.

Conclusions

Every year, multiple medications are being produced for the treatment of multiple diseases. Epilepsy drugs are a good example of this. Giving an appropriate treatment to these patients involves continuous review of literature and good understanding of pharmacology, pharmacodynamics, and pharmacokinetics of these drugs. Dialysis methods have come to improve the quality of life and elongate lives of patients with renal failure. As any other treatment, effects on drugs used for other illnesses, such as epilepsy, may be significant. Numerous studies have been done to calculate the amount of drug cleared by the different dialysis methods and the appropriate dose to supplement, if needed. Most of the information available involves hemodialysis and most is not understood with other dialysis methods. BZP, CLB, VPA, PHE, CBZ, and TGB are stable after HD and should not be supplemented. PB, PRM, ESM, VGB, GBP, PGB, TPM, LEV, LCS, RUF, and ZNS are cleared significantly by HD and a part to a total dose should be supplemented after each session. Other drugs like OXC, LMT, and ESL should be supplemented according to clinical scenario. The rest of the antiepileptics investigated have no clear data yet on clearance after dialysis. As always, more research needs to be performed to understand and define an appropriate conduct in the treatment of patients with epilepsy and renal failure.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human subjects performed by any of the authors.

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