Original article

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Pharmacological monitoring of antiepileptic drugs in epilepsy patients on haemodialysis

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ABSTRACT – *Aims*. To retrospectively evaluate the pharmacological profiles of antiepileptic drugs (AEDs) in epilepsy patients during haemodialysis using therapeutic drug monitoring data.
Methods. The serum concentration of AEDs was collected before and after haemodialysis, and the clearance rate and concentration-to-dose ratio were calculated as pharmacological parameters.
Results. Thirty-six patients were enrolled in the study (25 males, 11 females; age: 65.3 ± 14.8 years). In 24 of the 36 patients, epilepsy was associated with cerebrovascular disorders, and diabetes was the most common reason for haemodialysis in 16 patients. With regards to seizure type, focal aware seizures were less frequent than focal impaired awareness seizures and focal-to-bilateral tonic-clonic seizures. Interictal EEG showed intermittent rhythmic slow waves and intermittent slow waves more often than spikes or sharp waves. Levetiracetam was the most commonly used AED and led to the highest percentage of responders (80%; 16/20 patients). However, the clearance rate of levetiracetam during dialysis was highest among the antiepileptic drugs used, requiring supplementary doses after haemodialysis in all 20 patients. Valproic acid was not effective for focal epilepsy for patients on haemodialysis, and non-responders to phenytoin had low serum concentration of phenytoin both before and

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after haemodialysis. The pre-haemodialysis concentration of levetiracetam tended to be higher than the reference range, suggesting a potential risk of overdosing before haemodialysis. The pre- and post-haemodialysis concentrations of valproic acid tended to be lower than the reference range, suggesting a potential risk of underdosing. The concentration-to-dose ratios for levetiracetam, valproic acid, phenytoin, and carbamazepine were significantly lower after than before haemodialysis.
Conclusions. The majority of patients with epilepsy on haemodialysis had cerebrovascular diseases, and therapeutic drug monitoring for levetiracetam, valproic acid, and phenytoin, before and after haemodialysis, is needed to ensure proper dosing.

Key words: haemodialysis, elderly, epilepsy, therapeutic drug monitoring, antiepileptic drug

The prevalence of epilepsy in elderly individuals is increasing because of prolonged life expectancy (Hauser *et al*., 1993; Olafsson *et al*., 2005; Cloyd *et al*., 2006; Fiest *et al*., 2017). Japan leads the world in the rate at which its population is aging, with 27.3% of its population above age 65 (Hanafusa *et al*., 2015). Chronic kidney disease (CKD) is common in the elderly, and about 30% of men and about 40% of women over 65 years old in Japan have been diagnosed with Stage 3 CKD (Imai *et al*., 2007). The introduction of renal dialysis has markedly changed the rate of mortality due to CKD. In Japan, about 300,000 patients, with an average age of 66.6 years, receive haemodialysis (HD), and the number of patients is increasing (Hanafusa *et al*., 2015). Considering that the frequency of epilepsy is also increasing (Palmer, 2002), it is likely that patients undergoing HD will also need treatment for epilepsy.
Therapeutic drug monitoring (TDM) is particularly important during HD (Neels *et al*., 2004) because CKD and HD can alter the pharmacokinetic profile of some antiepileptic drugs (AEDs) (Asconape and Penry, 1982; Lacerda *et al*., 2006; Bansal *et al*., 2015). However, there are few reports on the influence of HD using high-efficiency dialyzers on AEDs in epileptic patients. Here, we performed a retrospective study on epilepsy patients receiving HD in order to evaluate the pharmacological profiles of AEDs based on analysis of TDM data.

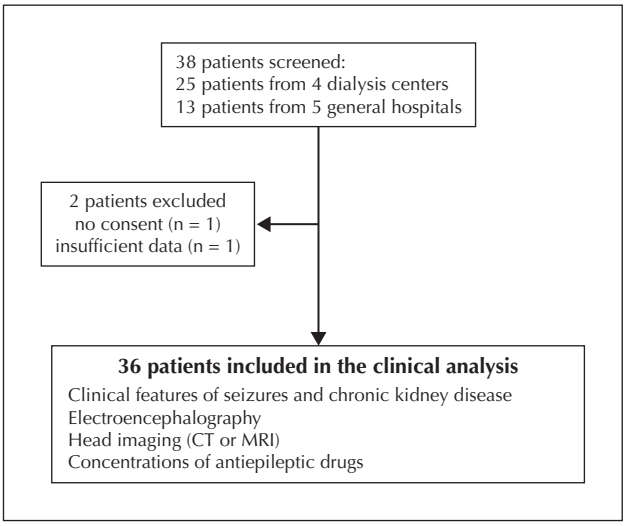

Figure 1. Flow chart of the selection of the 36 epilepsy patients on haemodialysis enrolled in the study. CT: computed tomography; MRI: magnetic resonance imaging.

Methods

Patients

We retrospectively analysed patients with epilepsy who received HD between June 2014 and May 2018. We collected patient data from nephrology departments of dialysis centres and neurology departments of general hospitals. In four dialysis centres, 25 out of 1,060 patients undergoing HD (2.36%) had been diagnosed with epilepsy. Two of the 25 patients were excluded due to a lack of informed consent and clinical data. Thirteen consecutive patients from five departments of neurology who had epilepsy and were undergoing HD were also included. In total, 36 epilepsy patients undergoing HD were included in the study (*figure 1*). This study adhered to the Ethics Guidelines for Epidemiological Studies endorsed by the Japanese government, and was approved by the Ethics Review Committee of Nagoya University Graduate School of Medicine. All participants provided written informed consent, except for those who died before starting the study and were included through an opt-out process.

Review of medical records

Epilepsy, seizure classification, and status epilepticus (SE) were diagnosed by two doctors, board-certified in epileptology/neurology, on the basis of medical interviews and documented seizures, EEG, and head imaging, in accordance with the criteria of the International

League Against Epilepsy (ILAE) (Trinka *et al*., 2015; Fisher *et al*., 2017; Scheffer *et al*., 2017). Patients with a discrete focus were diagnosed with focal epilepsy, which was specified as frontal, temporal, parietal, or occipital lobe epilepsy (FLE, TLE, PLE, and OLE, respectively). All subjects were Japanese and clinical data on age, sex, seizure onset age, epilepsy diagnosis, aetiology of epilepsy, age at the start of HD, and reason for HD were collected. We also evaluated seizure type, aura, the timing of seizures (during or between HD sessions), treatment, and response to AEDs. The seizures were categorized as focal aware seizure (FAS), focal impaired awareness seizure (FIAS), and focal-to-bilateral tonic-clonic seizure (FBTCS) in accordance with the classification of the ILAE (Fisher *et al*., 2017). A responder was defined as a patient who had no seizures for 12 months after the initiation of AED treatment, whereas a non-responder was defined as a patient who had one or more seizures within 12 months, despite AED serum levels within the reference range. Interictal EEG was set at a 200-Hz sampling rate with the 10-20 system, using open/closed eyes, photostimulation, sleep activation, and hyperventilation protocols (Neuropack Sigma, Nihon Koden Corp., Tokyo; Synafit, Avio, Tokyo) in accordance with the American Clinical Neurophysiology Society guidelines (Tatum *et al*., 2016). We evaluated the background activity (slow <8 Hz; normal 8-12 Hz; rapid >12 Hz) and interictal EEG findings. The interictal EEG findings were defined as regional or slow lateralizing (continuous slow [CS], intermittent slow [IS], or intermittent rhythmic slow [IRS]) and/or epileptiform discharges (spikes, spike-wave complexes, sharp waves, and polyspikes). In most patients, head magnetic resonance imaging (MRI) had been performed (fluid attenuation inversion recovery [FLAIR]: 1.5 Tesla or 3.0 Tesla, slice thickness of 2 mm). In five subjects, head CT was performed instead of head MRI. Two neurologists visually evaluated the cortical and white matter lesions for brain atrophy and the distribution of lesions.

Measurement of serum concentration of AEDs before and after HD

We measured the serum concentrations of AEDs in the arterial blood. The number of patients and samples were the following: LEV (nine patients; 34 samples), VPA (four patients; 23 samples), CBZ (two patients; 11 samples), PHT (phenytoin) (four patients; 37 samples), CLB (two patients; 14 samples), and PB (one patient; seven samples). The pre-HD arterial blood samples were taken from the cannula before connecting the patients to the dialyzer, and the post-HD arterial blood samples were taken from the cannula after HD was terminated. We compared the AED concentrations based on reference ranges (LEV: 12-46 mcg/mL; VPA: 50-100 mcg/mL; PHT: 10-20 mcg/mL; and CBZ: 4-12 mcg/mL) (Neels *et al*., 2004; Israni *et al*., 2006). The clearance rate during HD was calculated as 1-(the AED concentration after HD [mcg/mL]/the AED concentration before HD [mcg/mL]). Based on the pharmacokinetic profile of AEDs in patients with HD, AED concentration (mcg/mL) was plotted against dose (mg/kg body weight). The concentration-to-dose (CD) ratio was calculated by dividing the serum concentration (mcg/mL) by the weight-adjusted dose (mg/kg) before and after HD. The CD ratio (mcg/mL per mg/kg) has been used to describe the relationship between plasma AED concentration and dosage by pharmacologists (de Leon, 2004; de Leon *et al*., 2013). Therefore, in our study, we used the CD ratio as a pharmacological parameter.

Statistical methods

All data are presented as mean ± standard error of the mean (SEM) unless otherwise indicated. The significance of differences based on the CD ratio of AEDs was evaluated using one-sample *t*-tests with pre-HD and post-HD values (*figure 2C-F*). A p value < 0.05 was considered to indicate a significant difference. Calculations were performed using the SPSS 23.0J statistical software package (SPSS Japan, Tokyo, Japan).

Results

Clinical characteristics of epilepsy patients with HD

The study included 36 patients with epilepsy who were undergoing HD (*table 1*). Their mean age (± SD) was 65.3 ± 14.8 years; 25 were male and 11 were female. All patients had HD three times per week for 3-4 hours at a time. The age at epilepsy onset was 60.2 ± 14.8 years, and the age at initial HD was 53.9 ± 17.1 years. In 32 patients, HD preceded epilepsy, but in the remaining four patients (Patients 6, 13, 18, 26), epilepsy onset preceded HD. Among all 36 patients, epilepsy occurred 6.1 ± 9.4 years after starting dialysis. Thirty-three patients had focal epilepsy (FE), including 14 with multiple and unknown foci, ten with FLE, six with TLE, two with OLE, one with PLE, and three patients had genetic generalized epilepsy. The aetiologies of the epilepsy were as follows: brain infarctions (n = 12), haemorrhages (n = 11), haematoma (n = 2), cerebral contusion (n = 2), Alzheimer disease (n = 1), cavernous haemangioma (n = 1), CNS lupus (n = 1), hippocampal sclerosis (n = 1), VZV encephalitis (n = 1), and unknown (n = 8). Patients 13, 33, and 35 had both brain infarctions and haemorrhage, and Patient 21 had both cerebral contusion and haematoma. Diabetes was the most frequent reason for HD, followed by chronic glomerulonephritis.

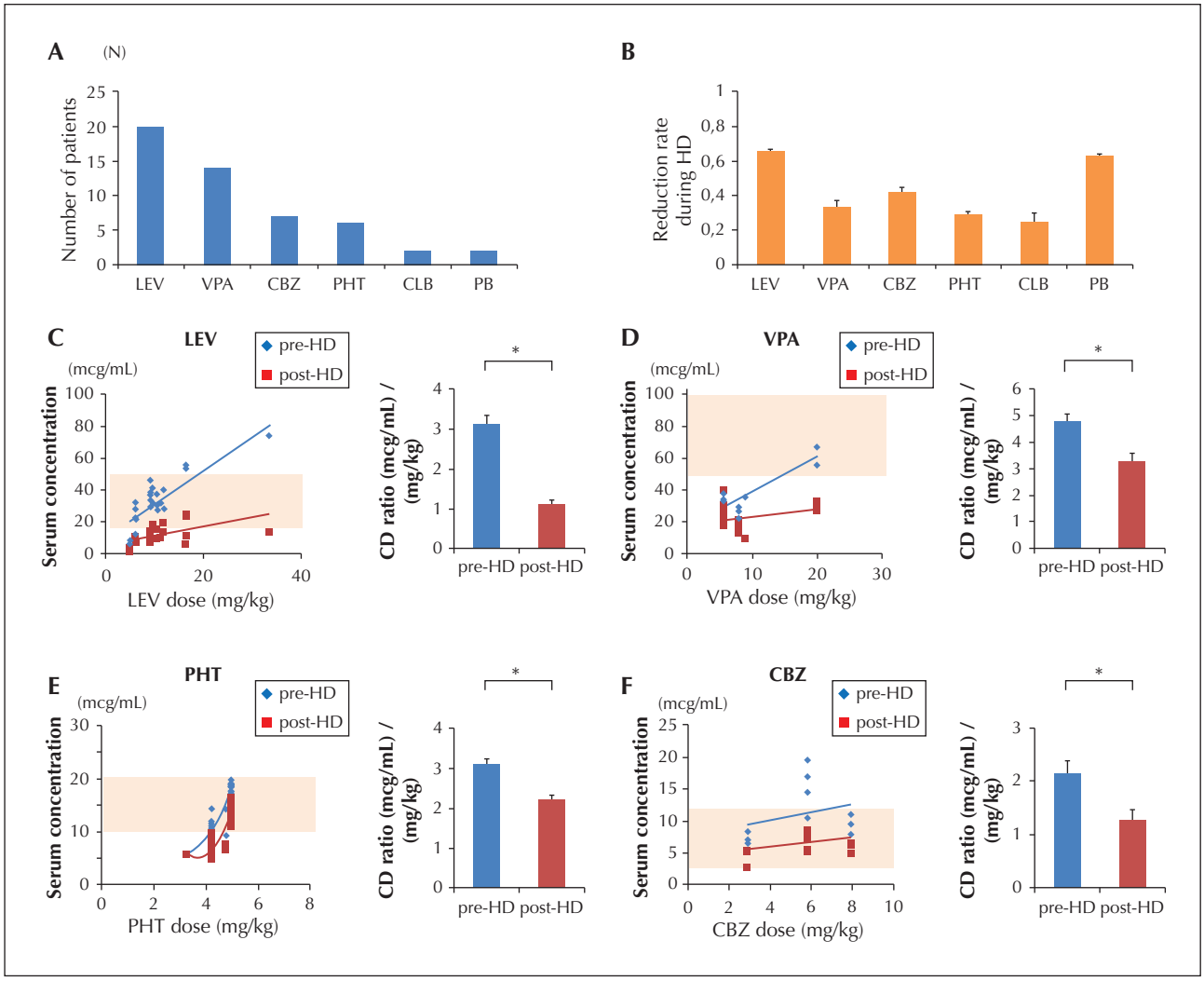

Figure 2. Antiepileptic drug use, clearance rate during dialysis, and pharmacokinetics in patients on haemodialysis (HD). (A) Number of patients using the indicated antiepileptic drugs (AEDs). (B) Clearance rate of AEDs during dialysis: LEV (nine patients, 34 samples), VPA (four patients, 23 samples), CBZ (two patients, 11 samples), PHT (four patients, 37 samples), CLB (two patients, 14 samples), and PB (one patient, seven samples). (mean ± SEM). (C-F) Dose and concentration data before (pre-) HD and after (post-) HD. (C) LEV (nine patients, 34 samples): pre-HD CD ratio = 3.15 ± 0.20; post-HD CD ratio = 1.12 ± 0.088. (D) VPA (four patients, 23 samples): pre-HD CD ratio = 4.81 ± 0.27; post-HD CD ratio = 3.30 ± 0.30. (E) PHT (four patients, 38 samples): pre-HD, CD ratio = 3.10 ± 0.12; post-HD CD ratio = 2.22 ± 0.11. (F) CBZ (two patients, 11 samples): pre-HD CD ratio = 2.14 ± 0.23; post-HD CD ratio = 1.28 ± 0.19. CD ratios are expressed as mean ± SEM, and the significance of differences was evaluated with one-sample *t*-tests for before-HD and after-HD values (*$p <$ 0.001). The horizontal red bar indicates the reference range: LEV at 12-46 mcg/mL; VPA at 50-100 mcg/mL; PHT at 10-20 mcg/mL; and CBZ at 4-12 mcg/mL. LEV: levetiracetam; VPA: valproic acid; PHT: phenytoin; CBZ: carbamazepine.

Seizure characteristics of epilepsy patients with HD

Seizure characteristics are described in *table 2*. Of the 33 patients with FE, eight had FAS, 16 FIAS, and 15 FBTCS. Three patients with genetic generalized epilepsy had generalized tonic-clonic seizures, and one of them had myoclonic seizures in addition to the generalized tonic-clonic seizures. Eleven patients had convulsive SE, three patients had non-convulsive SE (NCSE), and one patient had psychogenic non-epileptic seizures. Thirteen patients had auras. The seizures occurred during HD in 12 patients, between HD sessions in 22 patients, and both during and between HD sessions in two patients.

Interictal EEG was performed in 26 of the 36 patients. The background activity was slow (<8 Hz) in 16 patients and normal (8-12 Hz) in 10 patients. Eleven patients did not have any interictal IRS/IS, spikes, or sharp waves. IRS was seen in eight patients (Patients 2, 8, 9, 31, 32, 34, 35, and 36), and IS in two patients (Patients 30 and 33). In the present study, one out of eight patients with IRS

Table 1. Clinical characteristic of 36 patients.

Patient	Age/Sex	Age at onset of epilepsy	Epilepsy diagnosis	Etiology of epilepsy	Age at the start of HD	Etiology of HD
1	64/M	54	OLE	Cerebral hemorrhage	46	Chronic glomerulonephritis
2†	86/M	83	FE	Cerebral infarction	81	Diabetes
3†	67/M	63	FE	Unknown	61	Diabetes
4	57/M	53*	GGE	Unknown	52	Diabetes
5	71/M	62	FE	Putamen hemorrhage	42, 53**	Chronic glomerulonephritis
6	58/M	45	TLE	Cerebral infarction	48	Unknown
7†	88/F	87	TLE	Alzheimer disease	76	Diabetes
8	82/F	81	TLE	Unknown	71	Diabetes
9	62/F	60	OLE	Cerebral infarction	60	Diabetes
10	78/F	73	TLE	Unknown	64	Diabetes
11	79/M	79	FE	Unknown	78	Diabetes
12	59/F	59	FE	Cerebral infarction	42	Diabetes
13	76/M	64	FLE	Cerebral hemorrhage, infarction	65	Unknown
14	48/M	45	FLE	SAH	30	Chronic glomerulonephritis
15	61/M	59	FE	Medullary infarction	48	Unknown
16	61/M	60	TLE	Cerebral hemorrhage	53	Nephrosclerosis
17	63/M	59	FE	Cavernous hemangioma	55	Diabetes
18	47/F	38	FLE	SAH	46	Chronic glomerulonephritis
19	54/M	54	FE	Pons hemorrhage	42	Diabetes
20	57/M	57	FE	Cerebral infarction	20	Diabetes
21†	73/M	63	FLE	Cerebral contusion. Acute epidural hematoma	58	IgA nephropathy
22†	79/M	80	PLE	Acute epidural hematoma	78	Unknown
23†	77/F	77	FE	Cerebral infarction	70	Diabetes
24†	42/F	41	FE	CNS lupus	41	Lupus nephritis

Table 1. Clinical characteristic of 36 patients. (*Continued*).

Patient	Age/Sex	Age at onset of epilepsy	Epilepsy diagnosis	Etiology of epilepsy	Age at the start of HD	Etiology of HD
25	42/F	22	GGE	Unknown	17	Congenital malformation
26	37/M	0.75	GGE	Unknown	23	Chronic glomerulonephritis
27	39/M	39	FLE	SAH	39	IsA nephropathy
28	44/M	31	TLE	Hippocampal sclerosis	31	Unknown
29	82/F	79	FLE	VZV encephalitis, Lewy dementia	58	Chronic glomerulonephritis
30	69/M	67	FE	Churg-Strauss. Cerebral hemonhage	61	Diabetes
31	63/F	61	FLE	Cerebral infarction	44	Chronic glomerulonephritis
32	81/M	77	FE	Cerebral infarction	73	Chronic glomerulonephritis
33	80/M	65	FLE	Cerebral infarction. Cerebellar hemonhage	62	Nephrosclerosis
34	59/M	59	FLE	Cerebral contusion	50	Diabetes
35	88/M	88	FLE	Traumatic SAH. cerebral infarction	73	Diabetes
36	78/M	74	FE	Unknown	71	Diabetes, Nephrosclerosis

† = Had already died at the time of the analysis. GGE = genetic generalized epilepsy, FLE = frontal lobe epilepsy, TLE = temporal lobe epilepsy, PLE = parietal lobe epilepsy, OLE = occipital lobe epilepsy, FE = focal epilepsy; patients with multiple foci or unknown foci were defined as having focal epilepsy. SAH = subarachnoid hemorrhage. *The patient had febrile seizures with medical treatment in infancy, which resolved when he was an elementary school student. **Stopped HD at age 42 because of a renal transplant; began HD again at age 53.

had frontal intermittent rhythmic delta activity (FIRDA) (Patient 2), and the others had temporal intermittent rhythmic delta activity (TIRDA), occipital intermittent rhythmic delta activity (OIRDA), or multilobal intermittent rhythmic delta activity. Intermittent sharp waves or spikes were seen in two patients (Patients 10 and 28). Generalized spikes and waves were seen in three patients who had been diagnosed with SE (Patients 4, 25, and 29). Generalized periodic synchronization was seen in three patients (Patients 8, 9, and 30). LEV was the most commonly used AED (*figure 2A*) and supplementary doses were administered after HD in all 20 patients according to Japanese TDM 2018 guidelines (Japanese Society of Therapeutic Drug Monitoring, 2018) and previous reports (Israni *et al*., 2006; Lacerda *et al*., 2006). Sixteen patients responded to LEV, and four patients were unresponsive to LEV (*table 3*). A higher percentage of patients were unresponsive to CBZ, VPA, and PHT than LEV (*table 3*).

Comparison of the CD ratios between responders and non-responders during HD

The CD ratios of responders and non-responders are summarized in *table 4*. The pre-HD serum VPA level

Table 2. Seizure characteristic of 36 patients.

Patient	Seizure type	Aura	Timing (during HD or not)	Interictal EEG			Treatment	Response to AEDs
				BG	Findings	Distribution		
1	FAS, FIAS, FBTCS,SE	+	non-HD	Slow	None		PHT + CLB	Responder
2	NCSE	-	HD	Slow	IRS	Bilateral F	VPA	Responder
3	FIAS	-	HD	Slow	None		CBZ	Responder
4	Myoclonus, GTC	-	non-HD	Normal	Spike and wave	Generalized	VPA	Responder
5	FBTCS	-	non-HD	N.P			PHT → LEV	Responder
6	FAS, FIAS, FBTCS	+	HD	Slow	None		VPA + CBZ	Responder
7	FAS	-	HD	N.P			PHT → VPA → VPA +LEV	Non-responder
8	FBTCS, NCSE, SE	-	non-HD	Slow	IRS	Bilateral T	LEV	Responder
9	SE, NCSE	-	non-HD	Normal	IRS	Bilateral F-T-O	LEV	Responder
10	FIAS	-	HD	Normal	Spike	Bilateral T	CBZ	Responder
11	FIAS, SE	+	non-HD	Slow	None		LEV	Responder
12	FIAS, SE	-	non-HD	Normal	None		LEV	Responder
13	FAS, FIAS	+	non-HD	Normal	None		PHT	Responder
14	FIAS, sGTC	+	HD	N.P			CBZ → LEV	Responder
15	FIAS	+	HD	N.P			CLB	Responder
16	FIAS	+	non-HD	Normal	None		LEV	Responder
17	FBTCS	-	non-HD	Normal	None		CBZ	Responder
18	FIAS, FBTCS	-	non-HD	Normal	None		VPA → LEV	Responder
19	FBTCS	-	non-HD	N.P			PHT	Responder
20	FBTCS, SE	-	HD	N P			VPA	Responder
21	FIAS	-	non-HD	N.P			VPA	Responder

Table 2. Seizure characteristic of 36 patients. (*Continued*).

Patient	Seizure type	Aura	Timing (during HD or not)	Interictal EEG			Treatment	Response to AEDs
				BG	Findings	Distribution		
22	FIAS, FBTCS	-	non-HD		N.P		LEV	Responder
23	FBTCS, SE	-	non-HD		N.P		VPA	Responder
24	GTC	-	non-HD		N.P		VPA	Responder
25	GTC	+	HD	Normal	Spike and wave	Generalized	VPA	Responder
26	GTC, PNES	-	HD and non-HD	Slow		None	VPA, PB, LEV	Responder
27	FIAS, SE	+	non-HD	Slow		None	PHT → PHT + LEV	Responder
28	FIAS, FBTCS	+	HD	Slow	Sharp wave	Left T	CBZ, VPA, LEV	Non-responder
29	FBTCS	-	non-HD	Slow	Spike and wave	Left T	LEV	Responder
30	SE	-	non-HD	Slow	IS	Left T	LEV	Responder
31	FAS, FBTCS, SE	-	HD	Slow	IRS	Left F-T	LEV	Responder
32	FAS	+	non-HD	Slow	IRS	Left P-0	CBZ → discontinuation	Responder
33	FAS, FBTCS	+	HD	Slow	IS	Left F-T-P-0	VPA,LEV → VPA,CBZ	Responder
34	FAS	+	non-HD	Normal	IRS	Bilateral F, Left T	LEV	Responder
35	FIAS	-	non-HD	Slow	IRS	Left T	LEV	Responder
36	SE	-	HD and non-HD	Slow	IRS	Bilateral F, Left T	ATA → ATA. LEV	Non-responder

FAS = focal aware seizure, FIAS = focal impaired awareness seizure, FBTCS = focal-to-bilateraltonic-clonic seizure, SE = status epilepticus,NCSE = nonconvulsive status epilepticus, HD = hemodialysis, BG = background activity, IRS = intermittent rhythmic slow, IS = intermittent slow, F = frontal, T = temporal, P = parietal, O = occipital, VPA = valproic acid, PHT = phenytoin, CBZ = carbamazepine, LEV = levetiracetam, CLB = clobazam.

Table 3. Responders and non-responders to antiepileptic drugs.

	Responder	Non-responder	
Antiepileptic drug	**Number of patients**	**Number of patients**	**Responder rate**
LEV	16	4	0.80
VPA	10	4	0.71
CBZ	5	2	0.71
PHT	3	3	0.50

LEV = levetiracetam, VPA = valproic acid, CBZ = carbamazepine, PHT = phenytoin.

Table 4. CD ratios in responders and non-responders.

		Responder			Non-responder				
Antiepileptic drug		**Number of patients**	**Number of samples**	**CD ratio**		**Number of patients**	**Number of samples**	**CD ratio**	***P* value**
LEV	pre-HD	9	30	3.20 ± 0.22	pre-HD	1	3	2.52 ± 0.51	0.36
	post-HD	9	30	1.10 ± 0.097	post-HD	1	3	1.21 ± 0.27	0.73
VPA	pre-HD	4	23	4.81 ± 0.27	pre-HD*	1	4	3.68 ± 0.35	0.11
	post-HD	4	23	3.30 ± 0.30	post-HD	N.P.	N.P.	-	-
PHT	pre-HD	2	22	3.57 ± 0.095	pre-HD	2	16	2.44 ±0.11	<0.001
	post-HD	2	22	2.64 ±0.11	post-HD	2	16	1.64 ± 0.075	<0.001
CBZ	pre-HD	2	11	2.14 ± 0.23	pre-HD	N.P.	N.P.	-	-
	post-HD	2	11	1.28 ± 0.19	post-HD	N.P.	N.P.	-	-

CD, concentration-to-dose, LEV = levetiracetam, VPA = valproic acid, CBZ = carbamazepine, PHT = phenytoin N.P. = not performed, CD ratio = mean ± standard error of the mean (SEM), unpaired West. * Only the pre-HD concentration of VPA was available in the non-responder.

was notably, but not statistically, lower in the one non-responder than in responders. The pre- and post-HD CD ratios for PHT were significantly lower in the non-responders than in the responders.

Relationship between AED dose and serum concentration during HD

We evaluated the serum concentrations of LEV, VPA, CBZ, PHT, clobazam (CLB), and phenobarbital (PB) (*figure 2A*). The CD ratios before and after HD were used as pharmacological parameters. Eight patients received more than one AED (*table 2*). Thirty-three patients were responders, and three patients were non-responders (*table 2*). The clearance rate during HD was 0.65 for LEV, 0.33 for VPA, 0.41 for CBZ, 0.29 for PHT, 0.24 for CLB, and 0.63 for PB (*figure 2B*). In patients taking LEV, VPA, PHT, or CBZ, the CD ratio was significantly lower after HD than before HD ($p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, respectively) (*figure 2C-F*). In patients taking daily 1,000-mg LEV, the pre-HD blood concentration tended to be higher than the reference range (*figure 2C*). In 18 patients taking daily 500-mg LEV, the concentration ranged from 12.3 to 55.6 mcg/mL before HD (mean: 34.2 ± 1.88 mcg/mL). None of the 18 patients taking 500-mg LEV had side effects, although seizure control was insufficient in three patients (3/18, 17%; Patients 7, 28, and 33). Two patients who took daily LEV at 1,000 mg (Patients 26 and 27) had side effects such as drowsiness and dizziness. The pre-HD concentrations of LEV were 28.5 and 73.8 mcg/mL in two patients (reference range: 12-46 mcg/mL). The serum concentrations of PHT and CBZ were within the reference ranges, but those of VPA tended to be lower than the reference range both before and after HD (*figure 2D-F*).

Discussion

Clinical characteristics of epilepsy patients undergoing HD

Life expectancy has increased, resulting in an increasing number of aged people with epilepsy due to various structural brain anomalies (Hauser *et al*., 1993; Olafsson *et al*., 2005; Cloyd *et al*., 2006; Thurman *et al*., 2011). The need for HD also increases in the elderly, therefore the number of elderly people with epilepsy who are also receiving HD is likely to increase. However, few clinical studies have reported on patients with both epilepsy and a need for HD. In this study, among 36 epilepsy patients on HD, 23 patients with FE were more than 60 years old. The prevalence of epilepsy in the patients identified at the four dialysis centres was 2.36%, which is higher than that for epilepsy in the general population of individuals over 60 years old (0.72%) (Fiest *et al*., 2017). Brain infarctions, haemorrhages, and haematomas were seen in two thirds of the study population. This proportion was higher than in previous reports (15.7-46.7%) (Ramsay *et al*., 2004; Tanaka *et al*., 2013; Toyota *et al*., 2016). Epilepsy appears to have an aetiology unrelated to diseases that cause CKD, however, diabetes has been reported to be a possible risk factor for epilepsy (Marcovecchio *et al*., 2015; Lu *et al*., 2018). Taken together, the high incidence of epilepsy in our patients receiving HD may be due to concomitant cerebrovascular disorders and diabetes.

Seizure characteristics in epilepsy patients receiving HD

The seizure characteristics in our 36 epilepsy patients on HD were similar to those in previous reports on elderly individuals with epilepsy (McBride *et al*., 2002; Kellinghaus *et al*., 2004; Cloyd *et al*., 2006; Tanaka *et al*., 2013; Fiest *et al*., 2017): aura was infrequent (36%), and FIAS (48.5%) and FBTCS (45.5%) were seen more frequently than FAS (24.4%).

In this study, the incidence of SE (31%) was higher than in previous reports of SE (Rohracher *et al*., 2016; Malter *et al*., 2017; Yoshimura *et al*., 2018), suggesting that CKD requiring HD is a risk factor for SE. The incidence of SE is especially high in those more than 60 years old (Rohracher *et al*., 2016; Malter *et al*., 2017; Yoshimura *et al*., 2018) due to acute symptomatic disease, infection, metabolic brain disorders, or progressive neurodegenerative disorders (Trinka *et al*., 2015). In addition to SE, NCSE also tends to be more frequent in elderly patients than in non-elderly adults (Iftikhar *et al*., 2007; Cheng, 2014; Canas *et al*., 2018). Although NCSE (8.3%) was less frequent than SE (31%) in the present study, this may be due to under-diagnosis of NCSE in patients on HD, because drug-induced SE, uremic encephalopathy, disequilibrium syndrome, and electrolyte imbalances caused by HD may mimic NCSE (Misra *et al*., 2013). In summary, FIAS and SE were seen more frequently in the present study than in previous studies.

Interictal EEG was performed in 26 of the 36 patients. Among them, only five patients had apparent epileptiform discharge (spikes and waves, sharp waves, and spikes). The background activity tended to have a slower rhythm (62%), and IRS/IS were often seen (38%). Background and intermittent slow waves tended to be seen in patients with metabolic disorders, especially in those with encephalopathy who showed impairment of arousal and cognition (Kaplan, 2004). The background and intermittent slow waves in HD patients could be considered to reflect the degree of cerebral dysfunction, which is a possible predictor of the occurrence of epilepsy. FIRDA is reported to be a non-specific finding, but TIRDA and OIRDA are more specific epileptiform findings (Brigo, 2011). In the present study, one out of eight patients with IRS had FIRDA (Patient 2), and the others had TIRDA, OIRDA, or multilobal inter-rhythmic delta activity.

Serum concentration and effect of AEDs in patients receiving HD

Although many reviews on the use of AEDs in patients with renal failure have been published (Asconape and Penry, 1982; Israni *et al*., 2006; Lacerda *et al*., 2006; Bansal *et al*., 2015), the best choice of AED for patients on HD who have focal seizures or bilateral convulsions has not been determined by experts (Shih *et al*., 2017). In the present study, LEV was the AED most commonly used, and the responder rate with LEV was higher than that for VPA, CBZ, and PHT *(table 3*). However, the clearance rate of LEV during HD was highest among the AEDs we evaluated. The reason for the withdrawal of VPA and PHT was due to a lack of effectiveness to suppress seizures rather than adverse effects. There was no significant difference between the responders and non-responders for the CD ratio of VPA before HD (*table 4*). Although all the patients with genetic generalized epilepsy (Patients 4, 25, and 26) were responders, four patients with focal seizures (Patients 7, 18, 28, and 36) were non-responders, suggesting that the seizure type was a critical factor for the therapeutic effects of VPA in our cohort. However, the CD ratio for PHT in the non-responders was significantly lower than that in the responders (*table 4*), suggesting that the patients who did not respond to PHT were under-treated.

Pharmacokinetics of AEDs in patients receiving HD

It is necessary to monitor the therapeutic concentrations of AEDs in epilepsy patients on HD. As for TDM, it is important to establish whether AEDs are high or low protein-bound, and whether the AED is predominately eliminated by hepatic metabolism or renal excretion (Neels *et al*., 2004). LEV is a low protein-bound AED, predominatly eliminated by renal excretion, and VPA, CBZ, and PHT are high protein-bound AEDs eliminated by hepatic metabolism (Neels *et al*., 2004). In the present study, the clearance rate during HD was highest for LEV (65%) and lower for PB, CBZ, VPA, PHT, and CLB (from high to low), in concordance with previous reports stating that the clearance rate of AEDs that undergo renal excretion is higher than that of AEDs eliminated by hepatic metabolism (Neels *et al*., 2004; Israni *et al*., 2006; Lacerda *et al*., 2006; Bansal *et al*., 2015). Approximately 70% of LEV dose is reported to be excreted unchanged (Yamamoto *et al*., 2014), and the proportion of eliminated drug is similar to that based on our data with respect to the LEV clearance rate. With regards to high protein-bound AEDs, we found that 33% of VPA, 41% of CBZ, and 29% of PHT were reduced by the high-efficiency dialyzers. In previous reports, VPA was shown to be removed by 20% in patients with HD using low-efficiency dialyzers (Marbury *et al*., 1980) and 42% using high-efficiency dialyzers (Gubensek *et al*., 2008). The previous reports on CBZ intoxication showed that HD reduced the plasma concentration of CBZ by 22-50% (Israni *et al*., 2006). The clearance rate of PHT is reported to be 20% in patients with HD using low-efficiency dialyzers (Martin *et al*., 1977) and 41.3% using high-efficiency dialyzers (Frenchie and Bastani, 1998).

Timing of TDM and supplementation

The early literature states that the metabolism of high protein-bound AEDs occurs almost completely in the liver, and no dose adjustment is needed with high-efficiency HD relative to HD with low-efficiency dialyzers (Asconape and Penry, 1982). Therefore, the TDM of AEDs was measured routinely on non-dialysis days. However, there are a few reports on serum concentration of AEDs in epileptic patients on chronic-maintenance HD with high-efficiency dialyzers that remove larger amounts of AEDs (Gubensek *et al*., 2008; Bansal *et al*., 2015). In our study, we evaluated the clearance rate of AEDs before and after HD with high-efficiency dialyzers. The clearance rate of LEV is due to its low protein binding and the fact that it is primarily excreted unchanged by the kidney (Israni *et al*., 2006; Lacerda *et al*., 2006; Bansal *et al*., 2015) which suggests that supplementation will be required after HD (Israni *et al*., 2006; Lacerda *et al*., 2006; Bansal *et al*., 2015). The clearance of LEV is decreased in patients with renal failure by less than 30% (Dohey *et al*., 1999; Yamamoto *et al*., 2014), in concordance with the present finding that the serum concentration of LEV tended to be higher than the reference range before HD. The LEV concentration increased and induced adverse effects in two patients (Patients 26 and 27) taking daily LEV at 1,000 mg before HD, although previous reports recommend daily LEV at 500-1,000 mg (Bansal *et al*., 2015) or 250-500 mg twice a day (Israni *et al*., 2006; Lacerda *et al*., 2006). This suggests a potential risk of overdosing of LEV in patients requiring HD. It is thus necessary to measure the serum concentration of minimal protein-bound AEDs such as LEV both before and after HD, and adjust the supplementary dose accordingly.

In contrast, we found that the CD ratios for VPA, CBZ, and PHT, similar to that for LEV, were significantly lower after HD than before HD. Furthermore, our results show that the CD ratio for PHT in non-responders was significantly lower than that in responders. These results suggest that high protein-bound AEDs, as well as minimal protein-bound AEDs, require TDM before and after HD. The serum concentration of VPA tended to be lower than the reference range both before and after HD. This suggests a potential risk of VPA underdosing during HD. Measurement of the serum concentration on non-dialysis days may also be necessary to determine the supplementary doses of VPA, given the concentration rebound of this AED (Kandrotas *et al*., 1990; Dasgupta *et al*., 1996). We did not evaluate the CD ratios for PB and CLB because of the small number of patients. However, measuring the TDM for PB might also be necessary before and after HD, because its clearance rate during HD is high. TDM for CLB might be required at the trough on a non-dialysis day, because the clearance rate during dialysis is low. □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

Disclosures.
None of the authors have any conflict of interest to declare.

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TEST YOURSELF

(1) What were the clinical features of epilepsy patients undergoing haemodialysis?

(2) What proportion of LEV, VPA, CBZ, PHT, CLB and PB is reduced by haemodialysis?

(3) Which AED is commonly used for epilepsy patients on haemodialysis?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".