Epilepsia Open® The Open Access Journal of the International League Against Epilepsy

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FULL-LENGTH ORIGINAL RESEARCH

Effective withdrawal of antiepileptic drugs in premonitoring admission to capture seizures during limited video-EEG monitoring

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Epilepsia Open, 2(2):172–179, 2017
doi: 10.1002/epi4.12047

Summary

Objective: Withdrawal of antiepileptic drugs (AEDs) is commonly applied to capture seizures in video-EEG (vEEG) monitoring for patients with infrequent but intractable seizures. Because of the half-life of AEDs, AED withdrawal during only vEEG tends to be inadequate to provoke seizures within the vEEG admission. We hypothesize that prewithdrawal of long-half-life AEDs in premonitoring admission (PMA) is safe and effective to capture seizures in the limited time of vEEG. We determined the effect of half-life on the interval between AED withdrawal and seizure occurrence.

Methods: We collected 87 patients with three criteria: (1) seizure occurrence ≤3 per month; (2) AEDs ≥2; (3) AED withdrawal during their admission, among 126 consecutive patients who underwent vEEG in the Department of Neurosurgery, Hiroshima University Hospital between 2011 and 2014. We divided patients into two groups on the basis of half-life of AED: Group A (23 patients) with phenobarbital (PB) and/or zonisamide (ZNS); Group B (64 patients) with other AEDs. In Group A, PB and ZNS were withdrawn during 4-day PMA before vEEG started. Further AED withdrawal was performed during vEEG, depending on the seizure occurrence.

Results: The number of AEDs on admission was significantly higher in Group A (2–6, 3.5 ± 0.9; range, mean ±SD) than in Group B (2–5, 2.8 ± 0.8) ($p < 0.01$). All 23 Group A patients and 13 (20%) Group B patients underwent AED withdrawal during PMA. Seizures occurred during PMA in two patients in both Group A (9%) and Group B (15%). The first seizure occurred significantly longer after the start of withdrawal in Group A (6.1 ± 2.0 days) than in Group B (2.8 ± 1.3 days) ($p < 0.01$). Seizures were equally captured between both groups: 96% in Group A and 92% in Group B during vEEG.

Significance: For epilepsy patients who are treated with PB and/or ZNS, we recommend the planning of AED withdrawal during PMA before the start of vEEG to succeed in capturing seizures during the limited time of vEEG monitoring.

KEY WORDS: Customizing antiepileptic drug withdrawal, Video-EEG monitoring, Premonitoring admission, Half-life of antiepileptic drugs.

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Accepted January 21, 2017.

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Prolonged video-EEG

Prolonged video-EEG (vEEG) monitoring has been widely used to evaluate patients who are candidates for epilepsy surgery.[1] The detection of habitual seizures is essential for vEEG to evaluate seizure characteristics and localization of seizure foci.[2,3] Asano et al.[2] reported that a longer monitoring period was associated with a higher rate of successful diagnostic yields in children. However, for

Key Points

- Customizing antiepileptic drug (AED) withdrawal based on half-life is effective to capture seizures during video-EEG (vEEG) monitoring
- Withdrawal of long-half-life AEDs (PB/ZNS) during premonitoring admission (PMA) improves the capture of seizures within the limited time of vEEG
- Withdrawal from the last AED provoked the first seizure in more than 80% of patients in both groups
- Our withdrawal protocol achieved a high rate of seizure capture during the maximum 7 days of vEEG monitoring
- We recommend careful withdrawal of one to two AEDs rather than more than three AEDs to capture seizures and prevent adverse events

adult patients with infrequent seizures who were taking multiple antiepileptic drugs (AEDs), a lengthy stay may be required for vEEG monitoring because of the unpredictability of their seizure occurrences.[4]

Withdrawal of multiple AEDs

A withdrawal of AEDs is commonly performed to register a sufficient number of seizures during the limited days of vEEG monitoring. This procedure may increase the risk of secondarily generalized tonic-clonic seizures (GTCSs), seizure clustering, and status epilepticus.[5,6] Few guidelines on AED withdrawal during vEEG have been published. Henning et al.[6] described a large variation in patterns and paces of AED withdrawal. Previous reports applying AED withdrawal showed 81.0–92.6% diagnostic yield, with one or more seizures confirmed in the monitored adult patients with infrequent seizures.[4,6–11] There were various patterns of AED withdrawal in each institution. Therefore, the vEEG monitoring periods ranged from 1 to 37 days.

In patients with infrequent but intractable seizures who have been treated with multiple AEDs, the AED withdrawal during only the vEEG monitoring period can be insufficient to capture seizures because of the various half-lives of AEDs. In Japan, 23 AEDs have been approved by the Ministry of Health, Labor and Welfare. Among various AEDs, phenobarbital (PB) and zonisamide (ZNS) have longer half-lives than others when patients are not comedicated with enzyme inducers.[12] There was no report about specific AED withdrawal on the basis of the half-life of AEDs.

We hypothesize that prewithdrawal of PB and/or ZNS in premonitoring admission (PMA) is safe and effective to capture seizures in the limited time of vEEG. We provided a specific PMA before vEEG to withdraw AEDs. This report presents the customizing AED withdrawal during PMA and vEEG to capture sufficient seizures within vEEG monitoring.

Methods

Patient profiles

We reviewed the clinical records of 126 consecutive patients with intractable epilepsy who underwent vEEG monitoring (1 unit for vEEG) for presurgical evaluation in the Department of Neurosurgery, Hiroshima University Hospital, between January 2011 and December 2014. We collected 87 patients using three criteria: (1) seizure occurrence ≤3 per month; (2) taking ≥2 AEDs on admission; and (3) AED withdrawal during their admission.

We divided patients into two groups on the basis of half-life of the AED:[12,13] Group A consisted of 23 patients who had taken longer-half-life AEDs, including PB (70–140 h in adults) and ZNS (50–70 h in adults); Group B was 64 patients who had taken the shorter-half-life AED without PB and ZNS. The half-life of phenytoin (PHT) is dependent on its serum concentration.[13] Predicted half-life of PHT is 35–57 h. Thus, we did not include PHT in the category of long-half-life AEDs.

This study was approved by the Hiroshima University Hospital Institutional Review Board.

Admission schedule

Figure 1 demonstrates examples of our admission schedule, including PMA, vEEG, and AED withdrawal. On Friday, patients were scheduled to be admitted into the neurosurgical ward. They stayed for 4 days for PMA. The patients were instructed to stay within the hospital ward, and they were carefully observed by their caregiver and nurse. Serum levels of AED were examined on admission. On the following Tuesday, the patients were moved into the vEEG unit to start vEEG monitoring. A maximum of 7 days were assigned for vEEG.

AED withdrawal

In Japan, the Ministry of Health, Labor and Welfare had approved 23 AEDs as of 2014. Our patients have taken 13 types of AED as follows: carbamazepine (CBZ), levetiracetam (LEV), lamotrigine (LTG), sodium valproate (VPA), topiramate (TPM), zonisamide (ZNS), clobazam (CLB), gabapentin (GBP), phenobarbital (PB), clonazepam (CZP), phenytoin (PHT), sultiame (ST), and primidone (PRM). In Japan, ZNS was approved in 1989. In the United States, it was approved by the Food and Drug Administration (FDA) in 2000. ZNS is commonly used to treat partial and generalized seizures in Japan.

We defined the term "withdrawal" to include complete discontinuation of AED and reduction in dosage. We managed the withdrawal for only one AED a day. When a patient was taking ≥3 AEDs, one AED was discontinued per

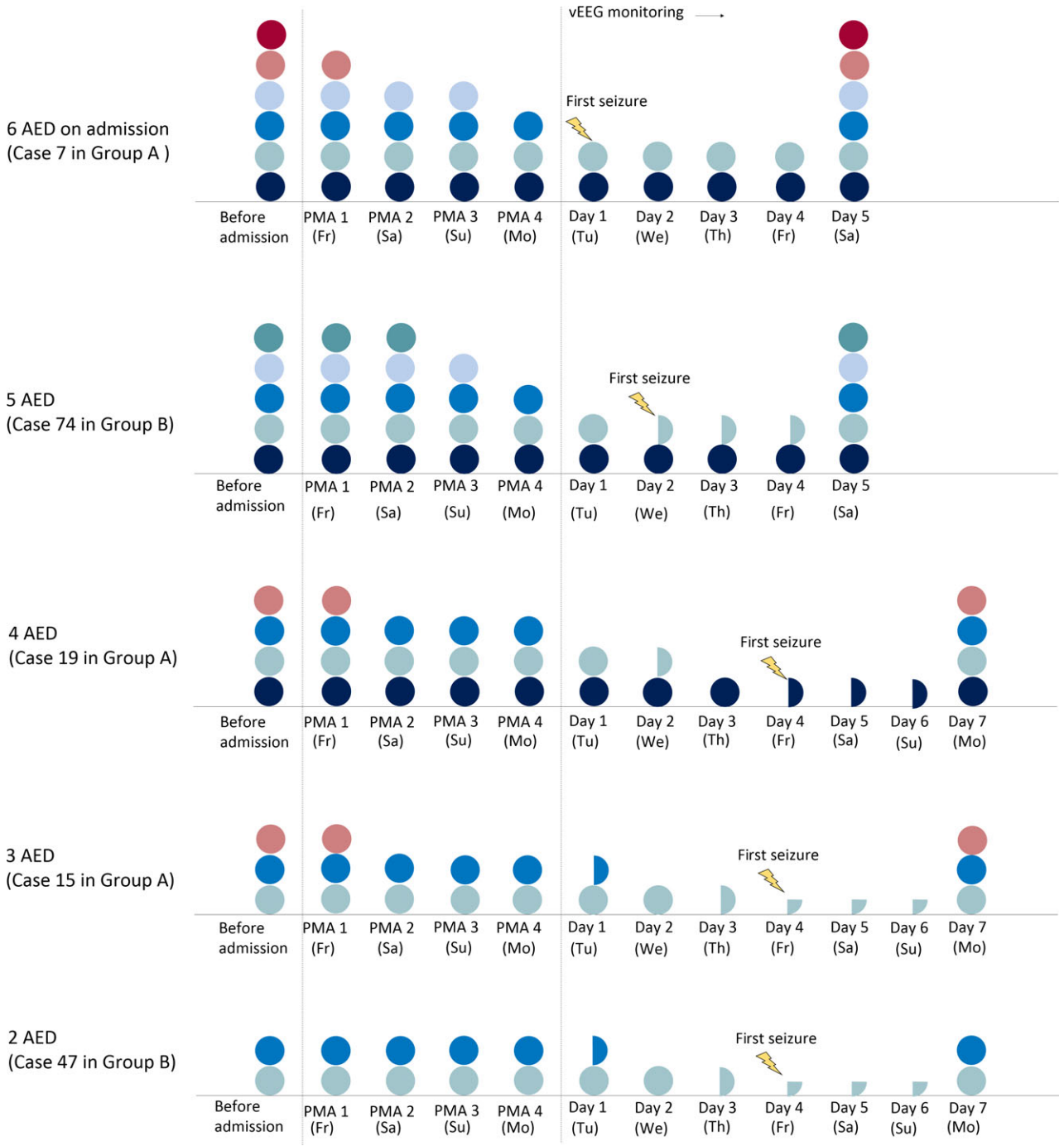

Figure 1.
Five representative cases with AED withdrawal during PMA and vEEG are shown. We withdrew one AED per day. At the start of vEEG on Tuesday, the patients were administered ≤2 AEDs. During vEEG, we performed more gradual AED withdrawal than during PMA. After the first seizure occurred, we did not further withdraw AEDs. Circles represent AEDs. Reddish circles represent either PB or ZNS. Bluish circles represent other AEDs.

day. When a patient was taking ≤2 AEDs, one AED was gradually reduced in dosage until the first seizure occurred. In Group A, both PB and ZNS were completely discontinued during PMA if patients had ≥3 AEDs. In the case of two AEDs on admission in Group A, the dosage of PB or ZNS was reduced by half during PMA. In Group B, one or two AEDs were discontinued during PMA if patients had ≥4 AEDs on admission.

At the start of vEEG on Tuesday, the patients were administered ≤2 AEDs unless they presented seizures during PMA. During vEEG, we performed more gradual AED withdrawal than during PMA. After the first seizure occurred, we did not further withdraw AED. Figure 1 describes the representative cases with AED withdrawal during PMA and vEEG. LTG needs a slow titration when it is restarted. We withdrew LTG last. We restarted all AEDs except LTG after a sufficient number of habitual seizures were captured.

Video-EEG monitoring

We performed prolonged scalp vEEG using the International 10–20 Scalp-Electrode Placement System with a single-reference electrode (BMSI 4000 and 6000; Nicolet Biomedical Inc., Madison, WI, U.S.A.). We used bilateral sphenoidal electrodes for the patients (≥15 years old) if necessary. Patients were instructed to stay still in bed during vEEG. When the patient felt aura or the caregiver was aware of a seizure, they pressed a button to alert staff. Aura itself was not counted as a seizure. All patients provided written informed consent for their participation in this study. We disconnected the patient when sufficient seizures were captured before 7 days in vEEG.

Adverse events

We investigated (1) the incidence of clustering of ≥3 seizures during 4 h; (2) ≥3 seizures during 24 h;[4,6,7,10] (3) unexpected secondarily GTCS in patients who had never presented secondarily GTCS during the previous 5 years; (4) nonconvulsive status epilepticus (NCSE), which we defined as continuous seizure activity without major motor signs, lasting longer than 30 min;[9] (5) convulsive status epilepticus, which we defined as a convulsive seizure lasting longer than 5 min or when consciousness was not regained between two consecutive convulsive seizures;[14] and (6) significant injury with intracranial bleeding or bone fracture of any part of the body.

Statistical analysis

We collected patient data such as sex, age, seizure duration, seizure profile, and etiology. We compared Group A and Group B based on the following data: number of AEDs and serum level on admission; presentation of seizures during PMA; presentation of seizures during vEEG; time from the start of AED withdrawal until the first seizure; time from the start of vEEG until the first seizure; seizures during each AED withdrawal; seizure types captured during vEEG; and adverse events.

We applied Pearson's chi-square test to compare the incidence of the first seizure and adverse events. We applied the independent sample t test to compare age, seizure duration, number of AEDs, time from the start of AED withdrawal to the first seizure, and time from the start of vEEG to the first seizure of the two groups.

Results

Clinical profiles

Table 1 describes the clinical profiles. We collected 87 patients (45 females; 42 males), aged 3–65 years (mean ± SD, 32.5 ± 15.3; median, 33). The seizure history ranged from 2 to 55 years (mean ± SD, 19.3 ± 14.1; median, 16). The age at vEEG ranged from 10 to 63 years (mean ± SD, 35.5 ± 15.2; median, 37) in Group A and from 3 to 65 years (mean ± SD, 31.4 ± 15.3; median, 32) in Group B. Seizure profiles consisted of simple partial seizure (SPS) in one patient, complex partial seizure (CPS) in 47, partial seizure with secondarily GTCS in 24, and tonic or tonic-clonic seizure in 15. The etiology consisted of hippocampal sclerosis and/or hippocampal atrophy on MRI in 14 patients, encephalitis in 13, neuronal migration disorder in 9, perinatal insult in 4, cavernous angioma in 3, brain tumor in 2, other causes in 4, and unknown in 38 patients.

Usage and serum level of AED

Table 2 describes usage and serum levels of AED. The AED on admission consisted of CBZ in 54 patients; LEV in 53 patients; LTG in 37; VPA in 27; TPM in 22; ZNS in 19; CLB in 15; GBP in 7; PB in 7; CZP in 7; PHT in 5; sultiame in 2; and primidone in 1. There were 59 different combinations of AEDs. The most frequent combination was CBZ + LEV in 8 patients. LEV + VPA and CBZ + LEV + LTG each were taken by 5 patients. The number of AEDs on admission ranged from 2 to 6 (mean ± SD, 3.5 ± 0.9;

Table 1. Patient profiles

Sex	
Female	45
Male	42
Age (years)	
Range	3–65
Mean ± SD	32.5 ± 15.3
Median	33
Seizure duration (years)	
Range	2–55
Mean ± SD	19.3 ± 14.1
Median	16
Seizure profiles	
SPS	1
CPS	47
Partial seizure with 2GTCS	24
Tonic/tonic-clonic seizure	15
Etiologies	
Hippocampal sclerosis/atrophy	14
Encephalitis	13
Neuronal migration disorder	9
Perinatal insult	4
Cavenous angioma	3
Brain tumor	2
Others	4
Unknown	38

CPS, complex partial seizure; SD, standard deviation; SPS, simple partial seizure; 2GTCS, secondarily generalized tonic-clonic seizure.

Table 2. Usage and serum level of AED on admission

AED	Half-life[a] (h)	No. of patients: All patients	No. of patients: Group A	No. of patients: Group B	Reference range[b] (μg/ml)	Serum level (μg/ml): All patients	Serum level (μg/ml): Group A	Serum level (μg/ml): Group B
Carbamazepine (CBZ)	8–20	54	14	40	4–12	8.39 ± 2.72	7.94 ± 2.69	8.54 ± 2.76
Levetiracetam (LEV)	6–8	53	11	42	12–46	26.2 ± 14.1	26.1 ± 13.1	26.2 ± 14.4
Lamotrigine (LTG)	15–35	37	8	29	2.5–15	5.39 ± 2.60	4.51 ± 2.73	5.65 ± 2.56
Sodium valproate (VPA)	11–20	27	7	20	50–100	60.6 ± 21.4	59.7 ± 11.6	60.9 ± 24.7
Topiramate (TPM)	20–30	22	6	16	5–20	7.0 ± 3.1	6.05 ± 1.51	7.38 ± 3.48
Zonisamide (ZNS)	50–70	19	19	–	10–30	16.4 ± 6.9	16.4 ± 6.85	–
Clobazam (CLB)	10–30	15	3	12	0.03–0.3	0.140 ± 0.073	0.108 ± 0.0756	0.155 ± 0.0717
Gabapentin (GBP)	5–9	7	1	6	2–20	10.8 ± 5.9	4.10	11.9 ± 5.67
Phenobarbital (PB)	70–140	7	7	–	10–40	18.2 ± 7.1	18.2 ± 7.09	–
Clonazepam (CZP)	17–56	7	2	5	0.02–0.07	0.026 ± 0.024	0.0221 ± 0.0108	0.0360 ± 0.0251
Phenytoin (PHT)	35–57[c]	5	2	3	10–20	15.3 ± 5.7	16.2 ± 7.64	14.8 ± 5.80
Others[d]	–	3	–	3	–	–	–	–

[a]Half-life in the absence of interacting comedication. Data from Patsalos et al.[12]
[b]Data from Patsalos et al.[12]
[c]The half-life of phenytoin is dependent on its serum concentration.[12,13] Predicted half-life is 35–57 h with a phenytoin concentration for the reference range of 10–20 μg/ml.[13]
[d]Two patients with sultiame and one patient with primidone.

median, 3) in Group A and 2 to 5 (mean ± SD, 2.8 ± 0.8; median, 3) in Group B. Group A patients took significantly more AEDs than Group B patients ($p < 0.01$). The mean serum level of AED on admission was within the reference range for all patients. The serum levels of AED in both Group A and Group B were similar for all AEDs.

Occurrence of the first seizure during PMA and video-EEG monitoring

In 36 patients (Group A, all 23 patients; Group B, 13 patients) whose AEDs were withdrawn during PMA, seizures occurred during PMA in 2 patients in both Group A (9%) and Group B (15%) (Table 3). In 51 Group B patients with two or three AEDs on admission, AEDs were not withdrawn during PMA.

Seizures occurred during PMA in 2 patients in Group A. A 28-year-old male with a history of encephalitis was on five AEDs (PB, LEV, TPM, VPA, and CZP). We discontinued PB on PMA1. He had a partial seizure with secondarily GTCS after discontinuation of LEV on PMA4. We temporarily restarted LEV on PMA4. There were no more seizures. We discontinued LEV at the start of vEEG. We captured a total of five partial seizures with secondarily GTCS during 3-day vEEG without adverse events on three AEDs. A 43-year-old male with a history of encephalitis was on three AEDs (ZNS, CBZ, and CLB). We discontinued ZNS on PMA1. He presented CPS once during each

Table 3. Number of AEDs on admission and seizure occurrence during PMA and video-EEG

	No. of AEDs on admission* Mean ± SD		No. of patients	Patients with seizures: PMA No. of patients	Patients with seizures: PMA Total no. of patients (%)	Patients with seizures: vEEG No. of patients	Patients with seizures: vEEG Total no. of patients (%)	Time until the first seizure (days, mean ± SD): From start of AED withdrawal*		From start of vEEG	
Group A (23)	6	3.5 ± 0.9	1	–	2 (8.7)	1	22 (95.7)	5	6.1 ± 2.0	1	3.2 ± 1.5
	5		1	1		1		2		2	
	4		9	–		9		4–9		1–6	
	3		10	1		9		3–10		1–6	
	2		2	–		2		7–8		4–5	
Group B (64)	5	2.8 ± 0.8	1	–	2 (15)[a]	1	59 (92.2)	4	2.8 ± 1.3	2	2.7 ± 1.2
	4		12	2		12		1–6		1–5	
	3		24[b]	–	–	24		1–5		1–5	
	2		27[b]	–	–	22		1–5		1–5	

AEDs, antiepileptic drugs; PMA, premonitoring admission; SD, standard deviation; vEEG, video-EEG monitoring.
[a]Two patients with seizures in 13 patients who underwent AED withdrawal during PMA.
[b]AED was not withdrawn during PMA.
*$p < 0.01$.

PMA3 and PMA4. ZNS was no longer administered. We never discontinued the other AEDs during vEEG. We captured a total of three CPS during 6-day vEEG without any adverse events on two AEDs (CBZ and CLB).

During vEEG, all patients except 4 who presented seizures during PMA underwent withdrawal of AEDs. Twenty-two (96%) patients in Group A and 92% patients in Group B presented seizures during vEEG. The number of seizures captured ranged from 0 to 13 (mean ± SD, 3.4 ± 2.5; median, 3) in Group A and from 0 to 10 (mean ± SD, 3.5 ± 2.2; median, 3) in Group B.

The first seizure occurred significantly longer after the start of AED withdrawal in Group A (2–10 days; mean ± SD, 6.1 ± 2.0 days) than in Group B (1–6 days; mean ± SD, 2.8 ± 1.3 days; $p < 0.01$).

The time from the start of vEEG until the first seizure did not differ between Group A (1–6 days; mean ± SD, 3.2 ± 1.5 days) and Group B (1–6 days; mean ± SD, 2.7 ± 1.2 days).

Correlation between progress of AED withdrawal and first seizure occurrence

In both Group A and Group B, the patients taking five or six AEDs did not present seizures when one AED was discontinued (Table 4; Fig. 2). When 72 patients (Group A, 19; Group B, 53) with two AEDs needed AED withdrawal, the seizure occurrence became more than 20%. When 51 patients (Group A, 14; Group B, 37) with one AED needed further AED withdrawal, seizure occurrence reached more than 80%: 13 of 14 (93%) patients in Group A, and 32 of 37 (86%) in Group B.

There was a significant correlation between the progress of AED withdrawal and the proportion of patients developing the first seizure at the time of withdrawal of the second AED. Group A patients had a significantly lower incidence of the first seizure than those of Group B ($p < 0.01$) only when they experienced withdrawal of the second AED (5→4→3, 4→3→2, 3→2→1, or 2→1→0 AEDs).

In Group A, the first seizure occurred during PMA in one of 11 occasions with four to three (4→3) AED withdrawal and one of 20 occasions with three to two (3→2) AED withdrawal. In Group B, the first seizure occurred during PMA in two of 13 occasions with four to three (4→3) AED withdrawal (Fig. 2).

Simple partial seizure occurred in only 1 patient in Group A. Complex partial seizures occurred in 12 Group A patients and 31 Group B patients. Partial seizures with secondarily GTCS occurred in 7 Group A patients and 17 Group B patients. Eighteen patients (Group A, 5; Group B, 13) of the 24 patients had experienced secondarily GTCS in their life before this admission.

Adverse events

There were no adverse events during PMA. During vEEG, clustering of ≥3 seizures occurred during 24 h in 5 (22%) Group A and 21 (33%) Group B patients. Frequent seizures of ≥3 during 4 h occurred in 3 (13%) Group A and 8 (13%) Group B patients. Unexpected secondarily GTCS occurred in 2 (9%) Group A patients and 4 (6%) Group B patients. Nonconvulsive status epilepticus occurred in 1 (4%) Group A patient and 1 (2%) Group B patient.

Two patients presented NCSE lasting longer than 30 min during vEEG after AED withdrawal. A 41-year-old male (Group A) had complex partial seizures with secondarily GTCS resulting from acute ischemic encephalopathy caused by a history of cardiac asystole and severe cardiac dysrhythmia. A 46-year-old male (Group B) with a history of cerebral palsy resulting from perinatal ischemia had complex partial seizures with secondarily GTCS. Both patients had NCSE in their seizure histories.

Table 4. Incidence of first seizure and adverse events in a correlation with progress of AED withdrawal

	Withdrawal of AED	No. of patients	No. of patients who presented seizure during each withdrawal (%)	Seizure types				Adverse events			
				SPS	CPS	Partial seizure with 2GTCS	Tonic/ tonic-clonic seizure	≥3 seizures in 24 h	≥3 seizures in 4 h	Unexpected 2GTCS	NCSE
Group A (23)	6→5	1	–	–	–	–	–	–	–	–	–
	5→4	2	–	–	–	–	–	–	–	–	–
	4→3	11	1 (9)	–	–	1	–	–	1	–	–
	3→2	20	3 (15)	–	2	1	–	1	–	–	–
	2→1[a]	19	5 (26)	–	3	–	2	–	1	–	1
	1→0[a]	14	13 (93)	–	7	5	1	4	1	2	–
Group B (64)	5→4	1	–	–				–	–	–	–
	4→3	13	2 (15)	–	1	1	–	1	–	–	–
	3→2	37	9 (24)	–	7	–	2	4	–	1	–
	2→1[a]	53	16 (30)	–	7	6	3	9	3	–	–
	1→0[a]	37	32 (86)	1	16	10	5	7	5	3	1

CPS, complex partial seizure; NCSE, nonconvulsive status epilepticus; SPS, simple partial seizure; 2GTCS, secondarily generalized tonic-clonic seizure.
[a]Discontinuation or partial reduction of dosage in one AED.

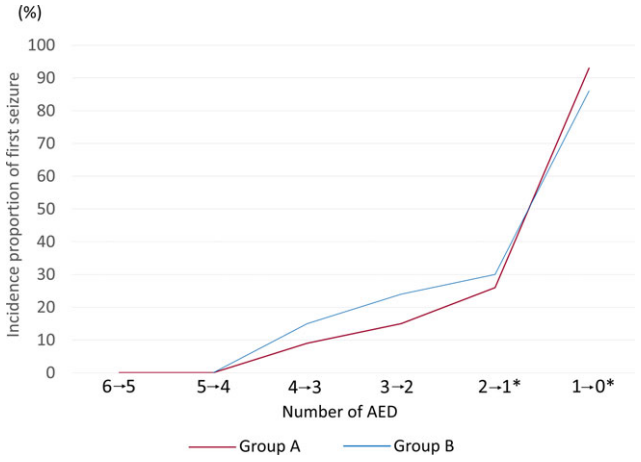

Figure 2.
The sequential line graphs show the incidence proportion of the first seizure in correlation with progress of AED withdrawal in Group A (red) and Group B (blue). As numbers of AEDs decrease, the incidence of the first seizure increases gradually. Withdrawal from the last AED (1→0) provokes the first seizure in more than 80% of patients in both groups: 13 of 14 (93%) patients in Group A, and 32 of 37 (86%) in Group B.
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They had similar episodes in their seizure history. Both patients recovered on the next day after intravenous injection of diazepam and fosphenytoin. There was no convulsive status epilepticus, cardiac asystole, significant injury of intracranial bleeding, or bone fracture of any part of the body during admission.

Discussion

Summary of findings

We customized the timing and order of AED withdrawal in consideration of half-life of AEDs and number of AEDs. PB and/or ZNS was intensively discontinued during PMA before the start of vEEG monitoring in Group A. The number of AEDs was significantly larger in Group A than that of Group B. All 23 Group A patients and 13 (20%) of 64 Group B patients underwent AED withdrawal during PMA. During PMA, seizures occurred in 2 (9%) of 23 Group A patients and 2 (15%) of 13 Group B patients who underwent AED withdrawal. During the maximum 7 days of vEEG, seizures were equally captured for both groups: 22 (96%) Group A patients; 61 (92%) Group B patients. The first seizure occurred significantly longer after the start of withdrawal in Group A than in Group B ($p < 0.01$). There was no difference in time of capturing the first seizure from the start of vEEG between the groups.

Consideration of long-half-life of AEDs

Yen et al.[4] monitored serum levels of CBZ, VPA, PHT, PB, and PRM at the time of first seizure during vEEG in 89 patients with temporal lobe epilepsy. When the first seizure occurred, the serum level of AED was subtherapeutic, but not at the minimum level. They described how the mechanism of AED discontinuation to provoke seizure is related to a loss of therapeutic effect of AED. The half-lives of PB (3–7 days) and ZNS (2–3 days) are longer than those of CBZ (8–20 h), VPA (11–20 h), and PHT (30–100 h, depending on dosage). The "reference range" is defined as a range of drug serum levels quoted by the laboratory that specifies a lower limit below which a therapeutic response is relatively unlikely to occur.[12] In this study, the mean serum levels of AED on admission were within the reference range for all AEDs. The serum level after discontinuation of each AED is estimated to decrease toward the subtherapeutic level over the time of half-life. The patients who took PB or ZNS required at least 2 days to reach the subtherapeutic level to capture the first seizure. We recommend starting AED withdrawal of long-half-life AEDs during 3–4 days of PMA, before the start of vEEG.

Valuable customizing AED withdrawal

There have been large variations in AED withdrawal in previous studies. In patients with temporal lobe epilepsy, Yen et al.[4] withdrew multiple AEDs within 4–6 days after the start of vEEG. They found nearly 50% of patients needed 7 or more days of vEEG monitoring to present seizures. Rizvi et al.[11] performed rapid withdrawal after the start of vEEG. All AEDs except PB were simultaneously titrated to half-dose at the start of vEEG and discontinued at 24 h. They captured ictal events in 90.5% of patients during 4.53 ± 1.44 (mean $\pm$ SD) days of vEEG.

Our seizure capture rate was equal between Group A and Group B: 96% in Group A and 92% in Group B. Our customizing AED withdrawal for the long half-life of PB and ZNS during PMA enabled us to register sufficient seizures in Group A as those in Group B patients without PB and ZNS. Decreasing the serum level toward the subtherapeutic level might be essential to provoke seizures in the patients with infrequent seizures who take multiple AEDs.

Safety of AED withdrawal

In our protocol, we withdrew AED one by one. The number of AEDs was decreased in a stepwise fashion during PMA and vEEG until the first seizure occurred. As the number of AEDs decreased, the incidence of the first seizure increased gradually. The withdrawal from the last AED provoked the first seizure in more than 80% of patients in both groups.

Previous studies showed clustering of three or more seizures within 24 h in 39.0–48.5%, those within 4 h in 11.0–17.8%, unexpected secondarily GTCS in 7.4–9.0%, and status epilepticus in 0–3.0% during vEEG.[4,6–11] Our protocol presented similar adverse events during only vEEG,

however, not in PMA. Our withdrawal protocol achieved a high rate of seizure capturing during the maximum 7 days of vEEG monitoring with similar adverse events as reported before. For patients with multiple AEDs, we recommend more careful withdrawal of one to two AEDs rather than three or more AEDs to capture seizures and prevent adverse events.

Limitations

There are four limitations to this study: (1) the serum level of each AED was not examined when the first seizure occurred. (2) The influence of drug interaction was not taken into consideration in our protocol of AED withdrawal. Serum-level monitoring of AEDs might improve understanding of the interaction during customized AED withdrawal. (3) This study has too few patients to give confidence that our protocol is safe enough for all types of epilepsy patients. MORTality in Epilepsy Monitoring Unit Study (MORTEMUS) reported 29 (0.02%) cardiorespiratory arrests and 16 (0.01%) sudden unexpected deaths in epilepsy (SUDEP) among 133,788 vEEG studies.[15,16] Fourteen (88%) of 16 patients with SUDEP underwent AED withdrawal. During both PMA and vEEG, we asked nurses and caregivers to strictly monitor patients and inform doctors of seizures. We have to pay careful attention and monitor these rare but serious adverse events when we withdraw AEDs to capture seizures. We have never experienced SUDEP in 10 years of vEEG. (4) This study was conducted on patients with refractory focal epilepsy undergoing presurgical evaluation. The conclusions should be confined to this particular group.

Conclusion

For epilepsy patients who are treated with PB and/or ZNS for infrequent but intractable seizures, we recommend the planning of AED withdrawal during PMA before the start of vEEG to succeed in capturing seizures during the limited time of vEEG monitoring.

Acknowledgments

Drs. Kota Kagawa and Hiroshi Otsubo were supported by EpLink—the Epilepsy Research Program of the Ontario Brain Institute (OBI). The OBI is an independent nonprofit corporation, funded partially by the Ontario government. The opinions, results, and conclusions are those of the authors, and no endorsement by EpLink or the OBI is intended or should be inferred. We thank Dr. Eisuke Hida of Hiroshima University Hospital for his invaluable assistance in statistical analyses.

Disclosure of Conflict of Interest

Author Koji Iida has received support from Otsuka Pharmaceutical Company and UCB Japan Company. Author Kaoru Kurisu has received support from Otsuka Pharmaceutical Company and Daiichi Sankyo Company. The remaining authors have no conflicts of interest. We confirm that we have read the Journal`s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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