

Successful, Short-Term Drug Exchange Protocol in Epilepsy: Transient Add-on of Intravenous Anti-Epileptic Drugs

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Abstract

Newer antiepileptic drugs (AEDs) are supposed to be more beneficial at controlling seizures than older AEDs. We substituted newer AEDs for older AEDs while conducting a transient add-on of an intravenous (IV) antiepileptic drug (AED) as a base therapy (AED adjustment), and in the present paper we evaluate the efficacy and safety of this method. The study participants were 40 consecutive referral patients with intractable epilepsy who had been treated with two or more AEDs but had epileptic seizure which spoiled their quality of life. Five of the patients were excluded because any IV AEDs exacerbated their clinical seizures and electro-encephalography (EEG). The mean age of the remaining 35 patients was 7.5 (range: 1.2 - 20.5). The patients had been on two to five AEDs (mean 3.3), and experienced seizures ranging from 0.2 to 100 times/day (mean 13.0). We kept the patients on one or two key oral AEDs and terminated the other oral AEDs simultaneously while they were treated with a base IV AED. After adjusting their dose, the patients were on two to four oral AEDs (mean 2.8) two years later, and the frequency of seizures was reduced to 0 to 10 times/day (mean 1.4). It took about one month of hospitalization to adjust the AEDs, and both seizure frequency and the number of drugs decreased significantly after AED adjustment ($p < 0.001$). There were no serious side effects of clinical seizures or in their blood and chemistry tests. The adjusted AEDs included newer ones, and the older ones were still necessary. AED adjustment was possible and useful for epileptic patients once a transient add-on of intravenous antiepileptic drugs was done.

Keywords: Anti-epileptic drug adjustment; Intravenous antiepileptic drug; Status epilepticus

Introduction

Intractable epilepsy is defined by the International League Against Epilepsy as failure of adequate trials of two tolerated and appropriately chosen and used anti-epileptic drug (AED) schedules, whether as monotherapy or in combination, to achieve sustained freedom from seizures [1]. For intractable epileptic patients, administration of other drugs sometimes spoils their quality of life (QOL). Newer AEDs, such as Gabapentin (GPT), Topiramate (TPM), Lamotrigine (LTG), Levetiracetam (LEV), and Rufinamide (RFN) have been readily available in Japan since 2006, 2007, 2008, 2010, and 2013, respectively, and the high efficacy of these AEDs in the treatment of intractable epileptic patients has been reported [2-5]. When a newer AED is introduced, it does not have the desired effect when used with several other AEDs [6,7]; physicians often attempt, therefore, to decrease the total number of AEDs before adding another drug, but a reduction in oral AED can potentially cause seizure exacerbation, e.g., frequent seizures, status epilepticus, and sudden unexpected death in epileptic patients [8]. Mattson and Cramer [9] and Schmidt [10] reported that it took 51 weeks or longer for them to completely reduce the number of AEDs on the clinic level, but seizures increased during the period of AED reduction. Therefore, we proposed a protocol by which hospitalized patients were put on a transient add-on intravenous (IV) AED as a base drug to stop inappropriate oral AED/AEDs before adding another AED. This paper examines the safety and efficacy of this protocol.

Subject and Methods

The authors confirm that all related trials for this intervention are officially registered as follows: the study was approved by the Hospital Ethics Committee of Medicine and Medical Care, University of Occupational and Environmental Health, JAPAN. Informed consent was obtained from all patients and/or one of the parents.

Forty intractable epileptic patients who were introduced to our hospital between November 1, 2010 and October 31, 2013, were consecutively invited to participate in this trial. Patients whose symptoms and clinical data showed that epileptic surgery was the first line therapy, such as hemimegalencephaly and mesial temporal sclerosis, and who were using specific treatments, e.g., ketogenic diet or ACTH, were not enrolled. Intractable epileptic patients using multiple AEDs after ACTH or without experience of ketogenic diet were included. We acquired written informed consent, which contained the trial methods and follow-up schedule. We evaluated which IV AEDs were effective by the patients' clinical seizures and frequencies of spike in real time video electro-encephalography (EEG) recording after hospitalization (day 0). The AEDs were: IV Midazolam (MDZ 0.1 mg/kg/dose)/5 minutes (slow IV); slow IV Fosphenytoin sodium hydrate (fosPHT; 10 mg/kg/dose); or slow IV Phenobarbital (PB 10 mg/kg/dose). Patients were treated with an effective IV AED (base IV AED) from day 0 (e.g., continuous IV MDZ 0.1 mg/kg/hour, slow IV fosPHT 5 mg/kg/dose/twice a day, or slow IV PB 5 mg/kg/dose/twice a day). One parent stayed with the patient during the entire admission period to observe his/her condition and to count the frequency of seizures.

We arbitrarily defined the seizure frequency as 100 times if patients

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had over 100 seizures in a day. We administered one or two key oral AEDs and withdrew all other oral AEDs at one time while maintaining the base IV AED on the day after admission for its concentration to come into effect. We prefer MDZ as a base IV AED because its concentration stabilizes in a short period. We evaluated the efficacy of IV MDZ (0.1 mg/kg/dose) on days 8 to 10 even if it worsened the patient's clinical seizures and or EEG in the initial trial, because the response to IV MDZ improved after withdrawal of several other oral AEDs [7]. In such cases of improvement, we altered the base IV AED from fosPHT or PB to MDZ.

We gradually decreased the base IV AED dose on day 9 or 12 (e.g., MDZ as 0.01 mg/kg/day, and fosPHT and PB as 1.0 mg/kg/4 days). After decreasing the IV AED, patients had seizures, so we checked their seizure type and decided which oral AED should be increased or added. We evaluated the efficacy of the AED by means of frequent video EEG recording and the patients' clinical state. We examined the following factors from the patients' medical files retrospectively: 1) patient's clinical profile, 2) type of base IV AED, 3) the number of oral drugs used and the frequency of seizures before and after AED adjustment, 4.1) side effects of a base IV AED and 4.2) adverse events such as seizure exacerbation while we withdrew several oral AEDs at one time, behavior problems, abnormality in blood tests, or any other changes that occurred during the follow-up periods, and 5) the length of stay

in our hospital for AED adjustment. We measured patients' primary endpoint three months after AED adjustment and their condition two years after adjustment as the secondary endpoint.

Statistical Analysis

Non-parametric Kruskal-Wallis test (SPSS) were used to compare the number of oral AEDs the patients used, the frequency of seizures before enrolment in the study, and primary and secondary endpoints after AED adjustment. If we found a significant difference among the factors of before treatment, primary endpoint and secondary endpoint, we divided the patients into three groups and compare the difference among groups: 1) Congenital group, whose cause of epilepsy was chromosomal, a genetic anomaly or a developmental delay from early infancy without any reason; 2) Acquired group, who had a medical history of severe asphyxia or anoxia, and whose MRI showed post-ischemic abnormality of asphyxia or encephalopathy/encephalitis; and 3) Cryptogenic group, who had intractable epilepsy after normal early infancy development. A *p* value less than 0.05 was considered significant.

Results

Patient backgrounds

Figure 1 is a flow chart of the patients in this study. Because there was a small number of patient, we initially analyzed all of them together. We found 17 patients in Congenital group, 14 in Acquired group, and nine in cryptogenic group.

Base IV AED and number of oral AEDs and seizures before and after AEDs adjustment

The patients' underlying conditions are presented in (Table 1). The mean patient age was 7.5 (from 1.2 years to 20.5 years). Five patients (one with Congenital, one with Acquired and three with Cryptogenic) who's EEG did not improve or worsened after the administration of any IV AED and whose clinical symptoms were exacerbated were excluded from further examination (Figure 1). Therefore, thirty-five patients analyzed in this treatment regimen. Most of the patients took multiple oral AEDs (mean: 3.3, range: 2 to 5, Table 1). The base IV AEDs were MDZ for 24 patients, fosPHT for 10 patients, and PB for one patient. When we asked the parent for the patients' history precisely and check their EEG, the physicians who had been introduced patients to us, often misdiagnosed epileptic syndrome of secondarily generalized epilepsy as generalized epilepsy; therefore they had chosen wrong combination of AEDs. In those cases, we withdrew all drugs except for one drug which was effective for partial epilepsy. They were followed-up for at least two years, and the longest follow-up was for six years. The number of oral

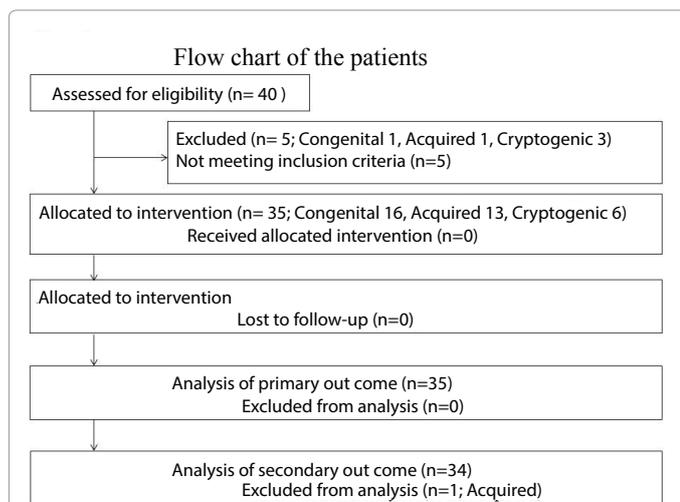


Figure 1: Forty patients participated in this study. Five patients whose EEGs did not improve or worsened after the administration of any IV AED or whose clinical symptoms were exacerbated were excluded from this study. Thus, we analyzed the results of thirty-five patients in this treatment. Cause of Epilepsy is 16 patients as Congenital, 13 as Acquired, and six as Cryptogenic.

Background disorder	Number of patients	Age (mean, range)	Before treatment (Mean, range)	First outcome (Mean, range)	Second outcome (Mean, range)
All patients	N=40	7.5 (1.2-20.5)	3.3 (2-5) 13.0 (0.1-100)	2.6 (2-4)	2.8 (1-4) 1.4 (0-10)
Congenital	N=17	5.9 (0.2-13.8)	--	--	--
AED Seizure	--	--	3.4 (2-5) 17.4 (0.1-100)	2.8 (2-4) 1.5 (0.0-5.0)	2.9 (2-4) 1.5 (0.0-10.0)
Acquired	N=14 (12)	9.5 (2.2-10.5)	--	--	--
AED Seizure			3.5 (2-5) 11.2 (0.7-100)	2.7 (2-3) 1.0 (0.0-5.0)	3.0 (2-4) 1.9 (0.0-10.0)
Cryptogenic	N=9	7.3 (4.3-12.5)	--	--	--
AED Seizure	--	--	2.8 (2-3) 5.4 (0.1-6.0)	2.2 (2-3) 0.0 ± 0.0	1.7 (1-2) 0.0 ± 0.1

AED: Anti-Epileptic Drugs; ASD: Autistic Spectrum Disorder

Table 1: Background disorders and Numbers of AEDs and Seizures of the patients.

AEDs taken before drug adjustment was two drugs for three patients, three drugs for 20 patients, four drugs for nine patients, and five drugs for three patients. The mean number of drugs taken after adjustment of AEDs at the primary endpoint was 2.6: two drugs for 14 patients, three drugs for 20 patients, and four drugs for 1 patient. The number at the secondary endpoint was one drug for three patients, two drugs for 10 patients, three drugs for 13 patients, and four drugs for eight patients. The AEDs had been reduced significantly ($p < 0.001$) after adjustment (Figure 2a). The main adjusted AEDs at the primary endpoint were Zonisamide (ZNS), Sodium Valproate (VPA), and Gabapentin (GBP), and the main added AED was Topiramate (TPM). At the secondary endpoint, the main adjusted AEDs were Carbamazepine (CBZ), ZNS, VPA, GBP and TPM, and the main added AEDs were Lamotrigine (LTG) and Levetiracetam (LEV). The older AEDs were still effective for some patients (Table 2).

The patients' mean seizure frequency was 13.0 times/day (range: from 0.1 to 100 times/day) before AED adjustment; after adjustment, it was 1.0 time/day (range from 0.0 to 5.0) at the primary endpoint and

2.8 times/day (range: from 0.0 to 10.0) at the secondary endpoint (Table 1). The types of remaining seizure were reflex seizure when patients were startled, partial seizure, or brief tonic seizure at night. There was no atstatic and/or tonic seizure during the daytime. The frequency of seizures decreased significantly at the primary and secondary endpoints ($p < 0.001$, Figure 2b). There was little side effect, although somnolence or excitement was observed in seven cases when we introduced a base IV AED, but these effects improved by just waiting for a few days or by reducing the dosage of the base IV AED. There was no side effect during the withdrawal of several oral AEDs at one time with the base IV AED, or during gradual withdrawal of the base IV AED. We found significant improvement with AED adjustment; therefore, we analyzed the patients' background disorder for epilepsies Congenital, Acquired or Cryptogenic--for further analysis (Table 1). There was a significant difference in frequency of seizures and number of AEDs; the frequency of seizures decreased significantly at primary endpoint ($p = 0.025$) for Cryptogenic group and the number of AEDs decreased significantly ($p = 0.006$) at the secondary endpoints for Cryptogenic group.

Adverse events at primary and secondary endpoints

One patient died of suffocation one year and six months after enrollment (the patient's background disorder was Acquired group). Another adverse event was exacerbation of seizures again for 10 patients after the primary end point (the underlying condition was Congenital in six of the patients and Acquired in four). Two congenital group patients had Tuberous sclerosis with growing subependymal giant cell astrocytoma, therefore we added Everonims with their AEDs. The use of Everonims resulted in complete seizure control. Patients in the Congenital group were two cases of West syndrome with Down syndrome; one was Lennox-Gastaut syndrome (LGS) with chromosomal and development abnormality. We added LTG for the former patients and Rufinamide (RFN) for the latter. LTG and RFN reduce the number of seizures effectively. The other patients in the Congenital group still suffered from daily epileptic seizures at the secondary endpoint. Two of the four patients in the Acquired group were West syndrome patients after ACTH therapy, and their epilepsy was well controlled with LTG. We introduced a Ketogenic diet (KD) for one other in the acquired group, and Callostomy for the other one. These treatments reduced the number of seizures effectively, but they still had several seizures in a week. Almost all the patients had improved awareness and behavioral activity, but their intelligence quotient scores did not improve. There were no changes in their blood cell counts or chemistry results.

The length of stay in our hospital for drug adjustment

The mean length of stay in our hospital was 31.4 days (range from 16 to 115 days). The length of hospitalization depended on the patient's background disorders and the combination of AEDs chosen for adjustment, but not on the number of AEDs the patients had used before adjustment.

Clinical course of the five excluded patients

Five patients were excluded because of their EEG did not improve or because their clinical symptoms worsened after the administration of any IV AED (Table 3). They were treated as outpatients, or sometimes inpatients when their seizure frequency exacerbated. One patient of the congenital group was diagnosed with Lafora disease, thus we changed the therapeutic strategy to supportive. She had suffered daily myoclonic and generalized tonic clonic seizures; therefore we cared her in dim light room and improved the frequency of her seizure. The seizure frequencies in one patient of the Acquired group decreased

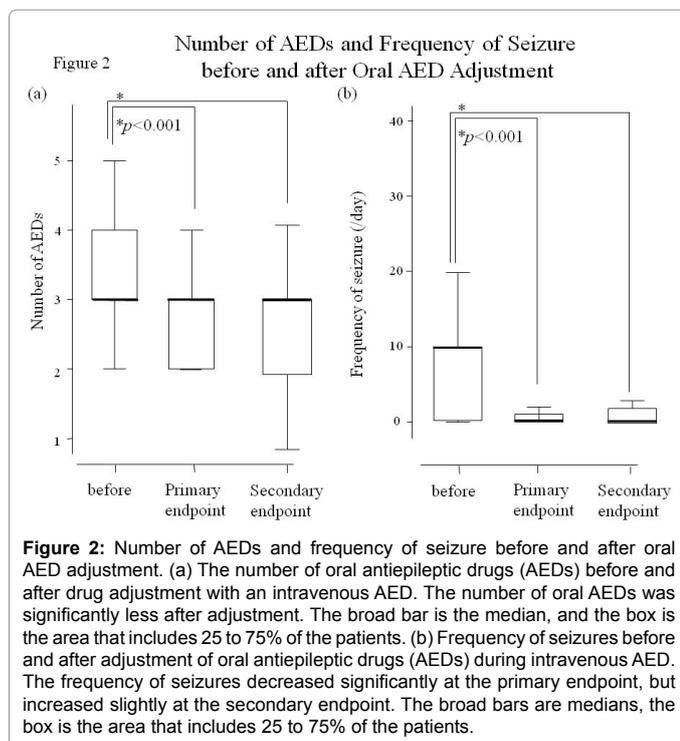


Figure 2: Number of AEDs and frequency of seizure before and after oral AED adjustment. (a) The number of oral antiepileptic drugs (AEDs) before and after drug adjustment with an intravenous AED. The number of oral AEDs was significantly less after adjustment. The broad bar is the median, and the box is the area that includes 25 to 75% of the patients. (b) Frequency of seizures before and after adjustment of oral antiepileptic drugs (AEDs) during intravenous AED. The frequency of seizures decreased significantly at the primary endpoint, but increased slightly at the secondary endpoint. The broad bars are medians, the box is the area that includes 25 to 75% of the patients.

Anti- epileptic drug	Before treatment	First Outcome	Second Outcome
Phenobarbital	5	4	3
Phenytoin	2	1	1
Ethosuximide	2	1	1
Carbamazepine	13	11	9
Zonisamide	16	3	3
Sodium valproate	19	13	14
Clobazam/ Clonazepam	15	16	14
Topiramate	16	22	15
Lamotrigine	13	12	17
Levetiracetam	11	11	17
Gabapentin	6	1	0
Rufinamide	0	0	2

Table 2: Change in anti-epileptic drug before treatment, primary and secondary outcomes.

Background disorder	Number of patients	Age	Management	No. of Seizure	Seizure outcome
Congenital	1	14	AEDs	10	4
Acquired	1	19	VNS, RUF	10	5
Cryptogenic	3	LES	Callosotomy,	30	0
	4	MAE	VNS, RUF,	50	0
	14	Unknown	VNS, KD VNS, KD, ES	4	4

LES: Late-Onset Infantile Spasm, LGS: Lennox-Gas Taut Syndrome, MAE: Myoclonic Astatic Epilepsy; AED: Anti-Epileptic Drugs, ES: Epilepsy Surgery, KD: Ketogenic Diet, VNS: Vagus Nerve Stimulation, RUF: Rufinamide.

Table 3: Characteristics and clinical course of excluded 5 patients.

when we introduced RFN as the fourth AED. Three patients of the cryptogenic group suffered from daily seizures with three or four kinds of AEDs. We tried VNS for them, and one patient with Myoclonic astatic epilepsy became seizure-free after introducing KD, one patient with Late-onset infantile spasm became seizure-free after introducing RFN as the fourth AED, but one was still suffering from daily seizures, without any improvement by VNS, KD or epileptic surgery. Three of five patients in this group were still suffering from daily seizures at the latest visit.

Discussion

Using a base IV AED we could achieve a significant decrease in seizure frequency in intractable epileptic patients and in the number of required oral AEDs, without serious side effects or adverse events such as status epilepticus, even after the withdrawal of two to four oral AEDs at one time during the administration of a base IV AED. Those effects were more remarkable for cryptogenic group than for Congenital and Acquired groups. Therefore, we should choose AEDs more cautiously for the epileptic patients of cryptogenic group than the other groups. We found three kinds of adverse events at the primary and secondary endpoints. One patient died one year and six months after AED adjustment, but we do not think that the cause of his death was related to our trial because his seizure frequency had improved greatly before his death.

As another adverse event, the seizures in ten patients were exacerbated after the primary endpoint, as shown in (Figure 2b). We sometimes experienced that patients' seizures improved a few months after AED adjustment but their seizures became exacerbated again. We could not manage the seizures only to increase the dosage of the AED, so we applied Everolims, a ketogenic diet, added another AED (LTG or RFN), and epileptic surgery treatment. LTG was extensively effective for residual seizure for West syndrome after ACTH therapy and RFN for drop attack for LGS and LGS-like epileptic syndromes.

In a third adverse effect, adjusted AEDs were effective for seizure control, but we sometimes needed to decrease the dosage of them or quit using them. The most representative AED was TPM. Patients sometimes had fever without sweat or felt general fatigue. For that reason, TPM was adjusted at the second endpoint. Our results showed that the adjusted AEDs were not only the older ones but also some of the newer ones, indicating that the physician had chosen a wrong combination of AEDs. Fukuda et al. [6] and Baulac [10] suggested that seizure control can be significantly improved simply by reducing the unnecessary AEDs and increasing the dose of the remaining ones. Our results also suggested that add on therapy of a newer AED will not improve a patient's epileptic seizures when they have already been taking several oral AEDs. Many reports also demonstrate that the interaction of multiple drugs exacerbates epileptic seizures [7,11-13].

Our results and previous reports strongly suggest that improvement

of patients' seizure control requires the correct diagnosis of the epileptic syndrome, the correct choice of AEDs, and the correct adjustment of the AEDs. This method imposed on the patients and their family a month of hospitalization, but the frequency and severity of seizures decreased, thus they could fulfill the treatment, excluding the five patients who could not be enrolled in this clinical trial. We did not find any previous reports on the administration of IV AED while reducing the number of multiple oral AEDs at one time. We admit that this method might not be universally applicable because of the lack of background knowledge. It is generally known that fosPHT worsens myoclonic and absence seizures, thus before including this oral AED adjustment, we think that an IV AED trial with simultaneous video EEG monitoring is essential.

We currently have six choices of IV AEDs in Japan for the treatment of frequent seizures and/or status epilepticus: diazepam, MDZ, PHT or fosPHT, PB, and Levetiracetum (LEV). We have been able to use LEV as an IV AED since 2015, therefore we could not use it in the present study. We also could use diazepam when we adjust oral AEDs because its effective time is too short. Lorazepam and VPA, which are not yet permitted in Japan, are recognized worldwide as antiepileptic drugs for IV use, and we think that we will be able to treat intractable epileptic patients more effectively using the method described in the present study when these IV AEDs become available.

The length of hospitalization with this treatment is approximately one month, and the length of hospitalization depended on the patient's underlying epileptic syndrome and the combination of drugs chosen. Mattson and Cramer [9] suggest that seizures in epileptic patients might be exacerbated even if doctors carefully reduce the dose of individual AEDs. Frequent seizures and occasional status epilepticus are concerns even under such careful AED reduction, which is why these authors mentioned that the patient should be hospitalized during AED reduction. Our method might have reduced the risk of AED change for intractable epileptic patients, although there might be a cost problem: in Japan, it costs 10 times as much when we hospitalized patients to use the base IV AED method than when we adjust patients' AEDs on an outpatient basis. Nevertheless, we believe that our method is cost effective because intractable epileptic patients usually have to visit the emergency department and/or they should have hospitalized several times when we try to reduce their AEDs on an outpatient basis.

Conclusion

In conclusion, our results strongly suggest that hospitalization and the administration of an intravenous antiepileptic drug when adjusting AEDs is a safe and effective method to improve seizure control in intractable epileptic patients.

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