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Bridge Therapy with Intravenous Antiepileptic for Optimizing Oral Antiepileptic Drugs

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

A seven year old patient with intractable epilepsy was admitted to our hospital. We used intravenous (IV) antiepileptic drug (AED) regimen to optimize the oral AEDs by adding newer AEDs, which have been reported to be beneficial when compared to older AEDs in controlling seizures. The patient was diagnosed with myoclonic, absence, astatic and tonic seizures. He was already on six oral AEDs, and we speculated that his seizures were intractable as he was on AED polytherapy. Therefore we substituted with newer AEDs and simultaneously treated with an IV AED as a base therapy (AED adjustment). The patient's EEG was exacerbated when slow infusion Midazolam (MDL) at 0.1 mg/kg/dose and Phenobarbital at 10 mg/kg/dose was used. Fosphenytoin

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sodium hydrate (fos-PHT) was the only IV AED which improved the patient's EEG. He had no seizures with IV fos-PHT at 10 mg/kg/day. We continued with treatment with Sodium valproate and stopped other five oral AEDs and did not notice any withdrawal effects or seizure exacerbation. Slow infusion of MDL (0.1 mg/kg/dose) improved his EEG significantly in a week, so we decided to stop fos-PHT and continue IV MDL 0.1 mg/kg/hr. Later, we gradually decreased the dose of MDL and choose oral AEDs in accordance with his seizure type. This reduced his oral AEDs to three.
This case suggests that: 1) use of IV AED as a base therapy, can adjust patients' AED treatment safely in a short period; and 2) In this particular case, newer AEDs was ineffective when administered along with AED polytherapy. Reducing the number oral AEDs administered to patients is a crucial goal when reassessing their oral AED regimen.

Keywords: Intractable epilepsy; polytherapy; anticonvulsant; readjustment; intravenous.

1. INTRODUCTION

Control of epileptic seizures by optimizating the number of antiepileptic drugs (AEDs) can positively impact the Quality of Life (QOL) in patients with epilepsy [1,2,3,4]. Patients with intractable seizures, however, are usually given high dosages and AED polytherapy [5]. In Japan, the newer AEDs -Topiramate (TPM), Lamotrigine (LTG), and Levetiracetam (LEV) have been readily available since 2007, 2008 and 2010 respectively, and their high efficacy for patients with intractable seizures has been reported [6,7,8]. Our goal was to reduce the number of AEDs that patients take after adding a newer AED in combinations (AED adjustment). We hypothesized that these newer AEDs do not show desired effects when used in higher dose and in combination.

Many clinicians have been conducted to treat epilepsy effectively with monotheraphy rather than treating with polytheraphy. Mattson et al. [3] suggested that if AEDs are carefully selected and reduced one at a time, it would not lead to exacerbation of seizures in patients with epilepsy. Even under such a careful reduction in AED, however, patients still experience frequent seizures, and sometimes status epileptics. Thus, we decided to adjust patient's AED regimen, and possibly reduced the number of AEDs, by using intravenous (IV) AEDs like Midazolam (MDL), Fosphenytoin sodium hydrate (fos-PHT) or Phenobarbital Na (PB) as a bridge therapy on an inpatient basis. We report on the efficacy and safety of this method in this case report.

2. CASE

A boy aged 7 years 11 months was accompanied by his father with good health and mother with a history of juvenile myoclonic epilepsy since she was 13 years. The patient's Apgar score at birth was 8 and 9 points at 1 and 5 minutes, while his height, weight and head circumference at birth were 50 cm, 3,074 g and 34.0 cm, respectively. Initially, the patient's development was normal. He obtained head control, social smile and tracking eye movement at 3 months, sitting at 7 months, and standing by himself at 10 months. His development leveled out at approximately 18 months. When he was 2 years, he experienced repeated febrile and afebrile generalized tonic-clonic seizures (GTCS). The inter-ictal sleep EEG showed a generalized 2.5 Hz spike and wave complex. He was prescribed Valproic acid (VPA) at dosages that were gradually increased from 10 to 30mg/kg, but there was no improvement in his seizures, of which he had 3 types: GTCS, myoclonic, and astatic. When the patient was brought to us, he was 7 years and was being treated with 6 oral AEDs (VPA 700 mg/day; Ethosuximide [ESM] 500 mg/day; Phenytoin [PHT] 135 mg/day; Lamotrigine [LTG] 10 mg/day; Levetiracetam [LEV] 1000 mg/day and Clonazepam [CZP] 0.5 mg/day). When admitted under our care, his height, weight and head circumference was 116 cm, 24.8 kg and 54.0 cm, respectively. He suffered from severe gingivitis, drowsiness, and experienced absence, myoclonic, and astatic seizures several times at daytime and generalized tonic seizures (GT) at night.

We felt that it was important to explain to him and his family about our review and diagnosis of his epileptic syndrome [9], and that we might be able to improve his condition by adjusting his AEDs. We told his parents that he might be suffering from myoclonic astatic epileptic syndrome, and believed that VPA would be the most effective AED treatment for him. We explained our plan to treatment with IV AEDs as a base medication in an attempt to decrease his oral AEDs at the same time. Written informed consent was obtained from the parents, and he was admitted

to our hospital with one of them staying with him during his entire admission. Routine blood, urine and cerebrospinal fluid examinations returned normal, as did his brain MRI scans. Sleep EEG showed a 3.0 Hz generalized spike and wave complex (Fig. 1 A-a).

We prescribed three IV AEDs under EEG monitoring to determine AED could serve effectively as a base for adjusting his oral AEDs (Day 1). MDL (0.1 mg/kg/dose, Fig. 1 A-b) for 1 minute and PB (10 mg/kg/dose, Fig. 1 A-c) for 5 minutes exacerbated his EEG to a generalized polyspike and 3 Hz spike and wave complex, respectively. Fos-PHT (10 mg/kg/dose) for 15 minutes was the only drug that reduced his spike and wave complex (Day 3, Fig. 1 A-d), so we decided to use IV fos-PHT (10mg/kg/once a day). We kept his VPA dosage at 700mg and simultaneously stopped his five other oral AEDs on Day 4, and did not notice any withdrawal effects or seizure exacerbation. On day 10, however, finding an exacerbation in the frequency of the spike and wave complex on his EEG (Fig. 1 B-a), we reintroduced the MDL (0.1 mg/kg/dose) for 1 minute along with fos-PHT and oral VPA (30 mg/kg; trough value was 85 µg/dl). We recorded his EEG during waking conditions and found that under these new conditions the MDL improved his EEG greatly (Fig. 1 B-b). Thus, we opted away from fos-PTH in favor of MDL (0.1 mg/kg/hr).

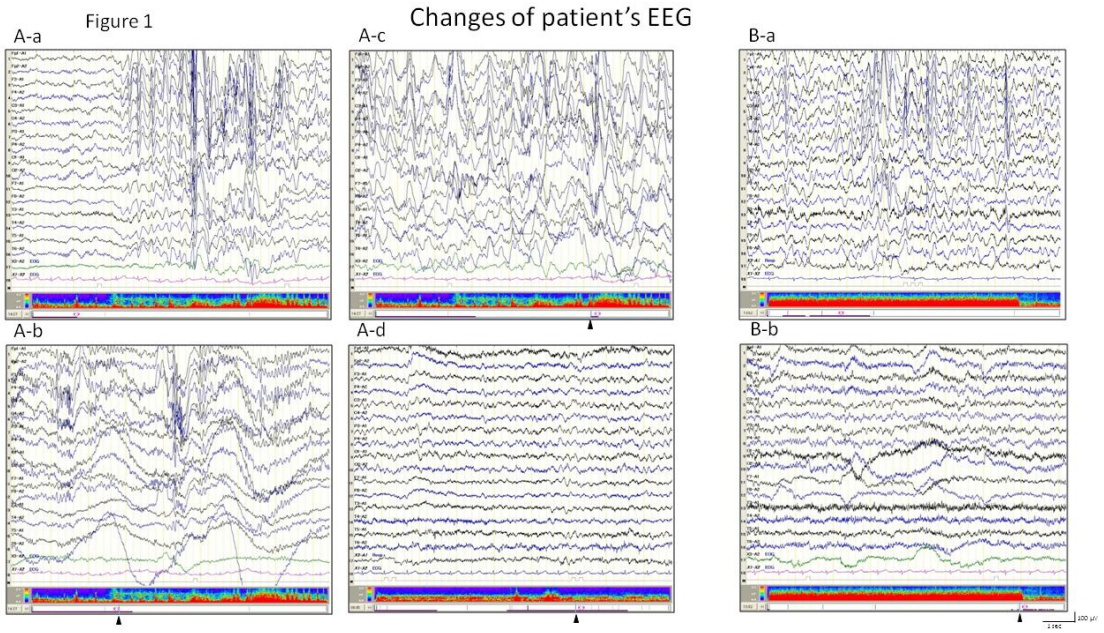

Fig. 1A-a: The patient's EEG while he was still prescribed 6 oral anti antiepileptic drugs (AEDs). His drowsy electroencephalography (EEG) shows 3.0 Hz generalized spike and wave complex. The pink indicators (▸] [◂) reveal the EEG position during a 30-minute recording session. A-b): The patient's EEG while he was still prescribed 6 oral AEDs. The black triangle (▲) shows where we used intravenous (IV) Midazolam (MDL). After using IV MDL, the frequencies of generalized polyspikes increased, so we did not choose MDL to adjust the oral AEDs. A-c): The patient's EEG while he was still prescribed 6 oral AEDs. The black triangle (▲) shows where we used IV Phenobarbital Na (PB). After using PB, the frequencies of generalized 3 Hz spike and wave complex increased. A-d): The patient's EEG while he was still prescribed 6 oral AEDs. The black triangle (▲) shows where we used Fosphenytoin sodium hydrate (fos-PTH). After using intravenous fos-PTH slowly, the generalized polyspikes and wave complex disappeared. Therefor we changed to fos-PTH as the base IV AED to adjust the oral AEDs. B-a): The EEG after we adjusted the 6 oral AEDs to VPA under fos-PTH. We can see generalized polyspikes and wave complex in his waking EEG record. B-b): After reducing the 6 oral AEDs to only VPA under IV fos-PTH, IV MDL of 0.1 mg/kg/dose (black triangle; ▲) yielded great and continuous improvement in the patient's EEG

We decreased the MDL from 0.1 mg/kg/hr to 0.08 mg/kg/hr, but this began to cause myoclonic seizures, so we decided to add and increase oral LEV up to 1,250 mg/day. As parents wanted to avoid gingival enlargement, we did not increase the VPA dosage. The patient was responding well at the blood concentration we had already achieved. As his liver enzyme level was slightly elevated, we gradually decreased the dosage of MDL to 0.04 mg/kg/hr. When the dose of MDL was decreased he began to suffer with astatic seizures. We tried increasing the dose of TPM from 1 mg/kg to 3mg/kg for a period of 2 weeks, but it had no effect on the astatic seizures. He also suffered from anhidrosis, so we stopped TPM and substituted CLB. After adding 15mg CLB along with VPA (600 mg/day) and LEV (1,250 mg/day), he still experienced tonic seizures at night for few seconds, but he was well enough that his family agreed to bring him on outpatient basis. He was discharged on Day 43.

Now after, one year of adjustment with AED regimen, he does not suffer from any daytime seizure while every month he has only few episodes of tonic seizures lasting about 10 seconds at night.

3. DISCUSSION

Using newer AEDs, we can select a rational polytheraphy to improve the QOL in patients with intractable seizures [5,10,11]. Although, after adding a newer AED there is often an exacerbation in the seizures, e.g., increases in frequency and sometimes status epileptics. To avoid such harmful effects, AEDs have to be carefully selected and the doses have to be adjusted one by one for each AED. Since 2007, we have been using IV AEDs to adjust oral AEDs on inpatient basis. In this case, the most useful IV AED is MDL, because variation in its concentration was observed in a short time frame while we can notice patients' seizure types and their frequency. After adding a newer oral AED we could easily evaluate its effectiveness. The half-life of fos-PHT and PB are long, thus we cannot immediately evaluate the effect of adding a newer AED. In the present case, while under 6 different oral AEDs, MDL exacerbated the patient's EEG, but after adjusting the oral AEDs under fos-PHT, MDL effectively improved his EEG. In this particular case, newer AEDs was ineffective when administered along with 6 oral AED polytherapy. IV AEDs could act as a bridge therapy for switching over to newer AEDs and optimize the number of AEDs in patients with epilepsy. However, larger multicentre trials are necessary to make specific recommendations based on our observations in this case.

4. CONCLUSION

We conclude that newer AEDs do not have the desired effect when large doses and combinations of AEDs are already being used. Using an IV AED is one of the best way to adjust AED treatment in patients with intractable seizures.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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