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Decreasing the Types and Quantities of Oral Antiepileptic Drugs Administered Alongside Intravenous Midazolam

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Authors' contributions

This work was carried out in collaboration between all authors. Authors TF, MS, MI and AS designed the study and wrote the first draft of the manuscript. Authors YM, ST and KK managed the literature searches and figures. All authors read and approved the final manuscript.

Case Study

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ABSTRACT

It is reported that 0.4 to 0.8% of the world's population suffers from epilepsy. About 30% of epileptic patients are intractable. Controlling their seizures is very important for society because many patients can participate in gainful employment. In this case study we report how we reduce and/or change the oral antiepileptic drugs (AEDs) taken (AED adjustment) by administering intravenous (IV) AED for an intractable epileptic patient. The patient was introduced to our hospital when she was 17 years old. She was born as a premature baby and had been suffering from partial seizures since she was 1 year old. We adjusted her oral AEDs in order to add newer AEDs, but the drugs did not work effectively. Thus, we hospitalized her in order to use continuous intravenous Midazolam (MDL) 0.1mg/kg/hr while we adjusted her AEDs. We were able to stop administering four out of five kinds of AEDs that the patient was taking simultaneously, without exacerbating her seizures. This case suggests that: 1) when intractable epileptic patients are taking a large number of oral AEDs, newer, additional AEDs cannot work effectively, and reducing the number of oral AEDs is crucial in adjusting their oral AEDs; and 2) IV AEDs enable a reduction in the

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number of oral AEDs in a short period of time without seizure exacerbation, thus facilitating safe adjustment of oral AEDs.

Keywords: Intractable epilepsy; poly therapy; anticonvulsant readjustment; intravenous anticonvulsant; newer anticonvulsant.

1. INTRODUCTION

Many intractable epilepsy patients simultaneously receive multiple antiepileptic drugs (AEDs) (Reynolds and Shorvon [1], Schmidt [2]), and this can impede therapy and the quality of patients' life (QOL; Maston et al. [3], Baulac [4]). In order to improve these conditions, we reduce the number and dose of AEDs that patients receive (AED adjustment). Newer AEDs, such as Topiramate (TPM), Lamotrigine (LTG), and Levetiracetam (LEV), have been readily available in Japan since 2007, 2008, and 2010, respectively. We try to reduce the number of AEDs a patient takes whenever we attempt to introduce yet another, newer AED, but we find that patient seizures are exacerbated when we add another of the newer AEDs. Hypothesizing that a newer AED does not have the desired effect when used along with a large number of other AEDs, since 2008 we have been using an intravenous (IV) anticonvulsant, e.g. Midazolam (MDL), as we decrease patients' total number of AEDs before adding a newer AED. Here we report the efficacy and safety of this method.

2. CASE

The patient is now a 20-year-old woman. Her gestational age was 28 weeks and birth weight was 608g. She had severe anoxic encephalopathy and intra-ventricle hemorrhaging, which resulted in tetraplegia and severe mental retardation. She has been suffering from intractable partial epilepsy since she was 1 year old. She was brought to our hospital when she was 17. Her height and weight were 138 cm (-3.7 SD) and 19.0 kg (-3.9 SD). Her interictal sleep EEG showed continuous bi-posterior polyspikes (Fig. 1A), meaning that she had partial electrical status epileptics. Her seizures would twist her neck to the left, straighten out her left arm and bend her right elbow, and her extremities displayed clonic movement for several minutes. The seizures occurred several times per day. She was prescribed Valproic acid (VPA) 350 mg/day, Zonisamide (ZNS) 180 mg/day and Clobazam (8 mg/day). Her seizures were clearly partial, thus we first thought to change from VPA to TPM. We decreased the VPA from 350 mg to 100 mg and increased the TPM from 40 mg to 100 mg, but her seizures were exacerbated and caused secondarily generalization seizure. We therefore had to increase the VPA to 600 mg. Next, we tried replacing the TPM with LTG, but when we gradually added LTG up to 30 mg, her partial seizure frequency did not change. She still suffered partial seizures daily, we decided to decrease the dosage of LTG. When she graduated from a high school for handicapped students, we negotiated with her parents for her hospitalization and treatment with an IV AED while we attempted to decrease her oral AEDs. Written informed consent was obtained from her parents, and she was admitted to our hospital with one of her parents staying with her during her admission. We tested MDL, Fosphenitoin (fosPHT), and Phenobarbital (PB) as IV AEDs under EEG monitoring to see which was most effective. IV MDL (0.1 mg/kg/dose) improved her EEG on her first day of hospitalization (Day 0), so, on Day 2, while continuing the IV MDL (0.1 mg/kg/hr) treatment, we kept her LEV dosage (500 mg/day; 25mg/kg/day) at the same rate and simultaneously stopped her four other oral AEDs (ZNS 180 mg/day, VPA 225mg/day, TPM 100 mg/day and LTG 20mg/day). There were no withdrawal effects or seizure exacerbation. On day 8, finding

that she was seizure free, we decided to reduce her IV MDL from 0.1 mg/kg/hr to 0.09 mg/kg/hr. When she then had a partial seizure, we increased the LEV dosage to 30mg/kg, but she still had partial seizures. Thus we added LTG in gradual increments, starting at 2.0 mg/day. We were able to terminate the IV MDL when the dosage of oral LEV reached 60 mg/kg (1250 mg/day) and LTG reached 2.5mg/kg (50 mg/day). Although she still had a few aversive seizures at night, she was well enough that her parents agreed to move her to outpatient status, and she was discharged on Day 37. Her clinical course is shown in Fig. 2.

We had been using LEV and LTG with ZNS, VPA and TPM, but the LEV and LTG were not effective. With the patient hospitalized, we decreased the number of oral AEDs while using IV MDL as a base medication, enabling us to improve her seizures with LEV (1250 mg/day) and LTG (50 mg/day). After the decrease in her oral AEDs, her EEG also improved (Fig. 1B). One year later, though, her number of aversive seizures increased. We used IV MDL, fosPHT and PB again, and found that PB improved her EEG. We substituted PB (3md/kg/day) for LTG, and now her seizure condition is improved.

Figure 1

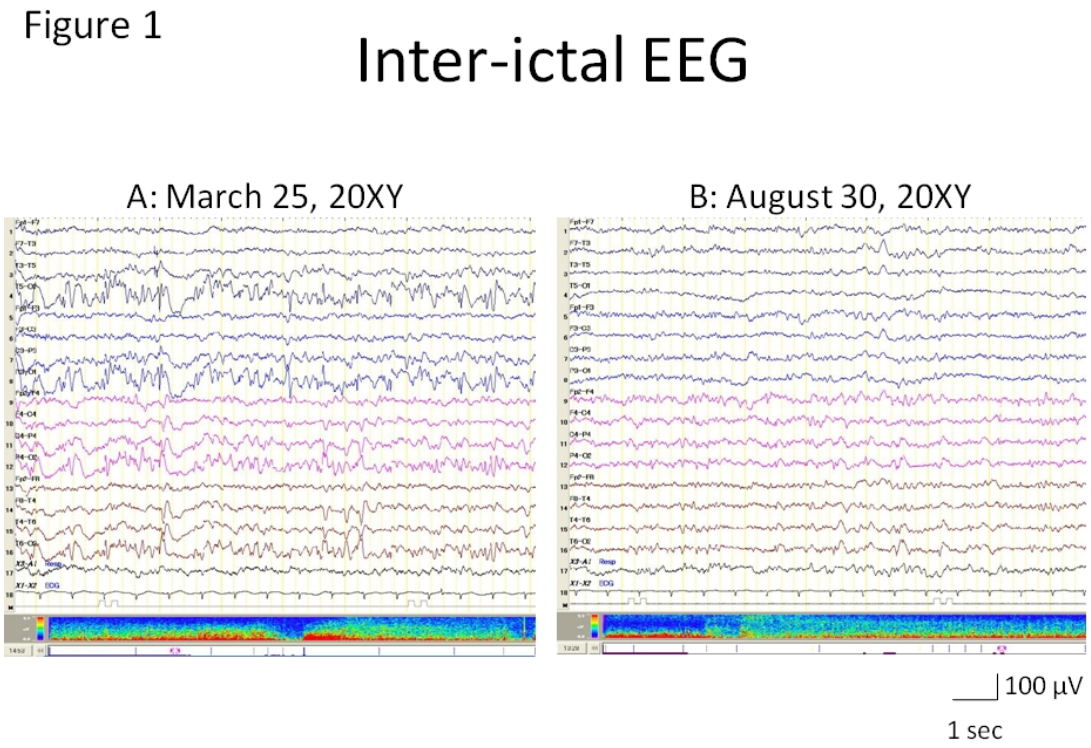

Fig. 1A. The patient's EEG while she was still prescribed 5 oral AEDs. Her drowsy state EEG shows continuous polyspikes in the bi-parieto-occipital area. The pink indicators (□] [□) reveal the EEG position during a 30 minute recording.
B. After changing oral AEDs, her EEG shows low amplitude intermittent spikes in the bi-parieto-occipital area

Figure 2

Seizure Frequency During Drug adjustment

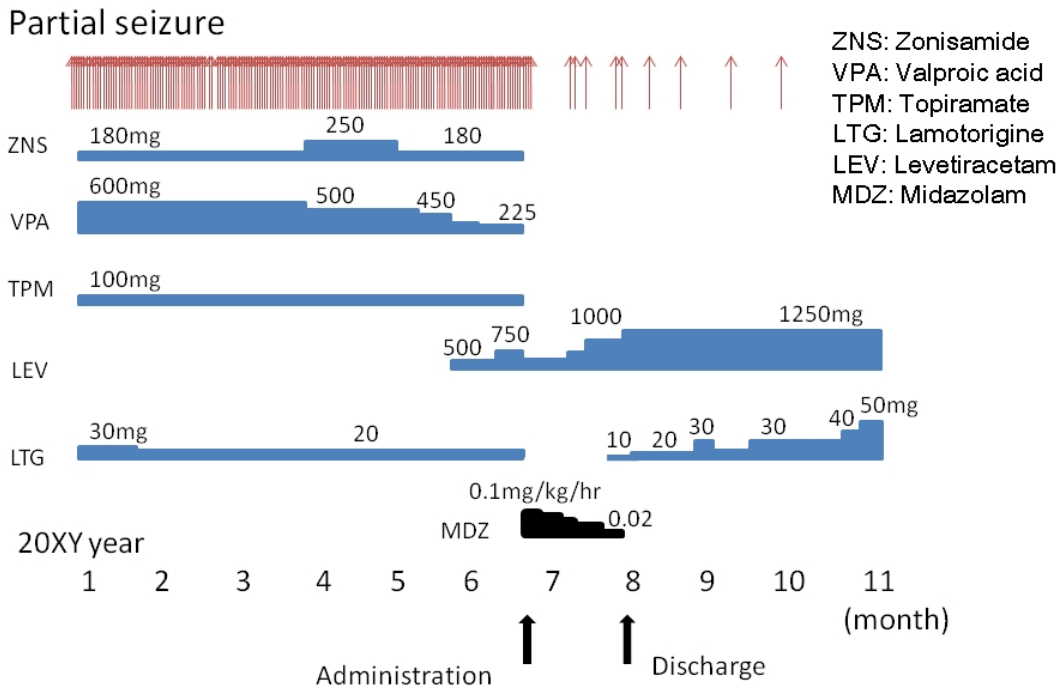

Fig. 2. The patient's clinical course is shown. Her partial seizures occurred only rarely after the adjustment of her oral AEDs. She was seizure free at 0.1 mg/kg/hr use of Intravenous Midazolam. At that point we began to gradually decrease the dosage of MDL. When her seizures returned, we increased the oral Levetiracetum. When the LEV dose was increased to 60 mg/kg/day, we selected Lamotrigine as a second AED. Using this method, we adjusted her 5 AEDs to just 2, thus improving her seizure frequency

3. DISCUSSION

We hypothesized the possibility of using newer antiepileptic drugs to adjust the quantities of oral AEDs for intractable epileptic patients, but the patient experienced seizure exacerbation, e.g., more frequent seizures and sometimes status epileptics, after adding a newer drug. To avoid such harmful effects, we sought to reduce the quantities of simultaneously administered AEDs (Brodie and Sills [5], Stephan and Brodie [6], Brigo et al. [7]). The problem is that it takes several months to years to adjust oral AEDs if the patient uses several oral AEDs. Thus, since 2007 we have been using an IV AED as a base therapy while the patients are hospitalized to adjust their oral AEDs. The most useful IV AED is MDL, because 1) as we vary its concentration over a short time frame we can observe patient seizure types and frequencies, and 2) after adding a new oral AED, we can easily evaluate its effectiveness. The clinical course of the patient in this case report suggests that introducing newer AEDs does not work effectively when introduced into a drug regimen

already containing several other AEDs. Therefore, we should seek to adjust the number of oral AEDs being taken before adding another. Changing to oral AEDs from intravenously administered AED is not a universal method, because, for one of reason, which IV drug is effective differs from patient to patient. Nonetheless, the results of our case study suggest that this is one of the best ways to adjust AEDs for intractable epileptic patients.

4. CONCLUSION

We might recommend that hospitalization and administration of an intravenous antiepileptic drug when adjusting oral AEDs as a safe and effective method to improve seizure control for intractable epileptic patients.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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