Effects of various antiepileptic drugs in benign infantile seizures with mild gastroenteritis

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Abstract

Purpose: This study sought to determine the appropriate choice of antiepileptic drugs (AEDs) for seizures during the acute phase in patients with benign infantile seizures with mild gastroenteritis (BISMG).

Methods: We retrospectively investigated the efficacy and dose of AEDs for BISMG by reviewing the medical records of 42 patients diagnosed with BISMG. In this study, AEDs were regarded as effective when seizures ceased for >24 h after administration.

Results: AEDs were administered to 39 of 42 patients (92.9%). Carbamazepine was effective in 21 of 21 patients (100.0%), phenytoin/fos-phenytoin in three of four patients (75.0%), midazolam in one of two patients (50.0%), lidocaine in one of two patients (50.0%), and diazepam in 13 of 36 patients (36.1%). Intravenous diazepam was effective in seven of 11 patients (63.6%) and suppository diazepam in 10 of 25 patients (40.0%). The median dose of carbamazepine was 5.0 mg/kg/day (range, 3.0-5.0 mg/kg/day) and the median duration of medication was 1 day (range, 1-5 days).

Conclusion: Treatment for 1 day with low-dose carbamazepine was effective for BISMG. Phenytoin/fosphenytoin and intravenous diazepam, not but suppository diazepam, were also effective. We recommend 1 day of treatment with low-dose carbamazepine as the first-line treatment for BISMG. The unnecessary use of AEDs for BISMG should be avoided after the acute phase because seizures in BISMG rarely recur.
Introduction

The condition of benign infantile seizures with mild gastroenteritis (BISMG) was first described in 1982 by Morooka [1] as benign convulsions associated with mild gastroenteritis. Since then, BISMG has been commonly reported in Eastern Asia, especially Japan [2-11] and more recently has been reported in European countries [12-16]. It is now widely known as a marginal syndrome of benign infantile seizures [17-18]. The clinical features of BISMG are: (1) afebrile seizures associated with gastroenteritis without clinical signs of dehydration or electrolyte derangement in previously healthy patients aged from 6 months to 3 years; (2) seizures often occurring in clusters; (3) normal interictal electroencephalogram; and (4) good seizure outcome and development. BISMG is not formally recognized as an epileptic syndrome and is categorized as situation-related seizures or “chanced” epilepsy [18-19]. Antiepileptic drugs (AEDs) for BISMG are commonly required in the acute phase because seizures are often clustered [1-16]. Benzodiazepines, including diazepam (DZP) and midazolam (MDL), and phenobarbital (PB) are often administered but their effectiveness is controversial [3-4, 8, 10-11, 13-16]. Some studies have shown that lidocaine (LDC), low-dose carbamazepine (CBZ), and chloral hydrate were effective for BISMG [4-7, 10]. Determining the appropriate AED in the appropriate dose that can be effective in the short-term would be of value. The purpose of this study was to identify appropriate AEDs for seizures during the acute phase of BISMG.

Subjects and Methods

We retrospectively investigated the efficacy of AEDs for BISMG by reviewing the medical records of 42 patients diagnosed with BISMG at Saitama Children’s Medical Center, Saitama, Japan between April 1, 2001 and March 31, 2013. The inclusion criteria for diagnosis of BISMG were: (1) age at onset from 1 to 36 months; (2) afebrile seizures associated with gastroenteritis without clinical signs of dehydration; (3) no underlying disorders or neurological abnormalities prior to onset; (4) body temperature ≤38 °C; and (5) normal laboratory examination results, including electrolytes and blood glucose. The exclusion criteria for diagnosis were acute brain pathologies, such as meningitis, encephalitis/encephalopathy, and trauma. We included patients with typical clinical features who did not undergo brain neuroimaging such as computer tomography or magnetic resonance imaging, electroencephalography, or lumbar puncture as it is well known that these examinations findings do not contribute to the diagnosis of BISMG [10].

We reviewed the medical records for the following clinical features: sex; age at onset of BISMG; family history of benign infantile seizures (BIS), epilepsy, or febrile seizure; interval from onset of gastroenteritis to first afebrile seizure; seizure duration; total number of seizures; seizure type; and treatment with AEDs. In this study, we regarded AEDs as effective when seizures ceased for more than 24 h after administration.

Statistical analysis was performed with the Mann-Whitney U-test for continuous data using SPSS software (ver. 19). Significance was considered at p<0.05.
This study was approved by the Ethics Committee of Saitama Children’s Medical Center.

Results

Patient characteristics

In total, 42 patients (20 boys and 22 girls) were reviewed in this study. The median age at onset of BISMG was 18.1 months (range, 4.4-32.7 months). Family history of BIS was found in one patient (2.4%), epilepsy in one (2.4%), and febrile seizure in nine (21.4%). The rotavirus antigen in stool was detected in one of four patients examined and norovirus antigen in eight of 14 patients, respectively. The median interval from onset of gastroenteritis to first afebrile seizure was 3.0 days (range, 1-5 days). The median seizure duration was 3.0 min (range, 1-5 min), and the median total number of seizures during the acute phase was three (range, 1-14). Generalized convulsive seizures were recorded in 34 of 42 patients (81.0%). The remaining eight patients (19.0%) had partial seizures, four with convulsive seizures and four with non-convulsive seizures.

AED treatment

Choice of AEDs and efficacy rate

AEDs were administered to 39 (92.9%) of 42 patients. As the first-line AED, CBZ was effective in six of six patients (100.0%), fosphenytoin (fos-PHT) in one of one patient (100.0%), and suppository and/or intravenous DZP in nine of 30 patients (30.0%; Figure 1). Second-line AEDs were needed in 23 of 39 patients (59.0%) whose seizures were not controlled by the first-line agents. CBZ was effective in 13 of 13 patients (100.0%), LDC in one of one patient (100.0%), phenytoin (PHT) in two of three patients (66.7%), and intravenous DZP in four of six patients.

Figure 1. Choice and effectiveness of AEDs for benign infantile seizures with mild gastroenteritis. AED: antiepileptic drugs, CBZ: carbamazepine, civ: continuous intravenous, DZP: diazepam, Fos-PHT: fosphenytoin, iv: intravenous, LDC: lidocaine, MDL: midazolam, n/N: number of effective administrations/number of total administrations, PHT: phenytoin, suppo: suppository, Sz: seizures.
Third-line AEDs were needed in three of 39 patients (7.7%). CBZ was administered as third-line treatment to two patients and MDL to one; all three patients achieved seizure cessation.

Overall, CBZ was effective in 100.0% of patients, PHT/fos-PHT in 75.0%, LDC in 50.0%, MDL in 50.0%, and DZP in 36.1%. Intravenous and suppository DZP was effective in 63.6% and 40.0%, respectively.

No patients experienced adverse effects due to administration of these AEDs.

**Dose**

The median total administered dose of DZP in 30 patients was 0.40 mg/kg (range, 0.30-1.13 mg/kg). Among 11 patients who received intravenous DZP, a median dose of 0.30 mg/kg (range, 0.10-0.60 mg/kg) was effective in seven patients and 0.30 mg/kg (range, 0.30-0.80 mg/kg) was not effective in four patients; there was no difference between the median doses and there was no statistical difference between the distribution of doses (p=0.625). Among 25 patients who received suppository DZP, a median dose of 0.37 mg/kg (range, 0.32-0.43 mg/kg) was effective in six patients, whereas 0.40 mg/kg (range, 0.31-0.50 mg/kg) was not effective in 19 patients; this difference was not significant (p=0.259). Six of 30 patients were treated with both intravenous and suppository DZP. The median dose of CBZ was 5.0 mg/kg/day (range, 3.0-5.0 mg/kg/day) and the median duration of medication was 1 day (range, 1-5 days). The median doses of PHT (three patients), fos-PHT (one patient), and MDL (two patients) were 8.0 mg/kg (range, 2.0-20 mg/kg), 22.5 mg/kg, and 1.6 mg/kg (range, 0.10-0.30 mg/kg), respectively. The dose of LDC in two patients was 2.0 mg/kg and the dose of continuous intravenous LDC in one patient was 2 mg/kg/h.

**Discussion**

We reviewed 42 patients with BISMG with regard to treatment in the acute phase. The main findings were that among 39 patients (92.9%) administered AEDs, first-line AEDs were effective in 16 of the 39 patients (41.0%), second-line AEDs in 20 of 23 patients (87.0%), and third-line AEDs in three of three patients (100.0%). Overall, CBZ was effective in 100.0% of patients, PHT/fos-PHT in 75.0%, MDL and LDC in 50.0%, and DZP in 36.1%. Intravenous and suppository DZP were effective in 63.6% and 24.0% of patients, respectively.

Since BISMG was first reported in 1982 [1], many reports of the clinical features and treatment options have been published [2-16]. AEDs are likely to be administered to patients with BISMG in the acute phase because of repetitive seizures. Although DZP was commonly used, its efficacy was not favorable [3-4]. Some studies have demonstrated the effectiveness of PB and LDC for BISMG in the acute phase [3-5] as well as low-dose CBZ and single-dose chloral hydrate [6-7, 10].

Our data also showed that low-dose CBZ (5 mg/kg/day) for 1 day in the acute phase was effective in 100.0% of patients, with no adverse effects. Low-dose CBZ for BISMG was first reported by Ichiyama et al in 2005 [6]. In their study, the dose of CBZ was 5 mg/kg/day, and the duration of administration was 6.4 days. Later, in 2011, Tanabe et al. [10] showed the efficacy of single-day therapy with CBZ, results which are similar to
ours. We suggest low-dose CBZ for 1 day as the first choice of AEDs for acute-phase BISMG. CBZ acts by blocking Na⁺ channels and inhibiting the influx of Na⁺ ions into neurons; LDC and PHT/fos-PHT also have the same mechanism of action. However, it remains unknown why these Na⁺ channel blockers inhibit seizures in BISMG, and further experimental studies including of the pathophysiology of this disease are needed.

The effectiveness of benzodiazepine such as DZP and MDL remains controversial. Some studies have shown that DZP was effective for BISMG in 13-39% of patients [4, 8], consistent with our data. However, there have been few previous studies investigating the administration route of DZP. In the present study, the effectiveness of intravenous DZP was higher than that of suppository DZP (63.6% vs 24.0%), and there was no significant difference in DZP dose between these two administration routes although the bioavailability using these two routes might differ. These data suggest intravenous DZP, not suppository DZP, as the first- or second-choice AED for BISMG in the acute phase.

LDC is recommended for BISMG by intravenous injection and by tape therapy [4, 5, 10]. However, Enoki et al. [7] noted two disadvantages of intravenous LDC: (1) the need for continuous intravenous infusion and (2) cardiac adverse effects. In two patients who received LDC in the present study, continuous intravenous therapy was effective in one patient and single intravenous injection was ineffective in another. Thus, we believe that LDC therapy generally requires short-term hospitalization and may therefore not be the optimal AED for BISMG. As no patients received LDC tape therapy in this study, further investigations are needed to assess the efficacy of this route of LDC administration.

PHT and fos-PHT are reported to be useful for BISMG in 66.7-80.0% of patients and 87.5%, respectively [4, 8, 20]. In the present study, PHT/fos-PHT was effective in 75.0% of patients, which is consistent with previous reports. However, the number of treatments was small in both this and previous studies. As fos-PHT is the prodrug of PHT, we consider that both agents might be expected to have the same degree of effectiveness. Thus, PHT/fos-PHT seems to be a suitable first- or second-line AED for BISMG.

The limitations of the study include the retrospective, open, non-randomized design with lack of a prospective protocol for choosing the AEDs. In addition, as no patients were treated with chloral hydrate in this study, the efficacy of this drug could not be evaluated. Although the choice and dose of AEDs was variable, no patients continued oral AEDs after the acute phase in this study. Three of 42 patients (7.1%) were not given any AEDs in the acute phase, two of whom had more than three episodes of seizures. This indicates that the decision to administer AEDs may depend on the anxiety of the patients’ parents and caregivers about seizure recurrence. Thus, guidelines for the indications and choice of AEDs for BISMG should be established to ensure that the most effective AED is used for a brief period only, if AED treatment is considered to be necessary at all.

In conclusion, low-dose CBZ for 1 day was effective for the treatment of acute-phase BISMG. PHT/fos-PHT and intravenous DZP were also effective, but not suppository DZP. We recommend 1 day of treatment with low-
dose CBZ as first-line treatment for BISMG. Continuation of AED treatment for BISMG after the acute phase should generally be avoided because the seizures rarely recur and such treatment is consequently usually unnecessary. Further studies are needed to determine the indications and choice of AEDs for BISMG.

Conflict of interest
The authors declare that there are no conflicts of interest associated with the present report.

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