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Original article

Ketogenic diet using a Japanese ketogenic milk for patients with epilepsy: A multi-institutional study

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Abstract

Background: In Japan, Meiji 817-B (M817-B), a powdered ketogenic milk, has been available since the ketogenic diet was introduced to infants and tube-fed children with medication-resistant epilepsy in the 1980s.

Methods: We retrospectively evaluated the efficacy, tolerability, and side effects of the ketogenic diet using M817-B as the main source of daily food intake for patients with epilepsy by sending questionnaires to the members of a subcommittee of the Japan Epilepsy Society that focuses on the proper use of M817-B.

Results: A total of 42 patients were enrolled. Age at the initiation of the diet therapy ranged from 3 to 244 months (median, 32.5 months). Thirty-four patients were fed via tube, and the remaining 8 were fed orally. About 93% of patients were able to continue the diet for 1 month, 74% for 3 months, and 64% for 6 months. The median period of continuation was 16 months. One patient was able to continue as long as 7 years. The ketogenic ratio was maintained at about 3.0. The seizure-free rate and responder (>50% seizure reduction) rate were about 10% and 30–40%, respectively during the 12 months on the diet. Mean serum beta-hydroxybutyrate increased to almost 4 mM at 1 month and was maintained during the diet period. Side effects, which required discontinuation of the diet therapy, occurred in 11 of 42 patients and included hypertonia, weight loss, vomiting, hypoglycemia, metabolic acidosis, and hypokalemia.

Conclusion: M817-B could be used long-term with demonstrated efficacy in seizure reduction, although there are some side effects that may require cessation of the diet therapy.

Keywords: Ketogenic diet; Ketogenic milk; Epilepsy; Meiji 817-B; Japan

1. Introduction

The ketogenic diet (KD) has been used worldwide for the treatment of medication-resistant epilepsy. Although the KD was introduced as early as the 1950s in Japan, only a limited number of institutions have employed the KD for the treatment of epilepsy [1]. Meiji 817-B (M817-B), a unique ketogenic milk, was developed in 1981 by the Meiji Corporation (Tokyo) and is provided free of cost by the company as a voluntary service to patients in Japan. It is a powdered ketogenic milk and is designed to have a ketogenic ratio of 3.0 when dissolved in water and is easy to prepare. The recent

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worldwide "KD boom" originating from Johns Hopkins Hospital (Baltimore, Maryland, USA) has drawn the attention of Japanese physicians and parents of Japanese children with epilepsy. As a result, the demand for M817-B has increased every year, even though the KD is still considered to be a last resort for treatment of intractable epilepsy in Japan [2].

We have not found any reports that have assessed the usefulness of M817-B for epilepsy. Thus, we carried out this retrospective study to clarify the efficacy, tolerability, and side effects of M817-B in Japanese patients with epilepsy.

2. Patients and methods

We investigated the efficacy, tolerability, and side effects of M817-B in patients with epilepsy treated with the formula by sending questionnaires to members of a subcommittee of the Japan Epilepsy Society that focuses on the proper use of ketogenic formulas.

2.1. Subjects

Patients who started the KD for the treatment of epilepsy using M817-B as their main source of daily meals at 4 hospitals (Shiga Medical Center for Children, Shiga; National Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorders, Shizuoka; Osaka University Graduate School of Medicine, Osaka; and Tokyo Women's Medical University, Tokyo) from January 4, 2006 to March 31, 2016 were enrolled. Those who had pyruvate dehydrogenase complex deficiency or glucose transporter type 1 deficiency were excluded. Those who took ketogenic formulas other than M817-B such as Ketonia®, KetoCal®, KetoVie®, KetoVolve®, and KetoCuisine®, or solid ketogenic meals orally during the initial 3 months on the diet therapy were also excluded. Patients' profiles were investigated as follows: age at the time of the investigation (October 31, 2016), sex, underlying etiology of epilepsy, age at seizure onset, classification of epileptic syndrome, seizure type, seizure frequency, interictal electroencephalographic (EEG) findings, and number of antiepileptic drugs (AEDs) used previously. We also investigated age at the initiation of the KD, nutritional routes, and concomitant AEDs.

2.2. Dietary specifics

M817-B was provided for the patients as basic meals. When a ketogenic ratio higher than 3.0 was needed, oil or fresh cream was allowed to be added, and when a ketogenic ratio lower than 3.0 was needed, commercially available regular milk was allowed to be added. There was no common start-up protocol for the KD using M817-B because this was a retrospective study. We investigated the ketogenic ratio, nutritional routes, and food consistency, i.e., liquid, paste, or solid, at 1, 3, 6, 12, 24 months, and at the final visit.

2.3. Efficacy in seizure reduction

We assessed the efficacy of the diet therapy for reducing the seizure frequency of each patient and each seizure type and for interictal EEG improvement at 1, 3, 6, 12, and 24 months on the diet therapy. Serum beta-hydroxybutyrate was also checked at each visit. Efficacy in seizure reduction was defined as "seizure-free" when seizures disappeared, "excellent" when a >90% seizure reduction was achieved, "good" when a >50% seizure reduction was achieved, "poor" when a >50% seizure reduction was not achieved, and "worse" when seizure frequency was aggravated. Efficacy on interictal EEG findings was defined as "excellent" when paroxysmal discharges disappeared, "good" when >50% of paroxysmal discharges were reduced, "poor" when <50% of paroxysmal discharges were reduced, and "worse" when paroxysmal discharges increased. We also investigated the correlation between serum beta-hydroxybutyrate and efficacy in seizure reduction. EEG data were collected between 10 and 14 months (12-month data) and between 22 and 26 months (24-month data). Modification of concomitant AEDs was allowed during the study period.

2.4. Tolerability and side effects

We assessed the tolerability and side effects of the diet therapy. We demonstrated the cumulative continuation of the KD using Kaplan-Meier analysis. We researched the reasons for discontinuation of the diet therapy. We also investigated the side effects that required medical intervention or discontinuation of the diet therapy. Because this was a retrospective study, the need for and timing of medical interventions to treat the side effects were left to the discretion of the medical providers.

3. Results

3.1. Patient profiles

We analyzed 42 patients (25 male and 17 female patients) from 4 hospitals (20 from Shiga, 10 from Tokyo, 8 from Shizuoka, and 4 from Osaka). The patient profiles, including the underlying etiologies, epilepsy classification, seizure phenotypes, interictal EEG findings, number of previously used AEDs and concomitant AEDs, age at seizure onset, and KD initiation, are shown in Table 1. All but 2 patients had daily seizures. AEDs prescribed concomitantly with diet therapy at initiation included valproic acid (n = 23), phenobarbital (n = 13), lamotrigine (n = 12), topiramate

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