Seizure 20 (2011) 558–563

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Comparative trial of low- and high-dose zonisamide as monotherapy for childhood epilepsy

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ARTICLE INFO

Article history:
Received 31 January 2011
Received in revised form 29 March 2011
Accepted 1 April 2011

Keywords:
Zonisamide
Child
Epilepsy
Cognition
Behavior

ABSTRACT

Purpose: To evaluate the effectiveness of zonisamide (ZNS) as monotherapy in children with newly diagnosed epilepsy.
Methods: This randomized, multicenter trial included a 2–4-week titration and a 24-week maintenance phase after randomization to low-(3–4 mg/kg/day) or high-(6–8 mg/kg/day) dose groups as target maintenance dosages. The primary outcome measure was the seizure-free rate over 6 months, while a secondary measure was the change in cognition and behavior from screening to the end of the maintenance phase.
Results: Out of 125 patients enrolled, 90 (49 low-dose and 41 high-dose) completed the study. Forty-one patients (63.1%) in the low-dose group and 34(57.6%) in the high-dose group achieved 6 months' freedom from seizures ($p = 0.66$). After treatment, the picture arrangement subtest improved in the low-dose group ($p = 0.047$) while the vocabulary subtest worsened in the high-dose group ($p = 0.020$). Comparing between the two groups, the vocabulary subtest in the high-dose group was significantly worse than that in the low-dose group ($p = 0.002$). Social competence, somatic complaints, depression/anxiety and delinquent and aggressive behavior in the low-dose group were significantly improved ($p < 0.05$). Moreover, total social competence, somatic complaints, delinquent behavior, externalizing, and total behavior problems were significantly more improved in the low-dose group than the high-dose group ($p < 0.05$).
Conclusions: ZNS is an effective monotherapy for newly diagnosed childhood epilepsy. Lower doses of ZNS have a similar efficacy and more beneficial neurocognitive effects compared to higher doses. When prescribing higher doses of ZNS, one must be aware of the possible manifestation of problems associated with language development, such as those affecting vocabulary acquisition.

1. Introduction

Zonisamide (ZNS) is an antiepileptic drug (AED) with a broad-spectrum action that has demonstrated good efficacy in controlling seizures as an add-on therapy in adult and pediatric epilepsy.[1–6] However, few studies have evaluated ZNS as a primary monotherapy in children with newly diagnosed epilepsy. Cognitive and behavioral effects are key considerations in the selection of AEDs because of their influence on the acquisition of new skills and on the ability to develop social strategies at crucial stages of

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doi:10.1016/j.seizure.2011.04.005

development. Generally, AEDs exert a dose-dependent effect on cognitive functioning. Here, we have used a dose-controlled study design to evaluate the efficacy of ZNS as monotherapy for seizure control and tolerability, including an analysis of neuropsychological effects, in children less than 16 years of age with newly diagnosed epilepsy.

2. Methods

2.1. Subjects

Children less than 16 years of age were eligible for the study if they had been diagnosed with epilepsy and had experienced two or more seizures in the previous 6 months. All subjects had normal intelligence at baseline (intelligence quotient [IQ] > 70), and the decision had been made to start medication. Exclusion criteria included evidence of a progressive cerebral lesion or a neurodegenerative metabolic disorder, pre-existing cognitive impairment at baseline that could interfere with future cognitive testing procedures, and a history of psychiatric disorder. Patients previously treated with AEDs were also excluded.

The study was conducted in 10 referral hospitals for pediatric epilepsy care. The protocol was approved by the institutional review boards of all of the centers involved. Informed consent was obtained from all participants and their guardians before any trial-related procedures were performed.

2.2. Study design

The study was a multicenter, randomized, open-label, parallel-group clinical trial of dose-comparison design with a low or high ZNS dose given as monotherapy. Each study center received a separate and independent randomization procedure by random code assignment. The study included a retrospective baseline phase of 6 months and a screening phase of 1 week during which eligibility was determined and all screening procedures were carried out. The 28-week treatment period included the initial 2–4 weeks of titration and 24 weeks of maintenance. Following the screening phase, the titration was started, during which either a low- or a high-dose was introduced.

In the low-dose group, ZNS was introduced at 1 mg/kg twice daily and increased by 1–2 mg/kg/day after 1–2 weeks. The maintenance dose for the low-dose group was 3–4 mg/kg/day. However, if a patient with partial seizures experienced one or more convulsive seizures or other types of seizures more than twice in 4 weeks, or if the seizure frequency or intensity increased in comparison with the baseline of other seizure patients, the dose was increased gradually. In the high-dose group, ZNS was

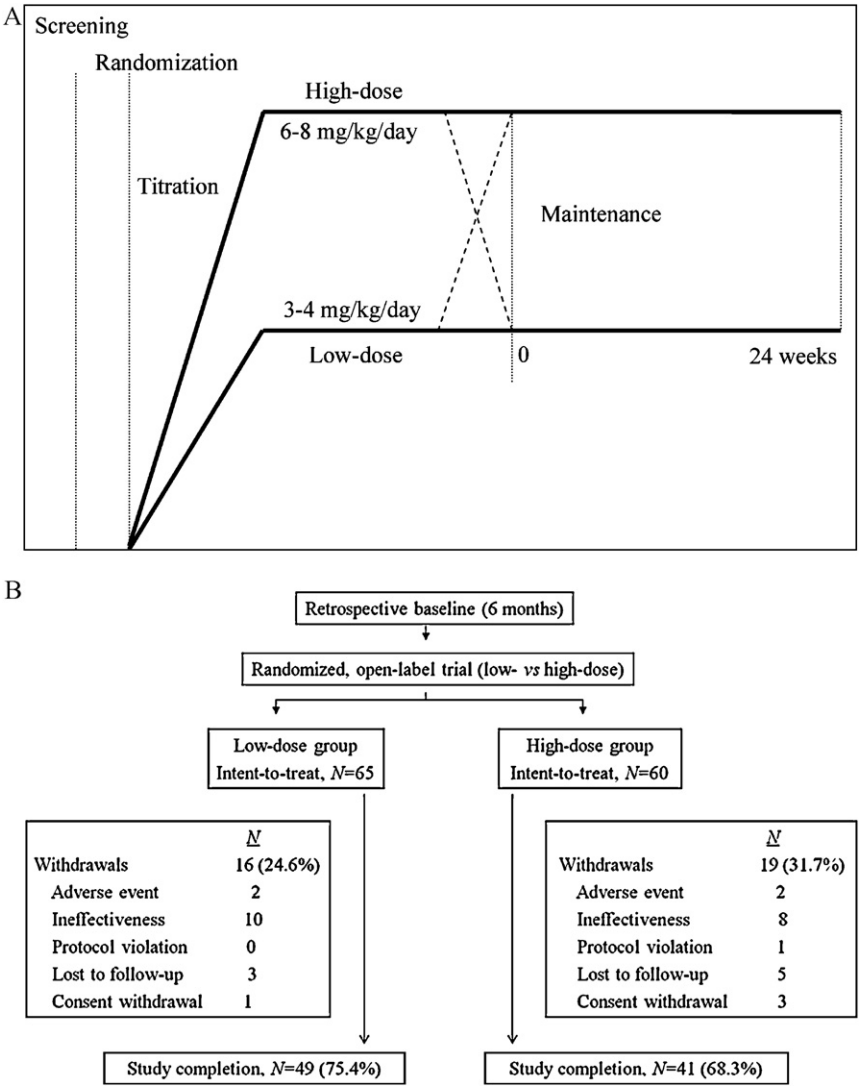

Fig. 1. Design (A) and progression (B) of the trial.