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Original article

Safety and tolerability of zonisamide in paediatric patients with epilepsy

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ABSTRACT

Background: Zonisamide has recently been approved in Europe for the adjunctive treatment of partial seizures (with or without secondary generalisation) in adolescents and children aged ≥6 years.
Aim: To further assess the safety of adjunctive zonisamide in paediatric epilepsy patients.
Methods: A pooled analysis of data from 17 studies (including four randomised, double-blind trials) was conducted. The safety population comprised patients aged ≤16 years receiving at least one dose of study drug. Assessments included treatment-emergent adverse events (TEAEs), clinical laboratory parameters, vital signs and electrocardiography.
Results: The analysis included 398 patients treated with zonisamide (<12 years, $n = 191$; 12–16 years, $n = 207$). All but seven patients received zonisamide as adjunctive therapy. Mean duration of exposure was 318.7 days (mean dose, 253.1 mg/day). Most TEAEs were of mild or moderate intensity. The most frequently reported treatment-related TEAEs were decreased appetite (15.6%), somnolence (12.1%), fatigue (9.3%), dizziness (6.0%), decreased weight (5.8%), irritability (5.8%) and headache (5.3%). Incidence of serious zonisamide-related TEAEs was low (3.5% overall). TEAEs most commonly leading to discontinuation were lethargy (1.0%) and fatigue (1.0%). TEAEs of decreased weight and decreased appetite occurred in 28 (7.0%) and 78 (19.6%) patients, respectively. Twenty-eight patients had decreased bicarbonate levels, but there were no reports of respiratory alkalosis or metabolic acidosis. No changes in vital signs of clinical concern were observed and there were no reports of clinically significant electrocardiogram abnormalities with zonisamide treatment.
Conclusion: Zonisamide demonstrated an acceptable safety profile when used as adjunctive treatment in paediatric patients.

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1. Introduction

Selection of the most appropriate treatment approach for a child with epilepsy is particularly challenging because it has implications not only for the child's current health status, but also for their longer-term neurodevelopment.[1] Moreover, children present with a differing range of epilepsies to adults, with some epilepsy syndromes seen only during childhood, meaning that the choice of antiepileptic drugs (AEDs) for children may differ from those chosen for adult patients.[2] Since 25–30% of children with epilepsy remain refractory to medical therapy,[3] there is a continuing need for new treatment options. Although it is recognised that some seizure types and syndromes may be common to both children and adults, and that adult regulatory data may therefore be applicable to children, a new AED must be adequately investigated for specific use in the paediatric setting, particularly in terms of its safety and tolerability.[4,5]

Zonisamide is a benzisoxazole derivative, chemically unrelated to other AEDs, that has a variety of modes of action, including inhibition of Na^+ channels and reduction of T-type Ca^{2+} currents.[6] It is currently licensed in Europe and the USA for the adjunctive treatment of partial seizures (with or without secondary generalisation) in adults.[7,8] In Europe, it is also approved as monotherapy for the treatment of partial seizures (with or without secondary generalisation) in adults with newly diagnosed epilepsy and has recently been approved for the adjunctive treatment of partial seizures (with or without secondary generalisation) in adolescents and children aged ≥6 years.[7] Approval for paediatric use was based on the results of a Phase III, double-blind, randomised, placebo-controlled, multicentre trial, which demonstrated that adjunctive treatment with zonisamide is significantly more effective than placebo in controlling seizures in children with partial seizures receiving a stable regimen of one or two other AEDs.[9] Zonisamide was also shown to be well tolerated compared with placebo, with no new or unexpected safety findings observed.[9]

We present here the results of a pooled analysis of safety data from 17 clinical studies (including the pivotal Phase III trial[9]) in which paediatric epilepsy patients received zonisamide. The objective of this investigation was to further assess the safety/tolerability of adjunctive zonisamide therapy in paediatric patients.

2. Materials and methods

2.1. Study design and patients

A pooled analysis was conducted to assess the safety and tolerability of adjunctive treatment with zonisamide in paediatric patients with epilepsy. Safety data were taken from all the completed clinical studies that recruited more than three paediatric, zonisamide-treated patients; were conducted according to International Conference on Harmonisation (ICH) standards and for which a clinical study report compliant with ICH E3 guidelines[10] was available. The analysis included 17 clinical studies (four randomised, double-blind trials; 13 uncontrolled, open-label studies, including six extension studies), details of which are summarised in Table 1. Data were pooled regardless of epilepsy indication, which included partial seizures, complex partial seizures, refractory partial epilepsy, progressive myoclonic epilepsy, primary generalised epilepsy and paediatric epilepsy (without further definition). Patients treated in extension studies included those treated with placebo in double-blind trials who then switched to zonisamide treatment and those treated with zonisamide in double-blind trials who continued to receive zonisamide in subsequent extension studies.

Since there was substantial variation across the treatment groups in dosing and duration of exposure among the studies included in the analysis (Table 1), it was not appropriate to compare zonisamide data with placebo data. However, data for paediatric patients who received zonisamide were compared descriptively with data from adult patients (age 18–65 years) who received adjunctive zonisamide, which were obtained from a primary safety database of zonisamide adjunctive therapy studies.

2.2. Study assessments and data analysis

Tolerability and safety were assessed by evaluating treatment-emergent adverse events (TEAEs); clinical laboratory parameters (haematology and clinical chemistry); vital signs (systolic blood pressure, diastolic blood pressure, pulse rate); physical examination (weight) and electrocardiography (ECG). Patients were counted once under each TEAE category, even if they experienced multiple events within that category. The incidence of TEAEs by severity, serious TEAEs, treatment-related TEAEs and TEAEs leading to discontinuation were also summarised. In general, a TEAE was considered to be serious if it resulted in death, was life-threatening, required hospitalisation (or prolongation of existing hospitalisation), resulted in persistent or significant disability/incapacity, or was a congenital anomaly/birth defect in a child of a subject exposed to study drug. TEAEs that could have jeopardised the patient, or required intervention to prevent one of the aforementioned outcomes, were also considered to be serious.

TEAEs of special interest associated with the administration of zonisamide were specifically assessed. These included weight loss, decreased appetite, hypersensitivity, skin eruptions (including rash), haematological events, suicidal ideation and behaviour, kidney stones, metabolic acidosis, disordered body temperature, pancreatitis and elevated pancreatic enzymes, muscle disorders, sudden unexpected death in epilepsy (SUDEP), epilepsy and liver function abnormalities. The number of patients with serum creatinine >135 μmol/L at any time was evaluated. Bicarbonate levels were assessed by evaluating the number of patients with an actual level ≤16 mmol/L and a decrease from baseline of ≥6 mmol/L. Weight changes were assessed by evaluating the number of patients with ≥5%, ≥7% and ≥10% change in weight from baseline.

Other assessments included the extent of zonisamide exposure (in terms of dosage and duration) and the use of concomitant AEDs.

Assessment of safety across the 17 studies was performed for the safety population, defined as patients aged ≤16 years at