ELSEVIER

Role of Intravenous Levetiracetam in Acute Seizure Management of Children

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Status epilepticus is defined as a seizure lasting beyond 30minutes. Children with intractable epilepsy undergo frequent hospital admissions secondary to status epilepticus or because of acute exacerbation of seizures. Intravenous levetiracetam became available in August 2006 for use in patients aged above 16 years. There are insufficient data about the efficacy and safety of intravenous levetiracetam in children. We retrospectively analyzed data from children treated with intravenous levetiracetam for status epilepticus and acute exacerbation of seizures. We acquired data from our institution's electronic medical records concerning patients with status epilepticus and acute exacerbation of seizures who received intravenous levetiracetam. Thirty-two patients (age range, 2 months to 18 years) had received a levetiracetam load of 25-50 mg/kg for status epilepticus. There were 17 (53.1%) males and 15 (46.8%) females. Response to intravenous levetiracetam in all patients was favorable. Status epilepticus ceased clinically and electrographically. Eighteen patients (56.5%) received intravenous levetiracetam after receiving fosphenytoin and Ativan with no response. No serious side effects were evident. Fifteen patients (46.8%) were discharged on levetiracetam monotherapy, and 9 (28.1%) received levetiracetam as adjunctive therapy after discharge from the hospital. Intravenous levetiracetam can be used adjunctively or as monotherapy in children with status epilepticus and acute exacerbation of seizures.

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Introduction

Levetiracetam injection is an alternative for adult patients (16 years and older) when oral administration is not feasible. Intravenous levetiracetam received approval by the United States Food and Drug Administration in August 2006. Studies indicate that intravenous levetiracetam is well-tolerated and has a favorable pharmacokinetic and safety profile, similar to that of oral levetiracetam in adult subjects [1,2]. It was also demonstrated that oral levetiracetam can be used in the treatment of status epilepticus [3–5]. Data were published about efficacy and safety of children of different age groups with epilepsy [6,7]. Here, we report on our experience with intravenous levetiracetam in status epilepticus and acute exacerbation of seizures.

Methods

Status epilepticus is defined as a seizure lasting longer than 30 minutes [8]. Children with intractable epilepsy undergo frequent hospital admissions secondary to status epilepticus or acute exacerbation of seizures. We retrospectively analyzed 32 patients who received intravenous levetiracetam between August 2006 and May 2008 at our institution. This study was approved by the hospital's Institutional Review Board. The variables included the patient's age, race, underlying diagnosis, type of seizures, indications for use of intravenous levetiracetam, loading and maintenance doses of intravenous levetiracetam, concomitant antiepileptic drugs, response to treatment, immediate side effects during and after infusion, and discharge of patients on monotherapy versus adjunctive therapy.

Individual doses were determined by our pediatric neurologist on a case-by-case basis. A bolus administration of 50 mg/kg in most patients was followed by a maintenance dose of 25 mg/kg every 12 hours. The given dose was infused for 15 minutes, based on adult intravenous data and pediatric oral data [9].

Results

We retrospectively analyzed 32 children, aged 2 months to 18 years, who had been treated with intravenous levetiracetam.

The following variables were taken into consideration.

Gender and Race

There were 17 males and 15 females. Among them, 12 were black, 6 were Hispanic, and 14 were white.

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Underlying Diagnoses

Thirteen patients had idiopathic seizures, 7 exhibited cerebral palsy, 3 manifested a brain tumor, 2 patients presented with hypoxic ischemic encephalopathy, 2 patients had undergone a postnatal stroke, and one patient each presented with a diagnosis of caudal regression syndrome, Lennox-Gastaut syndrome, myoclonic epilepsy, Dandy-Walker malformation, and cortical dysplasia. In 13 patients, despite an extensive medical history and the performance of tests such as neuroimaging and electroencephalograms, the underlying cause could not be determined. These patients were considered to manifest ''idiopathic epilepsy.''

Types of Seizures

Complex partial seizures comprised the most common type in our patients. They were evident in 22 patients. Six patients manifested both partial and myoclonic seizures. Two patients exhibited primary generalized seizures. One patient exhibited focal motor seizures, and another exhibited infantile spasms.

Indications for Use of Intravenous Levetiracetam

Sixteen patients presented with status epilepticus, and 15 with acute exacerbation of seizures. One patient presented with increased intensity of infantile spasms.

Response to Use of Intravenous Levetiracetam

Seventeen patients were receiving oral levetiracetam before admission as adjunctive therapy, and 6 were receiving it as monotherapy. Nine patients presented at our emergency room with new-onset seizures. Duration of signs ranged from 0.2-96 hours. The dose of intravenous levetiracetam was determined by our pediatric neurologist on a case-by-case basis. The majority of patients (25 of 32) received intravenous levetiracetam loads of 50 mg/kg, 4 patients received a loading dose of 25 mg/kg, 2 patients received 60 mg/kg, and one patient received 70 mg/kg. Intravenous levetiracetam was continued for 24-48 hours, depending on the patient's condition, with a maintenance dose of 25 mg/kg every 12 hours. Twenty-nine patients were switched to oral levetiracetam 25 mg/kg twice daily. Twenty-nine patients were discharged on oral levetiracetam and 17 were discharged on monotherapy (91%). They included 8 patients who presented with new-onset seizures. Nine (28%) were discharged with levetiracetam as adjunctive therapy. Comedications included topiramate, zonisamide, oxcarbazepine, and valproate.

No immediate side effects were evident during or after infusions. In one patient, levetiracetam was discontinued because of a rash. One patient developed behavior issues; vitamin B6 was added to the regimen. This patient responded to vitamin B6, and was able to tolerate levetiracetam upon 3-month follow-up at our pediatric neurology clinic. All patients responded to intravenous levetiracetam both clinically and electrographically. Clinical and electrographic improvement was seen 25-30 minutes after commencing the infusion (the infusion time was 15 minutes). Patients were monitored in the Pediatric Intensive Care Unit.

Concomitant Medications

Patients received Ativan in the emergency room as first-line treatment, followed by fosphenytoin. In total, 59% of subjects were unresponsive to fosphenytoin treatment. The patient population included 53% with acute exacerbations of seizures, 64% with status epilepticus, and 3% with increased intensity of infantile spasms. Most patients (72%) were undergoing treatment with antiepileptic drugs at time of admission. The most common antiepileptic drugs used at that time were levetiracetam (82%) and zonisamide (22%).

No patient was gradually withdrawn from levetiracetam during the immediate 1-week follow-up. Twenty-nine out of 32 (90.6%) patients were discharged on an oral levetiracetam dose of 25 mg/kg twice daily. Fifteen were seen in the Pediatric Neurology Clinic after discharge from the hospital. Three were seen for 8-month follow-up, 4 were seen for 6-month follow-up, 2 were seen for 10-month follow-up, and one each was seen for 1-month, 2-month, 3-month, 5-month, 7-month, and 14-month follow-up. Levetiracetam was well-tolerated in all these patients. Seven patients were followed in the Pediatric Clinic, and 2 patients were followed in the Pediatric Oncology Clinic, 6 months after hospitalization. No adverse effects were reported. Five patients were lost to follow-up.

Discussion

Our study data suggest that intravenous levetiracetam can be used as both adjunctive therapy and monotherapy in children with status epilepticus and acute exacerbation of seizures. In fact, 15 of our patients were discharged on levetiracetam monotherapy. Khurana et al. demonstrated that levetiracetam monotherapy is effective in pediatric epilepsy, in their retrospective analysis of pediatric epilepsy patients receiving levetiracetam at a single institution over a 3-year period [7].

Moreover, Altenmuller et al. reported on a case of termination of status epilepticus with the use of intravenous levetiracetam [10]. In our retrospective study, 46.87% of our patients with status epilepticus responded favorably to a load of intravenous levetiracetam; clinical and electrographic improvement occurred within 30 minutes. Our data demonstrated the efficacy of intravenous levetiracetam in status epilepticus. In fact, intravenous levetiracetam has proven effective in both status epilepticus and acute exacerbation of seizures in 56.25% of our patient population who had been unresponsive to fosphenytoin. Similarly, Goraya et al. stated that 3 out of 10 patients who responded to intravenous levetiracetam had been unresponsive to phenytoin and phenobarbital [6].

Baulac et al. indicated that intravenous levetiracetam can be used as an alternative to oral dosing in patients with

partial-onset seizures [11]. This was also the case in our patient population. Complex partial seizures with and without secondary generalization were evident in 68.75% of our patients.

Goraya et al. also demonstrated that intravenous levetiracetam was effective in various clinical situations in children of different age groups, including status epilepticus and acute exacerbation of seizures [6]. The underlying diagnoses in our patient data were also diverse, and included cerebral palsy, brain tumor, hypoxic ischemic encephalopathy, caudal regression syndrome, Lennox-Gastaut syndrome, myoclonic epilepsy, Dandy-Walker malformation, intraventricular hemorrhage, and cortical dysplasia. A large group of these patients also manifested idiopathic epilepsy.

Our study indicates that intravenous levetiracetam can be used in patients with new-onset seizures. However, our results are limited because of the small sample size and lack of long-term follow-up. We need larger, prospective trials to evaluate the safety, efficacy, and tolerability of intravenous levetiracetam in patients with pediatric epilepsy.

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