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Original Article

Levetiracetam in intractable childhood onset epilepsy

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Abstract. Levetiracetam (LEV) is a new antiepileptic drug (AED), which has a mechanism of action distinct from that of other AEDs suggesting a potentially valuable therapeutic profile. Our objective is to report our experience in treating children with intractable epilepsy. Prospective, open label, add on trial of LEV in treating consecutive children with intractable epilepsy (defined as recurrent seizures after at least three antiepileptic medication trials). Follow up by one pediatric neurologist was performed. Therapeutic response was recorded as complete (no seizures), good ($>$ 50% seizure reduction), fair ($<$ 50% seizure reduction), or none. Thirty children (58% males) aged 15 months-15 years (mean 5.8 years, SD 3.9) were included. Most children (80%) had daily seizures, were tried on multiple AEDs (mean 4.7, SD 1.5), and had cognitive deficits (86%). The epilepsy was symptomatic in 64%. The mean LEV dose was 41 mg/kg/day and the children were followed for 4–8 months (median 5 months, SD 2.5). After the introduction of LEV, six (20%) children became completely seizure free and 43% had $>$ 50% seizure reduction. The percentage of children with daily seizure was reduced from 80% before LEV to 27% afterward ($P < 0.0001$). Side effects were reported in 10 (33%) children in the form of decreased appetite, irritability, sedation, and seizure worsening. The majority were transient, however, LEV had to be withdrawn in four (13%) children because of lack of efficacy or seizure worsening. LEV is a novel AED with a broad spectrum of antiepileptic efficacy. The drug was well tolerated and most side effects were transient. However, larger controlled studies are needed in young children to establish the long-term efficacy and safety.

Keywords: Levetiracetam, treatment, child, intractable, epilepsy, seizure

1. Introduction

Intractable epilepsy has been associated with cognitive/behavioral problems and impaired psychosocial development [1–4]. Recurrent seizures also increase the risk of injury and even death [5–7]. Levetiracetam (LEV) is a new antiepileptic drug (AED), which has a mechanism of action distinct from that of other AEDs [8]. The synaptic vesicle protein, SV2A, was recently found to be the binding site of LEV in the brain [8]. LEV reduces high-voltage activated calcium currents, reverses the inhibition of gamma-aminobutyric acid and glycine currents, and acts on potassium channel conductance [9]. This novel mechanism suggests a valuable therapeutic profile over the other conventional AEDs. Although the efficacy and tolerability of LEV is well established in adults, few large studies are available in children. Clinical trials, in the form of case reports and small series, have shown that LEV is effective when used adjunctively in chil-

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dren with refractory seizures [9]. It was found effective against many seizure types including primary generalized tonic clonic seizures, partial and secondary generalized seizures, and Lennox-Gastaut syndrome [10–22]. Recently, LEV was found effective in infantile spasms [23], continuous spikes and waves during slow sleep [24], and progressive myoclonic epilepsy [25].

LEV was introduced in the USA in 2000, however, it only became available in Saudi Arabia in early 2004. To date, no regional data evaluating the experience in Saudi children has been published. In this paper, we report our short-term experience with LEV for the treatment of children with intractable epilepsy. We hypothesized that based on the available pediatric literature; LEV should be both effective and well tolerated in children with refractory epilepsy.

2. Materials and methods

A series of consecutive children with intractable epilepsy was identified prospectively over a 6 months period ending 1 February 2005. Patients were identified through referrals and consultations to the pediatric neurology service at King Abdulaziz University Hospital (KAUH) and King Faisal Specialist Hospital and Research center (KFSH&RC), both in Jeddah, Saudi Arabia. KAUH is the main teaching center of the Western region in collaboration with KFSH&RC. Both are multispecialty adult and pediatric hospitals providing tertiary medical care for most of the regional population of Western Saudi Arabia. Patient and disease related data were collected during the initial visit. Intractable epilepsy was defined as recurrent seizures that failed to respond to at least three AED trials singly or in combination despite of using maximum doses or doses resulting in therapeutic drug levels [26,27]. After obtaining verbal consent, LEV was added to the other AED therapy at a starting dose of 125–500 mg/day. The dose was doubled every week until the minimum effective dose was reached (achieving a seizure free outcome) or up to a maximum dose of 60 mg/kg/day. Follow up by one pediatric neurologist was performed to document therapeutic response and occurrence of side effects. The period of follow-up visits were not standardized. Therapeutic response was recorded as complete (no seizures), good ($>$ 50% seizure reduction), fair ($<$ 50% seizure reduction), or none (no response). The seizure outcome was assessed based on seizure diaries prepared by the parents.

The data was tabulated using Epi Info, version 6 [28], and the results were examined by Chi-square statistics to identify the magnitude of significant associations when present. A P-value less than 0.05 was considered statistically significant.

3. Results

Thirty children with intractable epilepsy were included. Their ages ranged from 15 months to 15 years, (mean 5.8 years, SD 3.9) with 58% males. Most children (62%) lived in the Jeddah area. Associated motor deficits were recognized in 48% and only 10% were attending a regular school program. Most children (86%) had mental retardation, which was severe in 52%. All children had medically refractory epilepsy that failed many AED trials ranging from 3–8 drugs (mean 4.7, SD 1.5). Most children (80%) had daily seizures. The epilepsy was idiopathic in 7%, cryptogenic (abnormal development and central nervous system examination with no recognized disease) in 29%, and symptomatic in 64%. The underlying etiologies are summarized in Table 1. The seizures were mixed in 13 (43%), partial $+/-$ secondary generalizations in seven (23%), myoclonic in five (17%), primary generalized tonic clonic in three (10%), and two (7%) children had infantile spasms. Electroencephalography (EEG) before the introduction of LEV revealed focal or multifocal epileptiform discharges in 18 (60%), generalized epileptiform discharges in three (10%), and hypsarrhythmia in two (7%) children.

LEV was added to the other AEDs, which ranged from 1–4 (mean 2.6, SD 1) at the time of enrollment. Initial dose ranged from 125–500 mg/day, which corresponded to 9–27 mg/kg/day (mean 15, SD 4.5), divided twice per day. Maintenance doses ranged from 375–2000 mg/day, which corresponded to 18–62 mg/kg/day (mean 41, SD 13). The children were followed for 4–8 months (median 5 months, SD 2.5). After the introduction of LEV, seven (20%) children became completely seizure free and 43% had $>$ 50% seizure reduction (Fig. 1). The percentage of children with daily seizure was reduced from 80% before LEV to 27% afterward ($P < 0.0001$) as shown in Fig. 2. Side effects were noted in 10 (33%) children in the form of decreased appetite (13%), irritability (10%), sedation (3%), and seizure worsening (7%). Three out of the four children with decreased appetite were also receiving topiramate. Most side effects were transient; however, the drug had to be withdrawn in four (13%) children because of lack of efficacy or seizure worsening.

Table 1
Causes of the intractable epilepsy in the study cohort

Diagnosis	Case number = 30 n (%)
Idiopathic or cryptogenic epilepsy	11 (36)
Congenital and developmental brain abnormalities	8 (27)
Hypoxic ischemic insult	3 (10)
Mesial temporal sclerosis	3 (10)
Degenerative/metabolic disorder	3 (10)
Post-meningitis or post-encephalitis	2 (7)

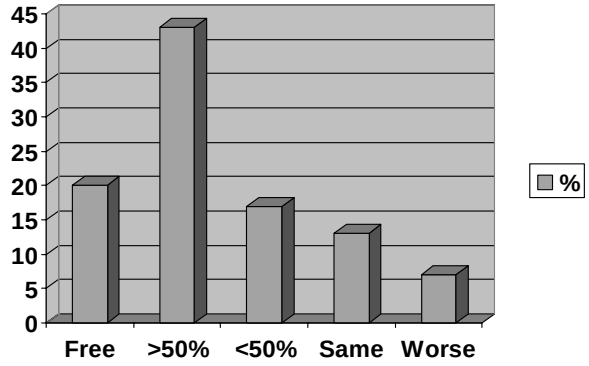

Fig. 1. Seizure outcome following the introduction of LEV shown in percentages of children achieving complete seizure freedom, $>$ 50% seizure reduction, $<$ 50% seizure reduction, same count (no change), or seizure worsening.

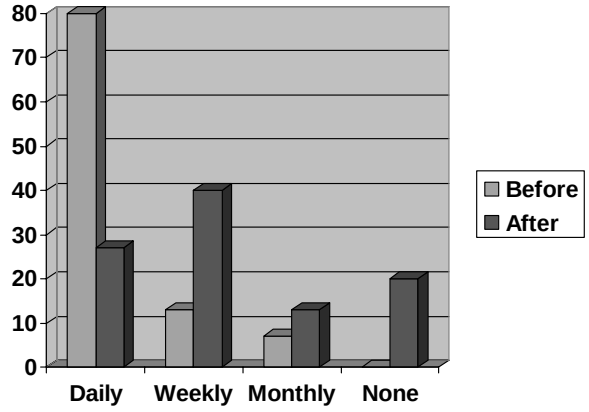

Fig. 2. Seizure count before (light bar) and after (dark bar) the initiation of LEV shown in percentages of children. The number of children with daily seizure dropped significantly and 20% became seizure free (none) on LEV.

4. Discussion

The study results confirm that LEV is an effective and well-tolerated AED in children with intractable epilepsy. Most of our patients had significant seizure reduction and 20% became completely seizure free. This is very impressive given that they had a long history of difficult seizure disorder with daily seizures and multiple seizure types that failed many AED trials. In addition to seizure control, the number of AEDs decreased following the introduction of LEV. Other authors found favorable response in up to 64% of children with intractable epilepsy, with 8–38% seizure free outcome depending on the type of epilepsy and duration of follow-up [9,10]. Higher efficacy and better tolerability were recently documented in a small monotherapy trial with a median seizure reduction of 81% when compared to 50% in add-on trial [11]. Our seizure free outcome was comparable to that reported in other studies, however, we had a higher overall seizure reduction rates. This could be related to the heterogeneity of our study sample, which included a variety of seizure disorders with different etiologies. As well, we had a relatively short follow up period (median 5 months), which may underestimates future seizure recurrences.

The usual LEV doses used in clinical trials ranged from 20–60 mg/kg/day in two divided doses [9,12]. Our maximum dose did not exceed 60 mg/kg/day (mean 41). Preliminary data on the pharmacokinetics in children suggests that they metabolize and clear LEV more rapidly than adults [1]. LEV is excreted mainly through the urine with no significant interactions with other AEDs [9]. The plasma half-life is $7 +/- 1$ hour with renal clearance 35% higher than adults [12]. Therefore, higher doses based on body weight are needed to achieve desired plasma concentrations [1]. Doses for young children should be 130–140% of those advised for adults [9,12]. Some authors recommended titration to effect and not absolute LEV dose to guide therapy in young children [13]. In a retrospective study involving 52 consecutive children, doses of up to 315 mg/kg/day were used in some of these children with surprisingly favorable tolerability [13]. Therefore, it is possible that higher doses ($>$ 60 mg/kg/day) may prove to be more effective in the future.

In our study, most LEV side effects were minor and the drug was well-tolerated. The drug was never discontinued because of side effects. The side effects were noted in 33% in the form of decreased appetite,

irritability, sedation, and seizure worsening. Other authors found that the most commonly encountered side effects were behavioral and manifest mostly in children with a history of behavioral problems [9]. Wheless and Ng [14] found aggression, sedation, and hyperactivity in up to 38% of 39 children with refractory epilepsy following the introduction of LEV. Acute psychosis was rarely reported in children and manifested in acute hallucinations, agitation, self harming behavior, and poor social contact [15,16]. Interestingly, several studies documented positive effects on behavior and alertness in 25–35% of treated children that could not be related directly to seizure control [11,17]. In comparison to the other studies, we had relatively lower cognitive side effects. This is likely the result of the slow rate of drug introduction and the tendency to use the minimum effective dose. Cognitive and behavioral side effects are generally more common with rapid AED dose titration [26,27]. In a large case control study involving 553 patients, slow titration with weekly increments lowered the risk of discontinuing LEV for behavioral reasons [18]. However, other authors used more rapid dose increments (10 mg/kg/4 days) with remarkable tolerability [19]. The other possible explanation for our lower cognitive side effects is the rate of mental retardation in our study sample. Most of our patients (80%) were mentally handicapped, which may interfere with parental recognition and reporting of cognitive side effects. However, in a recent study on 64 patients with mental retardation and refractory epilepsy, statistically significant ($P < 0.001$) improvements in several behavioral scores combining sleep, appetite, and alertness were encountered [10]. Finally, regarding decreased appetite, most of these children were also receiving topiramate, which is known to cause decreased appetite and weight loss [27]. LEV had to be withdrawn in 13% of our children because of lack of efficacy or seizure worsening, which was seen in 7%. These rates are generally lower than those reported in other studies, which may reach up to 22%, likely related to our slow titration and the tendency to use the minimum effective dose. Seizure worsening can be partially avoided with slow drug titration [9].

We conclude that LEV is a novel AED with a broad spectrum of antiepileptic efficacy. Although long-term safety and possible adverse effects of LEV have not been fully established in young children, it represents an option for children with high seizure frequency unresponsive to standard AED. The drug was well tolerated and most side effects were transient. However, larger controlled studies are needed in young children to establish the long-term efficacy and safety.

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