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REVIEW ARTICLE

A REVIEW OF USE OF LEVETIRACETAM AS AN ANTIEPILEPTIC IN CHILDREN AND NEONATES

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ABSTRACT

Levetiracetam, a pyrolidine derivative, is a newer antiepileptic drug whose efficacy and tolerability are already well known in adults. Few studies are available in children. Most studies suggest that levetiracetam is effective against partial and generalized epilepsy. The drug has also proven effective against photosensitivity, epileptic syndromes and epileptic and nonepileptic myoclonus. LEV is rapidly and almost completely absorbed after oral ingestion, is less than 10% protein-bound demonstrates linear kinetics and is minimally metabolized through a pathway independent of the cytochrome P450 system. It has no significant drug-to-drug interactions. The most common reported adverse events with LEV were somnolence, irritability, dizziness, nausea, influenza, and nasopharyngitis but these adverse reactions are mild and can be partially avoided with slow titration. Levetiracetam seems to have a broad spectrum of action and is, on the whole, well tolerated. This review, based on the international literature, aims to identify and make known the possible indications for levetiracetam in childhood.

INTRODUCTION

Several newer antiepileptic drugs (AEDs) have been introduced in recent years for childhood convulsion; however, approximately 25% of children with epilepsy experience treatment resistant seizures; or encounter intolerable adverse events following these drugs[(1)]. In children the aetiology of seizure, the pharmacokinetics, efficacy, and safety of these drugs may also be different than the adults [(2)].So there is an imperative need for a newer AED in paediatrics population with good efficacy or safety. Levetiracetam (LEV), introduced in 2000, is a newer antiepileptic, which is chemically unrelated to existing AEDs, with a novel mechanism of action, and has a better tolerability [(3)]. Though limited studies are available in children but most of those suggest that it has a wide spectrum of activity and is well tolerated among children [(4, 5)].There are review articles available on levetiracetam in western journals, however such review is not available in any of Indian journals. Here we review the mechanism of action, pharmacokinetics, and efficacy and safety profile of levetiracetam in childhood and neonatal seizure.

Mechanism of Action

Levetiracetam, a pyrolidine, the racemically pure S-enantiomer of pyrrolidineacetamide, is a newer antiepileptic with a novel mechanism of action. Unlike conventional antiepileptic there is no evidence for action on voltage-gated sodium channel, gamma- amino butyric acid, or glutamate-mediated synaptic transmission [(6)]. It selectively inhibits high-voltage activated calcium channels and reduces calcium release from intraneuronal stores [(7, 8)]. It binds with synaptic vesicle protein 2A (SV2A) [(1)], an integral membrane glycoprotein expressed ubiquitously in the brain and provides broad-spectrum (antiepileptic activity. A recent study has explored the hypothesis that levetiracetam may link a-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor channels in mouse cortical neurons, with a subsequent significant decrease of excitatory postsynaptic currents in cortical neurons[(9)].

Pharmacokinetics

Levetiracetam has a favourable pharmaco kinetic profile [(10)]. Levetiracetam has a linear pharmacokinetic profile, high oral bioavailability (close to 100%), and is not bound to proteins, with 95% being metabolized and excreted in urine [(11)]. The terminal elimination half-life of levetiracetam in children is 6.0 ± 1.1 (range 4.0-8.2) hours compared with 7.2 ± 1.1 (range 6-8) hours in adults. Therefore, while in adult twice-daily dose administration is optimum, three-times-daily dosing could be more appropriate in children [(12)]. The body clearance value of levetiracetam is 30-40% higher in children than the adults. Levetiracetam is mainly excreted by the kidneys, and its elimination correlates with creatinine clearance. Enzymatic hydrolysis by a plasma esterase is the major metabolic pathway. The starting dosage in children is 10mg/kg/day, and then titrated with increments of 10 mg/kg/day every 2 weeks. The usual maintenance dosage is 40-80 mg/kg/day (maximum 120mg/kg/day) in two to three equally divided doses .In children the maintenance dosage should be 130-140% higher than the adults due to faster clearance in them [(12)]

Levetiracetam is largely not protein bound; therefore, it does not compete with other drugs for binding sites [(13, 14)]. The pharmacokinetics of levetiracetam was also different in the neonates as compared to older children .Due to the higher volume of distribution in neonates, the loading dose should be higher (30 mg/kg). The dosing interval may need to be extended because of the reduced clearance in neonates. Therefore, a twice daily dosing schedule may be more appropriate than a three times daily schedule in neonates over the first several weeks of life. In infants with

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reduced creatinine clearance, the dosing interval may need to be extended even further [15].

Indication

In paediatric age group Levetiracetam was found to be useful for a wide range of epilepsies. It is approved for add on therapy in partial onset seizures both in adults and children. Recent double-blind studies showed the efficacy of LEV, as an adjunctive treatment in idiopathic generalized epilepsies, generalized tonic-clonic seizures and refractory myoclonic seizures [16, 17]. Although its use is approved as adjunctive therapy in children, recently it has been effectively used as monotherapy by some authors [18].It has also been used in specific epilepsy syndromes of childhood [19], and more recently in status epilepticus [18]. All these indications have been approved in all European countries and in the US.

Efficacy as Adjunctive Therapy

Generalised Seizure

Several studies have been published on the use of levetiracetam in generalised seizures. In a prospective study [20] out of 54 children 12 were presented with generalized idiopathic epilepsy and treated with levetiracetam .Complete elimination of seizures was seen in three children (25%), and a >50% reduction in seizure frequency than baseline, was seen in seven (58.3%) patients. Barron *et al* [21] retrospectively evaluated adjunct levetiracetam therapy in 18 children and found that ten patients had at least a 50% decrease in seizure frequency and six experienced a >75% reduction. Three patients became seizure free. Some other studies have been detailed in Table 1a and Table 1b.

Partial Seizure

There are some promising studies on levetiracetam as the adjunctive therapy in partial seizure is available (Table 1a and Table 1b). In a randomized, double-blind, parallel-group, placebo- controlled, multicenter trial in 101 children (4-17years) with partial seizures were treated with levetiracetam and 97 patients aged 3-17 years received placebo. Response rates (>50% seizure reductions) were 44.6% and 19.6% in patients receiving levetiracetam and placebo, respectively (p = 0.0002). Seven patients receiving levetiracetam and one patient receiving placebo become seizure free[25]. Based on this study, levetiracetam received US FDA approval as adjunctive treatment in partial epilepsy in children aged 4-16 years. Paul M et al[26] showed the median percentage of reductions of seizure frequency from base line over the evaluation period were 91.5% in the levetiracetam group (n = 63) and26.5% in the placebo group (n = 34). More than 50% responder rates were 62.5% and 41.2% (14 of 34) for levetiracetam and placebo respectively.

Refractory Epilepsy

Levetiracetam was found to be an effective alternative in refractory epilepsy when used as an add on therapy to one or two base line antiepileptic (Table 1a and Table 1b). An open-label trial [30] conducted in 198 patients (4 to 16 years) having at least four partial seizures per month and inadequately controlled with one or two concomitant anticonvulsants. Levetiracetam was found to be more effective than placebo in reducing the frequency of partial seizures, with a relative reduction over placebo of 26.8% (95% CI 14, 37.6; p = 0.0002). Seven patients (6.9%) receiving levetiracetam and one patient (1.0%) receiving placebo were seizure-free during treatment. Two large, multicenter European case series have been published on the long-term use and retention rates of levetiracetam in children with refractory epilepsy [31, 32].Results from the German study showed that 35 of 129 (27%) children were responders at 6 months, with a retention rate of 22.5% at 3 years [32]. In a retrospective, multicenter study in a large cohort of 200 children with refractory epilepsy showed that >50% reduction in seizure frequency found in 60% of patients and 14% were seizure free at the end of 2months. Seizure response rates remained high at 6 months with 40% improved (reduction of seizures) and 14% seizure free. A retention rate of 49% was reported at 1 year [31].

Absence Seizure

Despite extensive evidence of levetiracetam possessing anti absence effects in animal models there is surprisingly little information on its potential efficacy in patients with absence seizures. In an open-label prospective trial, 9 out of 21 children (42.9%) with newly diagnosed childhood or juvenile absence epilepsy treated with levetiracetam (31-70 mg/kg/day) were reported to be free from clinical and EEG seizures at the 6-month assessment [36]. In another multicenter trial 38 patients (4-16 years) were randomized in a 2:1 ratio to receive de novo monotherapy with levetiracetam (up to 30 mg/kg/day) or placebo for 2 weeks under double-blind conditions Nine out of 38 patients (23.7%) were responders in the levetiracetam group, compared with one of 21 (4.8%) in the placebo group (p = 0.08). Seven of 38 pts (18.4%) were both clinical and electrical seizure free on day 14 and17 pts were seizure free after one year of follow up [37].

Epilepsy Syndromes

Mostly the seizures in children associated in different epilepsy syndromes have poor response to conventional antiepileptic. The use of levetiracetam has shown encouraging results in patients with rolandic epilepsy, Jeavon syndrome and some epileptic encephalopathy, such as infantile spasms and Lennox-Gastaut syndrome. Levetiracetam was used in 21children (5to12.1years) with *benign epilepsy with centrotemporal spikes (BECTS)* with or without secondary generalization showed complete disappearance of seizures in all patients and no adverse events were also reported[38].A recent pilot study in six children (aged 6-12 years) with BECTS concluded that levetiracetam may also have a beneficial effect on language development[39]. Levetiracetam has been found to be effective as monotherapy in *Lennox-Gastaut syndrome*; and also found to be effective against myoclonic seizures and tonic- clonic seizures [40]. In another study [41] six patients (2.5-16 years) with treatment-resistant Lennox-Gastaut syndrome were initiated with levetiracetam (mean dosage 24 mg/kg/day) as add-on therapy. Complete cessation of tonic-clonic seizures and myoclonic seizures was observed in three & four patients respectively. A more 50% reduction of seizure frequency occurred in three patients with generalized tonic-clonic seizures, two with atonic seizures, and one with tonic seizures.

In *juvenile myoclonic epilepsy* levetiracetam was used and also showed its efficacy as monotherapy[42]. In 32 patients with epilepsy and a mean age of 13 years 3 months at seizure onset, levetiracetam was administered as the first antiepileptic drug(1000 to 2500 mg/day). At 6 months, 15 patients were seizure free, 14 were responders (>50% reduction in seizure frequency), and three had marginal effects (<50% reduction in seizure frequency). At 12 months, 29 patients were seizure free and three were responders .No significant adverse events were reported. These results were also supported in a pilot trial by Specchio et al[43], who investigated the correlation between levetiracetam-related EEG changes and its clinical outcome. Recently, levetiracetam have been tried in a three year-old girl with eyelid myoclonia with absence *(Jeavon syndrome)*, which had not responded to oral and intravenous benzodiazepines. This patient was enrolled in an open-label trial of levetiracetam monotherapy[44].

Efficacy as Monotherapy

Although levetiracetam has shown efficacy in children with epilepsy, when used as adjunctive therapy, limited data are available regarding its use as monotherapy. In a retrospective analysis [18] 18pts received

levetiracetam (14-60mg/kg) as monotherapy (either initial monotherapy or conversion to monotherapy) having either partial-onset epilepsy (n = 14; 74%) or generalized epilepsy (n = 4; 26%). Out of the 18 patients 61% (n = 11) became seizure free, 67% (n = 12) had >50% reduction in seizure frequency, and 33% (n = 6) showed no change in seizure frequency. The study concluded that levetiracetam appeared to be effective as monotherapy in children with epilepsy. Another retrospective study conducted on the effect of levetiracetam as monotherapy in 19 children with various seizure disorders demonstrated that 11 children (57%) had at least a 50% reduction in seizures or became seizure free [45]. Perry *et al* [46] analyzed the efficacy and tolerability of levetiracetam (n = 66) and carbamazepine (n = 20) monotherapy in children with partial epilepsy and demonstrated similar efficacy (based on the number of patients achieving seizure freedom of >6 months). Seizure freedom rates at 12 (p = 0.58) and 24 (p = 1.00029 months were also similar between the two treatment groups. Some more reports with findings are incorporated in Table 2.

Status Epilepticus and IV Levetiracetam

Although an intravenous formulation of levetiracetam has not been approved for the treatment of status epilepticus in children, available data indicate that it can be a useful alternative, especially in those who do not respond to benzodiazepines. In a retrospective analysis of a patient treated with intravenous levetiracetam showed its efficacy in acute repetitive seizure/status epilepticus when other anticonvulsants had failed or were contraindicated [50]. Khurana *et al* [18] reported a series of children with partial or generalized epilepsy (mean age 9.6 years) who were successfully treated with intravenous levetiracetam and the drug was well tolerated also. In a retrospective review among thirty-four patients (11-90 years) with status epilepticus with variable etiology concluded that the cessation of seizure in 71% of patients with IV levetiracetam. There were no serious adverse events documented in the patients' charts [51].

Neonatal Seizures

Phenobarbitone currently represents the antiepileptic drug (AED) of choice in neonatal seizure, despite being related to increased neuronal apoptosis in animal models and cognitive impairment in human subjects [52]. In contrast to most other established antiepileptic drugs LEV has not been found to increase apoptosis in animal models.LEV prevents neurdegeneration after hypoxia/ ischemia in rodent models or epilepsy, and it does not interfere with neuroprotective up-regulation of hypoxia inducible transcription factor 1 (HIF-1a). Levetiracetam (LEV) may have a more favorable profile since it does not cause neuronal apoptosis in infant rodents [53]. In a prospective feasibility study [54], levetiracetam was applied as first-line treatment in 38 newborns with EEG-confirmed seizures, after ruling out metabolic causes. Initial intravenous doses of 10 mg/kg were gradually increased to 45-60 mg/kg at the end of the week. Thirty infants were seizure free at the end of the first week and 27 remained seizure free at four weeks, while EEGs markedly improved in 24 patients at 4 weeks. In 19 cases, LEV was discontinued after 2-4 weeks, while 7 infants received LEV up to 3 months. No severe adverse effects were observed. In another prospective study [53], in six consecutive newborns levetiracetam was the first line AED administered in first two patients and in others after poor response to phenobarbitone. After 3 months, five out of six patients were seizure free under monotherapy with LEV. During a 3-month study period, only one child needed additional antiepileptic therapy. LEV was tolerated excellently in our small study group, with only one report of somnolence during titration. Few more published literature has been tabulated in Table 3; none of the studies had reported any serious adverse reactions.

Safety Profile

In very young patients under 2 years of age, 28 infants receiving levetiracetam as both monotherapy (10) and add on therapy (18) were enrolled [56].

Table 1a. Studies of levetiracetam as add on therapy in children

Type of seizure	Type of study	No of patients	Age (years)	Levetiracetam dose (mg/day/kg)	Results (%)	Reference
Generalized	Retrospective	18	10.3	29	>50 % seizure reduction (5.5%) >75 % seizure reduction (33.3%)	Barron *et al* 2001[21]
	Open label multicentre follow up	217	4-65	20-80	Complete seizure free- (22.6%) Seizure control (6 mo)-(56.2%)	Delanty *et al* 2012[22]
	RCT	164	4-65	20-80	Seizure free (24.1%) in study vs. (8.3%) in control P=0.009	Berkovic *et al* 2007[23]
	Prospective	54	_	_	100 % seizure reduction (25%) >50 % seizure reduction-(58.3%)	Allder *et al* 2002[20]
	Retrospective	59	9 mo-23 yrs	_	>50 % seizure reduction (53%) 100 % seizure reduction (20%)	Mandelbaum *et al* 2005[24]
Partial	Double blind multicentre RCT	101	4-17	60	>50 % seizure reduction (44.6%) 100 % seizure reduction (7%)	Glauser *et al* 2006[25]
	Prospective	67	6-13	33	Median seizure reduction (50%)	Lagae L *et al* 2005[27]
	Prospective open label trial	23	6-12	20-40	>50 % seizure reduction (52%) 100 % seizure reduction (8%)	Glauser *et al* 2002[28]
	Retrospective	43	5.2±4.4	45±33	>50 % seizure reduction (65%) 100 % seizure reduction (14%)	Herranz *et al* 2002[29]

Table 1b. Studies of levetiracetam as add on therapy in children

Refractory epilepsy	Partial	Multicenter	198	4-16	20-60	Seizure free > (6.9%)	Jensen & bourgeois et. al 2006[30]
		Open label	99	1-32	10-50	Seizure free (17.2%)	Coppola *et al* 2004(4)
	Partial & Generalised	Open label	33	4-16	10-60	Seizure free (27.3%)in partial seizure & (34.3%) in generalized seizure	Callenbach et.al 2008[33]
		retrospective	27	2-18	35	Seizure free (22%)	Hovinga *et al* 2001[34]
		Multicenter	285	0-17	10.5	Seizure free (6%)	Opp et.al 2005[35]
		Retrospective multicentre	200	3mo-19 yrs	8-100	Seizure free (49%)	Peake *et al* 2007[31]

Table 2. Studies of levetiracetam as monotherapy in children

Seizure type	Type of study	No of patients	Age (Years)	Levetiracetamdose (Mg/Day/Kg)	Results	Reference
Partial & Generalized	Retrospective	18	9.6	40-60	Seizure free 61%	Khurana et al.2007[18]
Partial	retrospective	20	< 10 yrs	10-70	Seizure free 80%	Frank J Ritter et al 2006[47]
Partial	Prospective	10	4-16	33	>50 % seizure reduction 81%	Lagae et al.[48]
Partial & generalized seizure	Retrospective	101	1 mo-20 yrs	30±8	100 % seizure reduction 60.3% >50 % seizure reduction 96.9 %	Sim GY et al. 2011[49]

Table 3. Studies of levetiracetam in neonatal seizure

TYPE OF STUDY	NO. OF PATIENTS	AGE GROUP	DOSE (mg/kg)	RESULTS (%)	STUDY (YEAR)
Prospective	38	Newborn	45-60	85 % seizure free	Ramantani G et al. 2010 [54]
prospective, open-label observational	18	>32 wks	14.3-39.9	85% complete seizure free	Stephanie et al.2011 [15]
Prospective pilot study	6	>2 kg	10-50	80 % seizure free	Alexandra F et al.2010 [53]
Retrospective	22	Newborn	50	86% seizure control	Owais et al.2001 [55]

Only one (4%) patient had worsening of seizures and two (7%) had behavioural changes (crankiness and irritability) which was reversible. In another study[57] conducted in 122 children, under 4 years of age with refractory epilepsy receiving levetiracetam (30 mg/kg/day) as an adjunctive therapy. Among those, side effects occurred in 34% of patients, but only16% had to discontinue treatment with levetiracetam, most commonly because of behavioural disturbances and/or irritability (8.2%). Life threatening adverse events was not reported .In particular changes in behaviour typically found at relatively lower doses [27, 35, and 40].

Out of 285 patients(2 to 18 years) mild to moderate side effects were reported in 128 patients (44.9%), most frequent being somnolence (23.9%), general behavioural changes (15.4%), aggression (10.5%), and sleep disturbances (3.2%). Levetiracetam was stopped in 8.1% of patients due to behavioural changes[35]. Another prospective, open-label trial among 129 children (mean age 10.6 years) with refractory epilepsy reported the overall incidence of side effects was 39.8%. All the side effects were moderate, often temporary, and always reversible. There was no significant difference between monotherapy and polytherapy group, and also between responders and non-responders group. Dose dependency of the side effects was not observed(34). In a randomized, placebo-controlled, multicenter study in children (n = 198, aged between 1 and 18 years of age) with poorly-controlled partial seizures, the patients were randomized to receive either levetiracetam (60 mg/kg/day) or placebo [25]. One or more adverse events were experienced by 88.1% of the levetiracetam group, compared with 91.8% in the placebo group. Serious adverse effects (not considered to be related to the drug) were reported in 7.9% of patients in the levetiracetam-treated group and 9.3% in the placebo group. In general, adverse events were not statistically different between the placebo and levetiracetam groups, and the tolerability profile of levetiracetam in children appeared to be similar to that previously reported for adults [58]. This trial demonstrated that levetiracetam is a safe and well tolerated therapeutic option, even in a pediatric population.

Conclusion

Levetiracetam has a broader spectrum of action against partial seizure with or without generalisation, generalised epilepsy, refractory epilepsy and in various types of epileptic syndromes in children. Recently it has been tried successfully even in neonatal seizures. It may be used both as monotherapy and adjunctive therapy in pediatric patients, even in young children. The usual dosage ranges between 40 to80 mg/kg/day and occasionally higher dosage required in pediatric patients (110-140 mg/kg/day). The efficacy of levetiracetam (reduction in seizure frequency) as monotherapy in children ranges between 70% and 75%, both in partial and generalized seizures and the majority become seizure free. The percentage of responders (50% or greater reduction in seizures) with levetiracetam as add-on therapy ranges between 30% and 70%, with good long-term retention rates, even in refractory epilepsy. Levetiracetam has shown good safety and tolerability in paediatrics patient with an advers effect profile similar to that of adult. Somnolence and behavioural changes are the most commonly reported side effects in all paediatric patients. The relative risk of neuropsychiatric manifestation in children is similar to adult.

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