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LEVETIRACETAM – EPILEPSY TREATMENT, PHARMACOKINETICS, MECHANISM OF ACTION, INTERACTION AND TOXICITY

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Abstract

Epilepsy is a common chronic neurological disorder that requires a long-term antiepileptic drug therapy. Epilepsy affects approximately 1% of the world's population, so about 50 million people worldwide have epilepsy. It more likely occurs among children and people over the age of 65. This chronic condition is characterized by recurrent, unprovoked epileptic seizures. Although there are many innovative methods of seizure control, such as neurosurgery, vagal nerve stimulations (VNS) and ketogenic diet, pharmacology is most forceful method of epilepsy treatment. Unfortunately, anticonvulsant drugs are not always effective; the number of non-responding patients is higher than 30% [2,25,29,31].

Levetiracetam (LEV) is one of the newest AEDs, marketed worldwide only since 2000 [29]. This novel antiepileptic drug has a unique and non-standard mechanism of action. The structure of LEV is similar to the prototypical nootropic drug piracetam. Its novel mechanism of action is connected with the synaptic vesicle protein SV2A in the brain. The elimination plasma half-live of LEV is approximately from 6 to 8 hours among adults. About 66% of the drug is excreted unchanged and 27% as inactive hydrolysis product [12]. LEV is mainly removed by the kidneys so that elimination parallels kidney function (renal clearance: 0,6 ml/min/kg) [3,12,32]. LEV was found to be well tolerated and effective in all types of seizures in adults and children [18]. It can be also used in combinations with other AEDs. The drug may also be useful in treatment of Lennox-Gastaut syndrome [9].

This article reviews available published data on LEV in the treatment of adults and children, including information about LEV`s pharmacokinetics, chemistry, mechanism of action, interactions and toxicity.

Key words: levetiracetam, antiepileptic drugs, seizures, epilepsy.

Abbreviations:
AEDs -antiepileptic drugs, LEV -levetiracetam, VNS – vagal nerve stimulation, CNS –central nervous system, MES - maximal electroshock, PTZ – pentylenetrazol, NMDA -acid-N-methyl–D–aspartate, AMPA - α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate, TPM - topiramate, OXC -oxcarbazepine, CBZ -carbamazepine, FBM -felbamate, LTG -lamotrigine, TGB -tiagabine, VGB -vigabatin, VPA –valproate, FDA -Food and Drug Administration.

Introduction:

Epilepsy is a brain disorder characterized by recurrent and spontaneous seizures. Some cases of epilepsy are inherited. The reasons of epilepsy can be congenital or acquired. A variety of insults to the brain can result in epilepsy, such as birth defects, birth injuries, stroke, vascular malformations, head injuries, brain infections or brain tumors, but definitely (approximately half of the cases) the causes can not be found clear- cut [42]. Epilepsy can appear at any age, but most often children and older adults develop the disease. Both the etiology and pathogenesis of epilepsy is complex. Epileptic seizures are consequence of an imbalance between inhibitory and excitatory mechanisms in the brain [2]. Typically, neurons in brain send electrical signals at a rate that is under 100 times per second but during the epileptic seizure it is unusually faster – approximately 500 times per second. There are two main types of seizures. Partial seizures start in a particular part of the brain, but may spread to the other parts, in distinguishing from generalized seizures which affect the whole brain all at once [4].

The treatment of epilepsy depends on the age of patient, appropriate classification of the seizure type and epileptic syndrome. The treatment of epilepsy should always begin with monotherapy [1]. Unfortunately, as many as 30% of all treated patients do not react to monotherapy with AEDs [40]. Then polytherapy with 2 or more drugs may be a solution. It is very important to remember that chronic medication with currently applied AEDs may cause a wide range of toxic and idiosyncratic reactions, teratogenesis, unexpected interactions with other drugs [28,29,40]. The most common complains include: nausea, tremor, ataxia, anorexia, weight loss, vomiting, anemia, sedation, leucopenia and many others.

LEV is well-tolerated AED especially among pediatric patients. LEV appears to be safe and effective AEDs with novel mechanism of action [9,31,41].

The aim of this review is to summarize the current and available literature data on levetiracetam (LEV) – and AEDs which may turn out beneficial in the treatment of at least some forms of epilepsy. LEV is marked under the trade name Keppra (manufactured by UCB Pharmaceuticals Inc.).

Chemistry and mechanisms of action:

Chemically LEV is a (S)-α-ethyl-2-oxo-1-pyrrolidine acetamide. The chemical formula –$C_8H_{14}N_2O_2$. Molar Mass (MM) of LEV – 170,209 g/mol. LEV has atypical chemical structure which is not similar to other anticonvulsants and its mechanism of action seems to be unique to known mechanisms of neurotransmission [41]. LEV is S-enantiomer of etiracetam, structurally similar to the prototypical nootropic drug piracetam. Only the S-enantiomer of LEV exhibits anticonvulsant properties. The three metabolites of LEV which representing approximately 27% of the administered LEV dose are not pharmacologically active [5,17]. LEV is easily water-soluble and decreasingly less soluble in chloroform, methanol, ethanol, acetonitrile and practically insoluble in n-hexane [27].

LEV binds to a unique binding site in the brain, the synaptic vesicle protein SV2A [9,28,40]. Nevertheless, very important is that LEV has no binding to membranes outside of

the CNS [9]. SV2A protein is a broad-spectrum anticonvulsant protein. The function of SV2A protein is binding and protecting against seizures in both models of epilepsy seizures – partial and generalized. In the study by Wheless JW [27], current evidence suggests that SV2A protein modulates synaptic vesicle fusion in the brain. LEV does not appear to affect normal brain physiology, so it is possible to modulate SV2A function only under pathophysiologic condition [21,27,41]. LEV is also known to selectively inhibit N-type calcium channels [20,27,41] and to block the inhibitionof GABA- and glycine- gated currents by negative allosteric modulators [35].

Preclinical studies:

Preclinical studies of LEV were investigated on mouses, rats, rabbits and dogs after a single oral dose [39]. LEV displays an unusually good preclinical profile in animal seizure and epilepsy models [33]. This novel anticonvulsant drug was first demonstrated in the early 1980s [19,34] but LEV and other new AEDs (gabapentin, lamotrigine, oxcarbazepine, pregabalin, topiramate, felbamate, zonisamide) have all reached the market since 1994 [6].

LEV in animal studies was completely absorbed. Similar to human model LEV did not bind to plasma proteins. LEV is eliminated by kidneys – excretion via urine is shown in Table 1. Animal tissues can produce acid metabolite of LEV. Mean plasma concentration were observed from 0,5 h in the rats to 1.5 h in the dogs and rabbits. Plasma elimination half-life was shorter then it assumes (Tabl. 1). Tissue concentration of LEV was higher than blood for kidneys, pituitary gland, thyroid gland, lower concentration then blood was for lens, spinal cord, fat, cerebellum and cerebrum. Although there were observed small, but not significant, differences between animals. There is no difference in the absorption, disposition and metabolism of LEV independently of animal sex [39].

Unlike other recently approved AEDs, LEV has got lack of anticonvulsant activity in two the standard animal screening models used for determination of AED efficiency: the maximal electroshock (MES) and pentylenetrazol (PTZ) seizure tests. [23, 39]. More over LEV has got very specificity property – a wide, safety margin between doses used in seizure protection and acute CNS adverse effects. Seizures protection was checked with agents such as pilocarpine (i.p.) and kainate (s.c.) which induce secondarily generalized seizures.

LEV has positive activity in a variety of animal models epilepsy (chronic, genetic, spontaneous, recurrent seizures) [36].

Tabl. 1. Comparative pharmacokinetics and metabolism of levetiracetam, a new antu-epileptic agent, in mouse, rat, rabbit and dog. [39].

	Mouse		**Rat**		**Rabbit**	**Dog**	
% of dose excretion via urine	81%		93%		87%	89%	
Mean peak concentration	0,5h		1.2 h		1.5 h	1.5 h	
% of acid metabolites (ucb L057 + ucb K115) after oral dose of LEV (54 mg/kg)	Female	Male	Female	Male	Female	Female	Male
	7,3%	7,4%	4,6%	8,4%	21%	16,1%	11,7%
Higher than blood concetration of LEV	-	-	**Pituitary**	**Pituitary Kidneys Bone marrow Thyroid**	**Kidneys Pituitary Thyroid**	**Kidneys Pituitary**	**Kidneys**
Lower than blood concetration of LEV	-	-	**Fat Lens Spinal cord Cerebrum Cerebellum**	**Fat Lens Spinal cord Cerebrum Cerebellum**	**Fat Lens Spinal cord Cerebrum Cerebellum Bone marrow Adrenals**	**Fat Bone marrow Adrenals Spinal cord**	**Fat Lens Spinal cord Cerebrum Cerebellum**

Clinical studies:

Antiepileptic potency of LEV has also been proven in all different subtypes of partial seizures among other things -simple partial, complex partial and secondarily generalized seizures in human [9]. LEV is well tolerated and highly effective in a wide range of seizure types.

According to Gamberdella A et al. [9], the efficacy of LEV has been tested in few groups covering: children and adults with epilepsy, healthy adults, patients with uncontrolled partial seizures and placebo controlled group. Four of these studies controlled adult patients, the last one was carried out among children aged 4 - 16 years. Doses of LEV given to adults included 1000 / 2000 / 3000 mg/day and were given twice a day. There were 559 patients investigated for 4 weeks, followed by 12-14 weeks of maintenance. In placebo group was 301 treated people. The percentage average of reduction seizures from 7% (for those receiving placebo) to 32,5% for patients receiving LEV. The result of this studies shows that the proportion of patients experiencing a 50% or greater reduction in seizure frequency compared with baseline was 27,7% (54/195), 31,6% (30/95) and 41,2% (111/269) for patients receiving 1000/ 2000/ 3000 mg/day respectively, compared with placebo group -12,6% (38/301). The percentage results of patients experiencing a 75% or greater reduction in seizures was 11,8% (23/195), 16,8 % (16/95), 22,3% (60/269) of patients receiving 1000 / 2000/ 3000 mg/day of LEV, compared with 3,3% (10/301) of placebo treated patients. In addition, 5,7% (32/559) of LEV treated patients become seizure free, compared with 0,6% (2/301) in the placebo group.

Regarding childhood epilepsy, in group of children treated with LEV over 53% (31/59) experience 50% or greater reduction in seizure frequency. In this group of 59 children, LEV less or more effective for all seizure types. Specifically, good to excellent seizure control (50- 100% reduction) was observed in 40% of patients with focal seizures, 55% with generalized seizures, and 61% with mixed seizures [24].

A large number of open studies have been carried out in other types of epilepsy. These have shown unquestionable efficiency, especially regarding generalized seizure disorders. LEV is useful in treatment of absence, myoclonus and tonic-clonic seizures in idiopatic generalized epilepsy. It is also very effective in treating myoclonus postanoxic myoclonus, the Lennox-Gastaut syndrome, atypical absence epilepsy and probably in generalized childhood epilepsy syndromes [37].

Pharmacokinetics:

The pharmacokinetics of LEV have been studied on groups of people including healthy adults, adults and children with epilepsy, the elderly and additionally subjects with renal and hepatic impairment [36]. LEV has got very simple pharmacokinetics profile: rapid absorption, excellent bioavailability, novel mechanism of action, minimal protein binding, lack of hepatic metabolism. Linear pharmacokinetics make LEV dosing straight-forward [6]. Dosing of LEV can begin with 500 mg orally twice a day, but some patients require up to 3000 mg/day [15].

LEV is well absorbed after oral administration [9,26], although an intravenous form may become available in the future [36]. Following oral administration of 250 mg to 5 000 mg, the bioavailability of LEV is as high as 95% to 100% [6,36]. Peak concentration occurs within 0,3 -2h of administration [26,29].

LEV appears to be distributed to intracellular and extracellular fluid with a volume of distribution of 0,5 up to 0,7 L/kg [9,43]. LEV is water-soluble and can freely and readily cross the blood-brain barrier [36]. LEV protein blinding, at less than 10% is not clinically relevant. In preclinical studies on rats, mice, rabbits and dogs, LEV rapidly distributes among all tissues with concentrations similar to dose in blood. Lower concentrations were affirmed in

the lens and adipose tissue and higher levels in kidneys. Brain concentration increases linearly and dose –dependently. It does not display brain region specificity, as indicated by its comparable distribution in the extracellular fluid of the hippocampus and frontal cortex [19]. Plasma concentrations of LEV were obtained in controlled trials but no study has demonstrated a relationship between plasma concentration and side effects or efficacy independent of dose LEV. One of positive properties is that LEV does not undergo hepatic metabolism, is not protein bound and lack drugs interactions.

The renal clearance of LEV is approximately 0,6 mL/ min/ kg or 40 mL/ min/ 1,73m² [43]. As reported by Engel et al. [6], within 24 hours of an oral dose of LEV, approximately 93% of the drug was excreted, about 66% as unchanged drug in the urine and 27% as inactive metabolites [6]. There is one major inactive metabolite – LO57. It accounts 24% of the dose and is formed in blood by hydrolysis of the acetamide group. It is suggested that this deamination process does not occur either the cytochrome P450 or UDP-glucoronyl transferase isozyme (UGT) system. It is especially important because LEV reveals less drug interaction than other AEDs. Two other minor metabolites account for 3% of the dose. The renal clearance of LO57 is 4,2 mL/ min/ kg [6]. LEV plasma half-live is 7+/- 1 hours in adults, but may be extended by an average of 2-2,5 hours. It concerns most likely the elderly [1,6-8,13]. Steady-state concentration LEV reached within 48 hours. Patients with renal function impairment should reduce prescribed doses [26].

Among children with epilepsy who are from 6 to 12 years old, the elimination half-life of LEV is approximately 6 hours. In distinguishing from adults total body clearance is about 30-40% higher [1,9,30]. Renal clearance of LEV is directly proportional to creatine clearance. The half-life is probably longer in neonates, even up to18 hours [29].

Interactions:

The potential interaction of LEV has been extensively investigated in many studies both of healthy volunteers and patients with epilepsy. Because LEV is not metabolized in the liver or bound to plasma proteins, LEV has a very low potential for drug interactions. However, drugs which are removed by tubular secretion potentially may interact with both - LEV and the major metabolite of LEV -LO57, because both undergo tubular retention [19].

A lot of studies have been undertaken to determine possible interactions between LEV and various commonly used drugs, including: topiramate (TPM), oxcarbazepine (OXC), carbamazepine (CBZ), felbamate (FBM), lamotrigine (LTG), tiagabine (TGB), vigabatin (VGB), valproate (VPA), diazepam, warfin, digoxin and the oral contraceptives. It has been documented that LEV can pharmacodynamically potentiate the acute neurotoxic effects of such AEDs as TPM and CBZ in rotarod test [22,23]. Similarly anticonvulsant and negative pharmacodynamic interactions LEV profile has been reported among patients receiving combinations of LEV and CBZ [23,38] and TPM. The combination of LEV and FBM is unfavorable because it causes increased LEV brain concentration [23]. Similarly, interactions between LEV and phenytoin were observed [19]. In experimental models of epilepsy in mice LEV with LTG and VPA were additivity. In this animal model neurotoxicity was affirmed. Combination of LEV and OXC shows that LEV has got synergy activity. Similarly with TPM. The possible interaction between LEV and zonisamide has not been investigated [9].

Toxicity:

After clinical studies there were preclinical studies examined the toxicity profile of LEV. It has been characterized after single and repeated intravenous (i.v) and oral administration among mice, rats and dogs. It has been proven that repeated oral administration of LEV in dosages of up to 1 800 mg/ kg/ day in rats, and 1 200 mg/ kg/ day in dogs, is well tolerated. Only in the rodents treatment related changes in the kidney and the liver were

reported, but in human it was not affirmed [19]. Animal data point to a relatively good tolerance of LEV. The LD50 values obtained after LEV oral administration in acute experiments were above LD>1 g/kg i.v. for mice.

Clinical trials shows that LEV is exceptionally well tolerated. It was proven on 1393 adult epilepsy patients, 1559 non-epilepsy patients and 672 placebo-controlled group [37].

The most commonly reported adverse effects during clinical trials in adults with LEV were mainly related to the CNS. Toxicity of LEV includes asthenia (15%), headache (14%), infection (13%), dizziness (9%) and ataxia (3%) [9,26]. These adverse effects were seen in the long-term therapy [2], and typically lessened and resolved with continued treatment. There was no evidence that recommended dose ranged from 1000 to 3000 mg/day, given guarantee-dependent relation response [10]. In none of the patients was the drug discontinued and changes in the white blood cell count had nothing in common. Flu syndrome was present on 10% of patients [37].

Similar (to the adults' trial) adverse effects, but with higher percentages, were reported in pediatric populations [9]. In many studies of LEV, up to 13% of pediatric patients experienced side effects from CNS symptoms. In most of these patients adverse neuropsychiatric symptoms such as apathy, hostility, agitation, anxiety, emotional lability and depression, were observed. Approximately 1% of pediatric or adult patients have experienced serious neuropsychiatric symptoms including hallucinations, suicidal ideations or psychosis [9]. LEV is especially well tolerated in children aged 6-12 years with onset [11]. Adverse events were observed between 24 and 44% of children who received LEV [36].

Little information is available regarding other adverse effects like idiosynchratis reaction on haematologic and hepatic systems [26]. LEV is categorized by the FDA as pregnancy category C (demonstrated teratogenicity in animals, human risk not known) [16]. In the analysis of pregnancy patients with epilepsy, 3 of 117 exposed had major congenital malformation, but it must be noted that all three were also exposed to other AEDs. There were also minor malformations in the LEV monotherapy group which included 39 monotherapy exposures. Four infants exposed to LEV monotherapy had a low birth rate [1,14]. Moreover, LEV is extracted in breast milk [6].

Final conclusions:

LEV is a novel potential AEDs with structure similar to the other drug – piracetam and unique mechanism of action (binding protein SV2A). LEV is well tolerated in both - adults and children, and effective in partial and generalized epileptic seizures. This novel, water-soluble drug is metabolized in kidneys. Not many interactions with other drugs was confirmed. It makes LEV a promising AED.

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