**Newer Anti Epileptic Drug :Levetiracetam**

Levetiracetam (LEV) is a new Antiepileptic Drug (AED) carrying special pharmacologic and metabolic properties .[1] Levetiracetam does not interact or interfere with commonly used drugs and other antiepileptic Drugs (AED).[2] It is possessing a favourable safety profile and the most frequently reported adverse events were somnolence, asthenia and dizziness along side nasopharyngitis,diarrhea constipation and even Steven Johnson Syndrome Lyell syndrome liver failure and hepatitis[3] . Overall, Levetiracetam is considered to have several advantages with least adverse effects over other antiepileptic drugs .The major advantage of Levetiracetam is, it’s easy administration and lack of drug to drug interactions i.e favourable pharmatokinetics. [4]

It is considered as novel - anti epileptic drugs with broad-spectrum for anticonvulsunt activity with unusually high safety margina and considered as promising alternative to VPA (Valporic acid )for many patients with lesser or no side effects .It was introduced in the Indian market as a new Antiepileptic Drug 2005. Basically it was synthesized in 1980 through follow up of chemical program for identifying 2nd generation nootropic agents.[5] Its chemical name is S- alpha ethyl-2-oxo-1pyrrolidineacetamide with molecular formula C8H14N2O2 with a molecular weight of 170.21. [6]

**Mechanism of Action**

Levetiracetam is said to have highly specific brain-binding site 120. Levetiracetam selectively binds to synaptic vesicle glycoprotein 2A(SV2A) in presynaptic terminals These SV2A receptors are present in neurons and other microgial cells , throughout the brain. SV2A interacts with Calcium sensor synaptotagmin through its N terminal (cytosolic) domain. These synaptic vesicles (SVs) are a specialized class of tiny (40–50 nmdiameter) secretory vesicles localized in presynaptic nerve terminals.SVs have two major functions:  
1st- the accumulation and storage of neurotransmitters. .   
2nd - the release of these neuro-transmitters[8].

When an action potential arrives at a nerve terminal, it causes an influx of calcium (Ca 2+ ) through voltage-gated Ca 2+ channels. This triggers the vesicles to release their contents within a fraction of a millisecond [9]. The neurotransmitters are secreted in multi-molecular packets, each containing several thousand neuro- transmitter molecules. At rest, nerve terminals release neuro-transmitter molecules spontaneously at a slow rate, giving rise to spontaneous miniature synaptic potentials[10] . SVs are released and reused in a simple but well-balanced cycle of exocytosis and endocytosis, it’s *yin* and *yang* elements [11]. The exocytosis process begins once the SVs are filled with neurotransmitters by active transport and are conveyed close to the active zone of the presynaptic plasma membrane, where they reside in a cluster ready to be recruited for exocytosis[12,13].

Vesicle clusters appear to be homogeneous, with little sign of any morphological boundary that might demarcate the functional pools. [14]. Biochemists have isolated many of the key proteins of SVs. These proteins fall into two major classes: .   
 **Class 1**:- transport proteins involved in neurotransmitter uptake .  
 **Class 2:-** trafficking proteins that participate in synaptic vesicle exocytosis,   
 endocytosis, and recycling.[15] .  
 The SV2A is expressed ubiquitously throughout the brain at different levels, with the exception of the facial and trigeminal nuclei[16]

As expected for a synaptic vesicle protein, SV2A is essentially absent in the neuronal soma[16]. Both in humans and in rats, SV2A immunoreactivity (IR) is present in synaptic layers throughout all subfields of the hippocampal formation. The strongest IR is observed in the stratum lucidum of CA3 (mossy fibers) and in the hilar region of the dentate gyrus (DG). Because SV2A is a protein localized in the terminal’s pre-synaptic axons of neurons, it’s expression is observed surrounding the dendrites or somata of the postsynaptic pyramidal neurons (CA1 and CA3), granular cells, and hilar cells[17,18].

SV2A is expressed in both glutamatergic and GABAergic terminals ; immune-cytochemical studies in the rat cortex, hippocampus, and cerebellum showed that SV2A co-localizes with vesicular glutamate transporters ( VGLUT ) 1 and( VGLUT ) 2 and with the vesicular γ -aminobutyric acid (GABA) transporter (VGAT).[16,18,19]]. Intriguingly, SV2A is mostly co-expressed with VGLUT1 and VGAT2 (82 % and 96 %, respectively) and less so VGLUT2 (42 %); however, the distribution is almost equal among all terminals [19].

The localization of SV2A in all SVs, together with its conservation across species, suggests that the protein is highly important in vesicle functioning [20]. Although it is well known that SV2A is not indispensable for neurotransmitter release, it’s function is clearly essential to normal neurotransmitter release for at least the more complex vertebrate nervous systems [21,22]. It’s function remains undefined, but most evidences suggests that SV2A potentially has multiple regulatory actions at diverse points in the synaptic vesicle cycle [21,22,23]

Levetiracetam has also role in modulation of presynaptic P/Q type voltage dependant calcium channels to reduce glutamate release and inhibition in dendate gyrus which may be contributing factor anti epileptic action of levetiracetam.[24]

It is well evident that Levetiracetam selectively inhibits N-type Ca2+ channels of CA1 pyramidal hippocampal neurons,suggesting the existence of a subtype of N-type channels sensitive to Levetiracetam. This may be involved in the molecular basis of antiepileptic action of Levetiracetam .[25] Further it has been shown that LEV may partly, mediate some of its antiepileptic effects via preventing this Zn modulation of presynaptic GABA**A** receptors as a antiepilectic agent.[26]

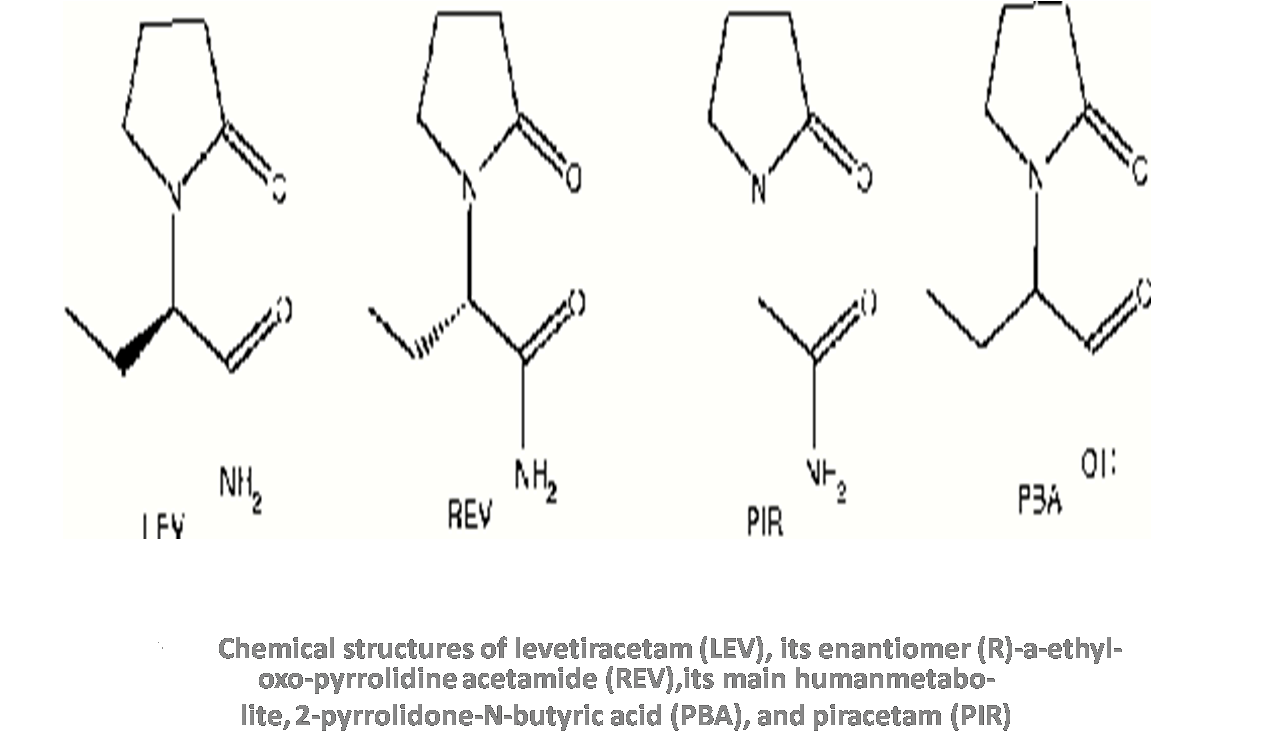
Levetiracetam has shown the effect of hyperalgesia which is at least in part mediated through GABA, opioid, 5-HT and a2-adrenergic receptors. Beside this levetiracetam has a non specific action on opioid, 5-HT receptor , which may be cause for side effects such as nausea, vomiting, dizziness.[26]

**Pharmacokinetics of Levetiracetam: Absorption and Distribution .** Levetiracetam is rapidly and completely (*>*95%) absorbed following oral ingestion with Tmax occurring at 1.3–5.2 hours. [28] The mean half-life (t1*/*2) of levetiracetam in serum is 6–13.3 hours [126,132]. Levetiracetam easily enters the cerebrospinal fluid (CSF) compartment with a Tmax of 3–7.3 hours.[28,29]

The mean t1*/*2 of Levetiracetam in CSF is 24 hours. This shows that the efflux or presense of Levetiracetam from the CNS compartment is twice as long as that from the blood [29]. Levetiracetam as carrying a prolonged duration of action, supporting a twice-daily dosing strategy [28].That is why Levetiracetam can be started with full dose (500 mg daily), without having need of any drug titration as like it is practiced for other anti epileptic drugs. Its major route of elimination is renal and its twice daily dosing is established in through early pharmacodynamic and phase - controlled studies conducted by reserchers.[7]

N-pyrrolidine butyric acid {PBA} is the major metabolite of Levetiracetam .The fraction of Levetiracetam metabolized to PBA is 2-4 %in case of mice and 2-5 % in the case of dog, but in the case of human it is 26 % .[5,7] PBA as a major metabolite of Levetiracetam structurally resembles Valporic acid analogue (VPA) except for the presence of a pyrrolidine ring instead of aliphatic chain at the second carbon atom .[1]

Unlike other epileptic drugs , Levetiracetam is extremely water soluble so this allows, it’s rapid and complete absorption after oral administration. . Levetiracetam is not metabolized by liver (not involving the hepatic cytochrome P450 [CYP] system)[28]  and hence Levetiracetam metabolism is free of non linear elimination kinetics and free of major drug-drug interactions and further Lack of protein binding also avoids problems of displacing highly protein –bound drugs [7]

 reference –issorehanet al [31]

**Figure no -2: showing chemical representation of levetricetam**   
 and its pharmatokinetic action has no significant differences in between sexes or races. Although some special population group require extra care[32] as such dosage of Levetiracetam should be adjusted for compromised renal function. In children, renal clearance is higher and dosage should be increased to approximately 130% of the adult dose on a per kg of body weight basis [28,34,35].

Elderly people as shows reduction in renal clearance and hence dosage should be lowered accordingly. Likewise, in patients showing renal impairment or suffering from hepatorenal syndrome, dosage reduction should be considered and followed [33]. Pregnant women undergo a variety of physiological changes including increased hepatic metabolism, decreased plasma protein binding, and fluctuating hormone levels. Renal functioning increases during pregnancy, meaning that plasma concentrations of drugs that are excreted by kidneys, like Levetiracetam, could decrease, and dose adjustment may be required.[33,35]

**Dosage and Administration of Levetiracetam**

It is available in markets as film-coated tablets containing 250, 500, 750, and 1000 mg  [36]. Levetiracetam can be administered without regard to meal times. The time at which peak concentrations occur in serum is delayed slightly but the maximum concentration (Cmax) is unaffected by food intake[28,36].   
 For epilepsy patients recommended dose of Levetiracetam (1000 mg/day) can be titrated uo to 2000 mg/day or 3000 mg/day to provide seizure free state with l no increased risk for adverse events or effects. Levetiracetam treatment is usually started at 500 mg twice daily and increased in two-weekly steps of 1000 mg/day to 3000 mg/day[36].   
 Reports indicate that the target range for daily dosage of 1000–3000 mg is 35–120 *μ*mol/L to achieve serum concentration in patients[28] to achieve epilepsy free state.

Levetiracetam is well tolerated up to a dosage of 4000 mg/day. At such high dosages Levetiracetam is reported for h increased incidence of somnolence and asthenia. Hence dose escalation above 3000 mg/day should be done only after careful analyses of the risk–benefit ratio, acknowledging it’s higher risk for adverse effects reported in several studies[37].   
 A liquid formulation ( 100 mg/mL) for oral ingestion has been developed for those patients with difficulties in swallowing. In 2006, an intravenous (i.v.) Levetiracetam formulation was approved for use as adjunctive therapy in the treatment of epilepsy by both the Food and Drug Administration (FDA) and the European Agency for Evaluation of Medicinal products (EMEA).

Levetiracetam administered by i.v. infusion is indicated in emergency situations and it appears to be well tolerated in healthy subjects, with safe pharmacokinetic profile 129,130. The intravenous formulation is provided in 5-mL glass vials containing 500 mg Levetiracetam (Levetiracetam 100 mg/mL), which should be infused over 15 minutes.  
  
A**dverse effects of Levetiracetam . .**   
  
 It is seen that Levetiracetam is reported for resulting in rhabdomyolysis,158 myoclonic encephalopathy in renal failure patients[38] , Levetiracetam induced rage and suicidability ,[39] and acute psychosis [40],severe acute glomerulonephritis[41]  
  
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