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COMPREHENSIVE REVIEW AND STUDY ON ANTI EPILEPTIC DRUG LEVETIRACETAM

AUTHOR: R. NARESH BABU (Associate professor) , MOLLETI ABHISHEK Department of pharmaceutics, Nirmala college of pharmacy, Atmakur, Mangalagiri, Guntur(district) Andhra Pradesh.

ABSTRACT

Levetiracetam is an antiepileptic drug approved for use as an adjunctive agent in partial-onset seizures in adults. This approval was recently extended to children over 4 years of age. Among the currently approved antiepileptic drugs, levetiracetam is unique in its mechanism of action. Its CNS binding site, the synaptic vesicle protein SV2A, was discovered recently. Levetiracetam is a new anticonvulsant agent with a favourable tolerability profile and a low potential for drug interactions. It has shown efficacy as adjunctive therapy in patients with treatment-refractory partial onset seizures with or without secondary generalisation in clinical trials. In most studies of levetiracetam when given with other seizure medicines, 20 to 40% of people had at least a 50% decrease in their seizures. (This means that the number of seizures each month was at least cut in half.) Most people did not have many problems with side effects in these studies. Direct comparative trials with other anticonvulsant agents are not yet available, but placebo-controlled clinical evidence to date suggests that levetiracetam (1000, 2000 and 3000 mg/day) is a useful option as adjunctive therapy in patients with this subtype of epilepsy.

KEY WORDS: Anticonvulsant , Synaptic vesicle protein, Adjunctive therapy

COMPREHENSIVE REVIEW AND STUDY ON ANTIEPILEPTIC DRUG LEVETIRACETAM

SUBMITTED BY:

M.P.S. Abhishek

I. Soumya

G. Ravi Teja

D. Pravallika

M. Showreelu

FOUNDER:

R. NARESH BABU (Associate Professor)

CO- FOUNDER:

M. P. S. ABHISHEK.

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INTRODUCTION:

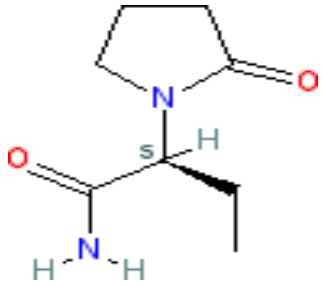
LEVETIRACETAM:

Levetiracetam is an antiepileptic drug approved for use as an adjunctive agent in partial-onset seizures in adults. This approval was recently extended to children over 4 years of age. Among the currently approved antiepileptic drugs, levetiracetam is unique in its mechanism of action. Its CNS binding site, the synaptic vesicle protein SV2A, was discovered recently. Binding at this site may be important for the antiseizure activity of levetiracetam and the role of this binding site and its modulation by levetiracetam is an area of active research in epilepsy. Levetiracetam is generally safe, has near to ideal pharmacokinetics and does not interact with other medications. The most serious adverse events are behavioral in nature. Recent studies suggest that levetiracetam may be effective in generalized epilepsies, status epilepticus, pain and selected movement disorders. Intriguing studies using the kindling model of epilepsy suggest that levetiracetam may protect against the development of kindling and chronic epilepsy. A parenteral formulation of levetiracetam may soon become available and may lead to larger studies of levetiracetam in status epilepticus. [1]

HISTORY:

Levetiracetam (LEV) is one of the newest AEDs, marketed worldwide only since 2000. It was initially approved in the US only as adjunctive therapy for partial-onset seizures. However, more recent trials earned it approval as adjunctive therapy for primary generalized tonic-clonic seizures and myoclonic seizures of juvenile myoclonic epilepsy, and a recent comparative monotherapy trial earned it approval for use as initial monotherapy in the European Union, though not in the US. In addition, the recent approval and marketing of an intravenous preparation has added to the versatility of this AED.[2]

STRUCTURE:



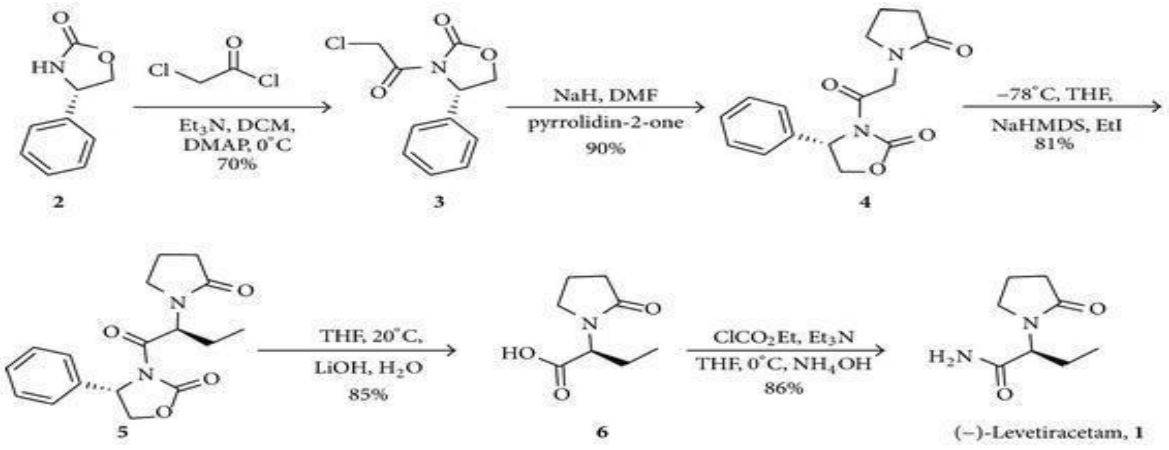
ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

PROPERTIES:[3]

Molecular weight	170.21 g/mol
Color/From	White to off-white crystalline powder
Odor	Faint
Taste	Bitter
Melting point	115-119C
Solubility	104g/100ml
Vapor pressure	3.5.10-6 mm Hg at 25 c
Optical Rotation	Specific optical rotation: -90 deg at 25 °C/D (c = 1 in acetone)
Log P	-0.6

SYNTHESIS OF LEVETIRACETAM

The literature methods for the synthesis of levetiracetam typically involve chiral pool approaches starting from enantiopure α-amino acids, resolution of etiracetam or advanced racemic intermediates, asymmetric hydrogenation over Rh(I) or Ru (II) complexes, and deracemization of 2-bromobutyric acid using N-phenyl Panto lactam as a chiral auxiliary. As a part of our research program, aimed at developing stereo controlled syntheses of bioactive molecules [12–17], K. Chandra Babu [1], R. Buchi Reddy [3], E. Naresh [1], K. Ram Mohan
[1] G. Madhusudhan [1] and K. Mukkanti [2] reported a new and enantioselective synthesis of levetiracetam (1) using versatile N-sulfonimine as starting material and (S)-t-BSA as a chiral auxiliary. It demonstrates the versatility and important extended application of N-sulfonimine in the preparation of variety of biological active and pharmaceutical important molecules.[4]



SNO	PATENT NUMBER	TITLE OF PATENT RELATED TO SYNTHESIS
1.	US007132552B2	Process for producing levetiracetam
2.	WO2004069796A2	Process for producing levetiracetam
3.	US 20070172521A1	Levetiracetam formulations and methods for their manufacture
4.	CN102038657A	Levetiracetam tablet and preparation method thereof
5.	WO2006090265A2	Processes for the preparation of levetiracetam, its intermediate and the use of levetiracetam in pharmaceutical compositions

Step 1

- (-)-(S)-alpha-ethyl-2-oxo-1-pyrrolidine acetic acid (150 g. 0.87 mol) was dissolved in methanol (235 g, 300 ml) at 45° C. and thionyl chloride (56 g. 0.47 mol) was added dropwise over 30 min.
- The reaction mixture was stirred at 45° C. for additional 15-30 min until complete conversion of (-)-(S)-alpha ethyl-2-oxo-1-pyrrolidine acetic acid was observed via HPLC (unreacted (-)-(S)-alpha-ethyl-2-oxo-1-pyrrolidine acetic acid s2%, by HPLC 96 area).
- At reaction completed, the volatiles were distilled off at moderate temperature and reduced pressure (35°–40° C., 150-200 mbar) until 10% of the whole volume was eliminated, then the mixture was reintegrated with fresh methanol up to initial Volume.
- After that, the reaction mixture was neutralized by bubbling ammonia gas at 20° C. up to a pH value equal to about 5, and stirred at 20°C. for 1 h. A limited amount of salts (about 44 g) precipitated and was filtered off. The resulting methanol solution was directly transferred to the autoclave.

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

Step 2

- The reaction mixture was pressurized up to about 3 bar with ammonia gas at 20°C., and stirred until complete conversion to (-)-(S)-alpha-ethyl-2-oxo-1-pyrrolidineaceta mide was observed via HPLC.
- . Then, once the reaction mixture was taken out of the autoclave, the residual salts formed (about 20 grams) were filtered off and the methanol solution was distilled up to a minimum Volume at moderate temperature and reduced pressure (35°-40°C., 150-200 mbar).
- Acetone (115 ml) was added and the mixture was distilled again at moderate temperature and reduced pressure (35°–40°C., 150-200 mbar) to minimum volume. After that acetone (300 ml) was charged over the residue and the mixture was heated and refluxed for 30 minutes. Finally, the solution was cooled down slowly to 0°C. and crude levetiracetam was isolated by filtration.
- Crude levetiracetam (molar yield 73.1%, (R)-enantiomer: 1.171%) was then submitted to a final purification process in one step to give pure levetiracetam.
- Acetone (750 ml) was charged over crude levetiracetam and the mixture was again stirred and heated to reflux. Once refluxed for about 30 minutes the hot mixture was filtered to remove residual salts and cooled slowly to 0°C.
- Pure levetiracetam ((R)-enantiomer: 0.01%) was obtained by filtration and drying under vacuum at 40° C. Overall molar yield was 60.0% by mole of the starting amount of (-)-(S)- alpha-ethyl-2-oxo-1-pyrrolidine acetic acid (ponderal yield 78.4% by weight).

Example 1

- Step -1was repeated, but the neutralization step with ammonia at the end of step 1 was omitted. At the end of step 2,
- crude levetiracetam was isolated (molar yield 73.1%, US 2011/0065932 A1 (R)- enantiomer: 2.21%). After the purification step, pure levetiracetam (molar yield 64.4%, (R)- enantiomer: 0.58%) was obtained.
- It was repeated using an excess of thionyl chloride (114 g. 0.96 mol) with respect to (-)- (S)- alpha-ethyl-2-oxo-1-pyrrolidine acetic acid. Further, when the complete conversion of (-)- (S)-alpha-ethyl-2-oxo-1-pyrrolidine acetic acid was observed, the reaction mixture was distilled off at moderate temperature and reduced pressure (35°–40°C., 150-200 mbar) until dryness. Decomposition of about 13% by weight of the intermediate product to starting product (-)-(S)-alpha-ethyl-2-oxo-1-pyrrolidine acetic acid was observed.[5]

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

MECHANISM OF ACTION:

The exact mechanism through which levetiracetam exerts its anti- epileptic effects is unclear, but is thought to be unique amongst other anti-epileptic medications. Current knowledge suggests that levetiracetam binding to synaptic vesicle protein 2A (SV2A) is a key driver of its action. SV2A is a membrane-bound protein that is found on synaptic vesicles and is ubiquitous throughout the CNS[7] . It appears to play a role in vesicle exocytosis[10,12] and in the modulation of synaptic transmission by increasing the available amount of secretory vesicles available for neurotransmission.[9]Stimulation of presynaptic SV2A by levetiracetam may inhibit neurotransmitter release,[8]but this action does not appear to affect normal neurotransmission. This has led to the suggestion that levetiracetam exclusively modulates the function of SV2A only under pathophysiological conditions.[7] Levetiracetam and related analogues showed a correlation between affinity for SV2A and anti-epileptic potency, further suggesting that action at this site contributes to the anti-epileptic activity of the drug.[10,12] Levetiracetam has also been shown to indirectly affect GABAergic neurotransmission (despite having no direct effect on GABAergic or glutamatergic receptors) and modulate ionic currents.[9] Similarly, levetiracetam has been shown in vitro to inhibit N-type calcium channels.[8] How, or even if, these actions are implicated in its anti-epileptic action have yet to be elucidated

PHARMACOKINETICS:

Absorption: Levetiracetam is rapidly and nearly completely absorbed following oral administration, with a reported absolute oral bioavailability of essentially 100%.[10,11,12] T_{max} is approximately 1.3 hours after dosing, and C_{max} is 31 μg/mL following a single 1000mg dose and 43 μg/mL following repeated dosing.[10,12] Co-administration of levetiracetam with food delays T_{max} by approximately 1.5 hours and decreases C_{max} by 20%.[10,11]

Volume of distribution:

The volume of distribution of levetiracetam is approximately 0.5 to 0.7 L/kg.[11,12]

Protein binding:

Levetiracetam and its metabolites are largely unbound to plasma proteins (<10%).[12,10,11]

Metabolism: Levetiracetam is minimally metabolized within the body - the major metabolic pathway appears to be the enzymatic hydrolysis of its acetamide group which produces an inactive carboxylic acid metabolite, L057, which accounts for approximately 24% of the total administered dose.[10,11]The specific enzyme(s) responsible for this reaction are unclear, but this pathway is known to be independent of hepatic CYP enzymes and has been proposed to be driven primarily by type B esterases in the blood and other tissues.[6] Two minor metabolites involving modifications to the pyrrolidone ring have been identified, one involving hydroxylation of the ring (constituting 1.6% of the total dose) and the other involving opening of the ring structure (constituting 0.9% of the total dose).[12,10,11]

Route of elimination: Approximately 66% of the administered dose of levetiracetam is excreted in the urine as unchanged drug,[10,11] while only 0.3% of the total dose is excreted via the feces.[12] The primary inactive metabolite of levetiracetam, L057, is also found in the urine as approximately 24% of the administered dose.[12]

Half-life: The plasma half-life of levetiracetam is 6-8 hours and is not affected by dose or repeat administration. Half-life is increased in the elderly (by about 40%)[12]and thosewith renal impairment.[10,11]

PATENTS:

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2	US20090263.481A1	leviteracetam formulations	Thursday, October 22, 2009	*https://patents.google.com/patent/US20090263481A1/en*
3	US20100055.177A1	Modified release composition of levetiracetamand process for the preparation thereof	Thursday, March 04, 2010	*https://patents.google.com/patent/US201*

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5	CA2581831A1	Pharmaceutical compositions comprising levetiracetam and process for their preparation	Thursday, February 01, 2007	*https:// patents. google. co m/paten t/CA258 1831A1 /de*
6	EP2442804B1	Derivatives, reagents, and immunoassay fordetecting levetiracetam	Wednesday, April 25, 2012	*https:// patents. google. co m/paten t/EP244 2804B1 /en*
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9	US7858122B2	Extended release formulation of levetiracetam	Tuesday, December 28, 2010	*https:// patents. google. co m/paten t/US785 8122B2 /en*
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17	WO2 0 0 4 0 8 3180	Novel crystalline forms of levetiracetam	Thursday, September 30, 2004	*https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2004083180*

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S. NO	**NAME OF THE JOURNAL**	**TITLE OF WORK**	**VOLUME AND EDITION**	**DATE OF PUB**	**URL**

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1	Seizure	The safety and efficacy of add-on levetiracetam inelderly patients with focal epilepsy: A one-year observational study	*Volume 20, Issue 4*, May 2011, Pages 305-311	May 2011	*https://www.sciencedirect.com/science/article/e*

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ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

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SUMMARY:

Levetiracetam is used in combination with other medications to treat certain types of seizures in adults and children with epilepsy. Levetiracetam is in a class of medications called anti convulsants. It works by decreasing abnormal excitement in the brain. The drug is mostly used in Keppra {tablet dosage form}. The drug is available in oral dosage form (highest dose-1000mg/l), Intravenous(1000mg/l). Levetiracetam comes as a solution (liquid), an immediate-release tablet, an extended-release (long-acting) tablet, and as a tablet for suspension (a tablet to take with liquid) to take by mouth. The solution, immediate-release tablet, and tablet for suspension are usually taken twice a day, once in the morning and once at night, with or without food. The extended-release tablets are usually taken once

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daily with or without food. Try to take levetiracetam at around the same time(s) every day. Follow the directions on your prescription label carefully, and ask your doctor or pharmacist to explain any part you do not understand. Take levetiracetam exactly as directed. Do not take more or less of it or take it more often than prescribed by your doctor. Levetiracetam drug has 56 patents and 17 publications.

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CONCLUSION:

Levetiracetam is a new anticonvulsant agent with a favourable tolerability profile and a low potential for drug interactions. It has shown efficacy as adjunctive therapy in patients with treatment-refractory partial onset seizures with or without secondary generalisation in clinical trials.

In most studies of levetiracetam when given with other seizure medicines, 20 to 40% of people had at least a 50% decrease in their seizures. (This means that the number of seizures each month was at least cut in half.) Most people did not have many problems with **side effects** in these studies. Direct comparative trials with other anticonvulsant agents are not yet available, but placebo-controlled clinical evidence to date suggests that levetiracetam (1000, 2000 and 3000 mg/day) is a useful option as adjunctive therapy in patients with this subtype of epilepsy.

Therefore, we conclude that Levetiracetam has a novel mechanism of action and unique pharmacokinetic profile to be used as a desirable antiepileptic choice in an acute inpatient setting. Our conclusions, on the other hand, are based on existing data which include case reports, case series, retrospective studies, and some prospective trials. However, there are limitations in that there are neurobehavioral side-effects of the drug. We believe that there is a need for larger, prospective, multicenter, randomized double comparative blind trials in order to further clarify the role of this anticonvulsant in acute seizure management.

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