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REVIEW ARTICLE **OPEN ACCESS**

Levetiracetam-Induced Multiple Adverse Drug Reactions- A Review of Case Series

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ABSTRACT
Adverse drug reactions (ADRs) are a significant source of morbidity and mortality and constitute a significant public health issue. ADR can be termed as hazardous, unexpected, and unwelcome side effects that can arise from drug use.These reactions happen as a result of self-medication or using prescription medications in excess. So,one should only take medications that have been properly prescribed if one wants to avoid having an unfavourable drug reaction. Epilepsy is a chronic disease that affects millions of people worldwide. Levetiracetam (LEV), an AED with a unique mechanism of action through an interaction with the synaptic vesicle protein 2A,has beendemonstrated to be effective in controlling seizures and is well-tolerated (SV2A). Among other antiepileptic drugs , Levetiracetam is known for very fewer adverse events.In this article we discussed about levetiracetam induced multiple adverse drug reactions and its mechanism through various case studies.
KEYWORDS: *Self-Medication, Adverse drug reactions, Prescribed Drugs, Bizarre Effects, Chronic effects, Levetiracetam, Antiepileptic Drugs.*

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INTRODUCTION

Epilepsy affects around 50 million people globally [1]. It is a long-term neurological condition characterized by repeated, spontaneous seizures brought on by excessive neuronal activity and impropersynaptic synchronization [2], which harms neurons, causes inflammation, and releases reactive oxygenspecies (ROS). Epileptic seizures are divided into three categories by the International League Against Epilepsy (ILAE): focal-onset, generalized-onset, and unknown-onset seizures (formerly known as partialand generalized seizures) [3]. As a result, the selection of an appropriate pharmacological therapy differs depending onthe various types of seizures.

Antiepileptic drugs (AEDs; also known as antiseizure drugs) effectively control seizures, but only in about 2/3 of people with epilepsy [4]. Furthermore, it has become clear in recent years that the currentmethod of treating epilepsy with AEDs that only controls seizures are insufficient because it does notaddress the comorbidities that epileptic patients present with [5, 6]. These facts have spurred research intonewer medications with fresh mechanisms of action that might be more potent and have a more tolerableside effect profile. Levetiracetam (LEV) stands apart from the other AEDs due to its distinct and primary mode of action through the interaction with the synaptic vesicle protein 2A.(SV2A) [7-9]. LEV is a second-generation anticonvulsant medication that has been shown to have superior tolerability and greater efficacy when compared to other AEDs; as a result, it has progressively risen to the top of the medicine list [10]. Although LEV is primarily used as an AED, it has also been studied for usage in other clinical settings as an anti-hyperalgesic, anti-oxidant, an anti-inflammatory, and asatreatmentforneuropathic pain, all of which have the potential to be very effective [11-14]· Several studies haveidentified numerous additional molecular targets in addition to the SV2A protein via which LEV may operate directly or indirectly [15-17]. Important research has also demonstrated that LEV has antioxidant, anti-inflammatory, and anti-epileptogenic properties [6, 8, 19, 20, 21]. Current research has identified LEV asa multitarget medication with intriguing features that can address some of the present needs in epilepsyandother disorders [22].

Levetiracetam [(S)-a-ethyl-2-oxo-1-pyrrolidineacetamide] is abroad-spectrum AED that was approved by the USFDA in 1999 for adjunctive therapy in partial-onset seizures in adults and subsequently for children aged 4 years and older, for myoclonic seizures in adults and adolescents older than 12 years with juvenile myoclonic epilepsy and for primarily generalized tonic-clonic seizures in adults and children aged 6 years and above with IGE. The use of LEV for supplementary therapy of partial-onset seizures in new borns and children beginning at the age of one month in Europe was only recently approved (September 2009). It is also permitted as a monotherapy for patients 16 years of age and older experiencing partial-onset seizures [23, 24].

PHARMACODYNAMIC:

ADR: Direct toxicity studies and hypersensitivity reactions that result from pharmacokinetic and pharmacodynamic changes to the drug products can be used to categorize adverse reactions by their mode of action [25]. Direct toxicity reactions can be attributed to a substance's or its metabolite's toxic effects, which can cause noxious chemical reactions, physiological dysfunction, Genetic damage, or damage tocellular structures and tissues. These toxic effects can be seen in numerous organ systems [26, 27]. On theother hand, hypersensitivity reactions, which include allergic and anaphylactic events, can be identified when a person's immune system displays an excessive response to a drug or its metabolites [28]. The skin, liver, lungs, bone marrow, and kidneys are only a few of the organs that have been mentioned as having directcy to toxic effect and an overactive immune response [29, 30].

LEVETIRACETAM: Levetiracetam has antiepileptic properties, however, the exact processes through which it works are unclear. The most significant mode of action, however, is thought to involve binding tothe particular synaptic vesicle protein 2A. (SV2A). The release of vesicular neurotransmitters that are calcium-dependent is mediated by the SV2A protein, which is a component of secretory vesicle membranes. The rate of vesicle release seems to be slowed down by levetiracetam's binding to SV2A [31].

PHARMACOKINETICS:

ABSORPTION: Levetiracetam has a very high (96%) bioavailability and is quickly absorbed. After oral dosing, the peak plasma concentration is reached in about a hour. Eating does not change the amount of absorption, although it can delay the duration to optimum concentration by roughly 30minutes. When patients are unable to take oral drugs, the intravenous formulation is employed. During intravenous usage, peak plasma concentration is attained in 5 to 15 minutes. The pharmacokinetic profile otherwise is identical to an oral formulation.

DISTRIBUTION: Levetiracetam does not compete with other medications for protein binding sites because less than 10% of its molecule is attached to proteins. The kidneys eliminate about 66% of it unaltered since it is not extensively digested.

METABOLISM: The acetamide group is hydrolyzed by enzymes, which is the primary metabolic pathway. Metabolites are eliminated by the kidneys and have no pharmacological effect. The role of thehepatic cytochrome P450 system is minimal (2.5%). [32]

EXCRETION: A significant excretion mechanism that is related to creatinine clearance is glomerular filtration with partial tubular reabsorption. In adults, the plasma half-life is roughly 6 to 8 hours, but in the elderly due to the decline in creatinine clearance with age, the plasma half-life can be increased by 2 to 3 hours. Those with renal impairment must have their doses adjusted. Due to levetiracetam's lack of hepatic metabolism and strong protein binding, pharmacokinetic interactions are reduced. The blood concentration of levetiracetam is proportionate to the doseover a 500–5000 mg dosing range because of its linear pharmacokinetics. Two days of twice-daily dosing result in as table state. Although the boundaries between toxic and therapeutic amounts are unclear, monitoring blood levels can be used to gauge compliance [33].

INDICATIONS:

Myoclonic seizures: It is approved for adjunctive therapy in treating myoclonic seizures in adults and juvenile myoclonic epilepsy in adolescents12 years and older [34]. Partial seizures can be used as adjunctive therapy for treating partial seizures in adults and children one month or older with epilepsy [35].

Primary generalized tonic-clonic seizure: Levetiracetam is used for adjunctive therapy to treat aprimary generalized tonic conic seizure in adults and children over five years old with idiopathic generalized epilepsy [36]. It is sometimes used off-label (non-FDA-approved) for status epilepticus and seizure prophylaxis in subarachnoid hemorrhage [37]. Levetiracetam is also used off-label for the prophylaxis of traumatic brain injury (TBI) and supratentorial neurosurgery [38]. Levetiracetam is also used off-label used for seizures in palliative care [39].

ADMINISTRATION:

Oral and intravenous (IV) versions of levetiracetam are also readily available. The total daily dose of IV levetiracetam is the same as the oral dose. Infusions lasting 15 minutes are used to administer it. A loading dose has not been proven to be effective. Oral forms can also be found in immediate-release and delayed-release varieties. The immediate-release formulation's bioavailability and metabolism are comparable to those of the extended-release version. The extended-release version has a 3-hour longer time to reach peak plasma concentration, though.

Adult Dosing

The minimum recommended dose is 500 mg twice daily. The maximum ecommended dose is 3000mg per day. The dose commonly used is 1000 to 3000 mg IV infusion at a rate of 2 mg/kg per minute or a single dose of 60mg/kg [40].

Pediatric Considerations

Children older than five years old can use levetiracetam safely (with caution). The suggested starting dose is 20mg/kg divided in to 2 doses each day. A maximum dose of 60mg/kg per day can be administered after titrating it upto 20mg/kg every two weeks.

Renal Impairment

As levetiracetam is eliminated through the kidneys, renal impairment slows the rate of elimination, requiring dose reduction. As a result, dosage adjustment is necessary in accordance with the manufacturer's labeling.

For a creatinine clearance 30-50(mL/min/1.73m^2)-250to750mg every 12 hours is recommended.

For creatinine clearance<30(mL/min/1.73m^2)-250 to 500mg every12hours is recommended.

ESRD patients on dialysis 500 to1,000mg every24 hours. After dialysis, a 250 to500mg additional dose is recommended [41].

Pregnancy: Upto a 50% dosage increase during the third trimester; subsequent dose reduction after delivery may be necessary [42].

LEVETIRACETAM-INDUCED ADVERSE DRUG REACTIONS:

Lev-InducedRage-

The first patient was a male patient, age 29, who suffered left hemiparesis and intractable seizures after falling from a two-story structure at the age of two months. He had a 28.4 kg/m2 body mass index (weight: 86 kg, height: 1.74 m). At first, he took phenobarbital (600 mg BD) and sodium valproate (60mg tds). Levetiracetam was administered in place of his phenobarbitone, with a starting dose of 250mg twice daily for one week before increasing to 500mg twice daily for the following four weeks. After using levetiracetam for a week, he started acting aggressively, losing control, and attacking his siblings. When levetiracetam was stopped, the see thing rage subsided only to return when it was restarted; for this reason, levetiracetam was completely stopped. The Naranjo score, which indicates the likelihood of an adverse drug reaction, was 8 (i.e., +1 for the presence of prior conclusive reports on this adverse reaction, +2 for the appearance of the adverse event following initiation of the suspected drug, +1 for improvement of the adverse event following discontinuation of the suspected drug, +2 for the re-emergence of the reaction following re-administration of the drug, and+2 for the absence of a different explanation for the adverse event) [45].

Lev-InducedRage-

After two weeks of initiating adjunctive levetiracetam at a starting dose of 250 mg twice a day for thefirst week and then 500 mg twice daily after that, the second patient, a 23-year-old woman, displayed furious rage and repeatedly attempted self-immolation with a knife. For her treatment-resistant epilepsy,she was taking clonazepamin addition to carbamazepine.Her BMI was 20.31kg/m2 (weight: 52 kg, height: 1.60 m). The fury and suicidal thoughts subsided and then returned as a result of the relatives' withdrawal and subsequent reintroduction of levetiracetam. The Naranjo score was 8, justlikewith thepreviouspatient. Theangerthat levetiracetam had sparked subsided when itwasstopped.[45]

Lev-InducedUrticaria-

The patient in this instance was a 22-year-old woman who was a study participant for an academic thesis at the Dr.R.P.G.M.C.,Kangra in Tanda, Himachal Pradesh.The patient was referred by a secondary healthcare facility in the Kangra district to Dr. R.P.G.M.C., Kangra at Tanda. The patientcomplained of three episodes of abnormal body movements that began on the right side of the bodyand spread to the entire body, along with clenching of the teeth and loss of consciousness. The patient has a history of biting their tongue during seizures. After about 15 to 20 minutes, the patient had post-ictal disorientation. The seizure did not have an aura and began suddenly without any particular daily routine. Clinical testing revealed that the patient had a case of focal seizures with secondary generalization. The patient had no known history of food or drug allergies. As a participant in anacademic thesis, the patient was randomly

assigned to the levetiracetam study group after providing written informed consent. Levetiracetam 500 mg tablet, taken orally twice a day (12th hour), was prescribed for the patient. After taking the third dose of levetiracetam, the patient complained the following morning via telephone of a rash, itching, and swelling of the body. The patient was instructed to stop using the levetiracetam medication and go to the hospital for additional care.Blood biochemistry measurements showed a 4-to5-fold increase in serum alkaline phosphatase. The results of the general physical examination were normal. For the treatment of focal seizures, levetiracetam was terminated, and the patient was given a prescription for 200 mg of lacosamide twice a day (12^{th} hour). The patient was encouraged to continue treatment and have routine follow-ups despite not reporting any drug-related side effects from lacosamide medication [43].

Lev-Induced Gingival Hyperplasia-

A generalized seizure in a 14-year-old kid was referred for evaluation. He did not have any coexisting conditions and had a typical prenatal period and development. A neurological evaluation came outclean. A modest wide spreadel ectrophysiological impairment was visible on the electroencephalogram.The results of the brain's magnetic resonance imaging and blood tests were both normal.His levetiracetam dosage was increased to 250 mg twice daily. He started taking the medication five dayslater and started showing signs of gum swelling and several excruciating mouth ulcers. No previoushistory of fever, sore throat, rash, or use of any other drugs was present. Upon examination, it was discovered that the upper and lower gums had gum hypertrophy and that the inner gums had oralaphthae. He had adequate oral hygiene and no cervical lymphadenopathy, pharyngeal congestion, orpalate erythema. Leucocyte and eosinophil levels from blood tests were ordinary. After speaking withhis parents, it was decided not to replace Levetiracetam with any other antiepileptics because of thesimilar adverse event profile of this class of medications. Levetiracetam was stopped. When checked again after one month, the oral aphthae and gum hypertrophy had disappeared, and he was reportedly seizure-free [44]

Lev-Induced Pancytopenia

A male newborn aged four months experienced four episodes of convulsions for which the new born was hospitalized and given levetiracetam as first-line monotherapy at a dose hospitalized of 20mg/kg/day.Following the onset of levetiracetam, seizures were under control. Haemoglobin (Hb), 12.5g/dL, total leukocyte count (TLC), 9600/L, differential leukocyte count (DLC)- polymorph (P) 55, lymphocyte (L) 37, monocyte (M) 5, eosinophil (E) 3; absolute neutrophil count (ANC), 5280/L, and platelet count (PC), 1.6 lacs/L were the results of his blood tests. However, after only five days oftreatment, he started to experience lower limb swelling, which was followed by stomach distension aweek later. He was referred to our facility eight days into his treatment and arrived in shock, with hyponatremia, and severe prerenal failure with edema. The kid was sleepy when he was admitted. His blood pressure was 62/38 mm Hg, his respiration rate was 60/min, and his pulse was 190 beats perminute. His capillary refill time increased to 4 seconds. Grunting, subcostal indrawing, and bilateralcrepitations were all visible in the respiratory system. His liver measured 10 cm in the mid clavicular line, and his abdomen was bloated. He also had an umbilical hernia. He had swollen lower extremities. He experienced pancytopenia, acute prerenal failure, septic shock, hyponatremia, platelets dropping from 1.6lacs/L to 68,000/L, Hb from 12.5 to 9.5g/dL, and ANC dropping from 5280 to 265/L.[46]

Lev-Induced Hypomania-

A 52-year-old male was diagnosed with status epilepticus due to a long-lasting seizure. Before discharge, the patient was referred to psychiatry with the symptoms of loud and abusive speech, agitation, and refusal of treatment. According to the information received from his daughter, he had been receiving 300mg of phenytoin per day for epilepsy. Due to the increase in seizure frequency, LEV was initiated at 500mg twice daily and had been titrated to 1500mg per day 2 months previously. Despite having no psychiatric complaints and psychiatric admissions before, complaints such as irritation decreased need for sleep, increased energy, loud speech, and excessive, abusive speech began 2 weeks after the LEV was titrated to 1500mg per day. In the mental status examination, he was oriented and cooperative. His attention was distractible. He was speaking loudly, and his thoughts were fast, and reached his goals. His mood was irritable and had a labile affect. He did not have any delusions or hallucinations. His Young Mania Rating Score (YMRS) was estimated as 18. He was diagnosed withmedication-induced bipolar disorder. LEV was discontinued and olanzapine 5mg/day treatment wasinitiated. He was discharged on the 5th day, and on his follow-up on the 2nd week, his daughter mentioned that LEV had stopped 1 week before. Her father was not using abusive words, he was sleeping better, and his energy had returned to normal. On this follow-up, YMRS was found to be 4 and Olanzapine was discontinued. A causality assessment was carried out using the Naranjo ADR
probability scale. 14 The Naranjo score was found to be 4, which showed a‘possible’ causality [47]

Lev-Induced Anaphylaxis In Neonates

Due to fetal discomfort, a male newborn who was 40 weeks gestation and weighed fetal3300 g had tobe delivered via Caesarean section. His Apgar scores at birth were 2 at 1 minute and 6 at 5 minutes. Seizures, acute hypoxia, and pneumothorax were all diagnosed after he was admitted to the hospital. He was sent to Megpark Hospital since his seizures weren't responding to the initial anti-seizure treatments.After receiving 10mg/kg of levetiracetam intravenously, an erythematous rash an urticaria appeared 2 seconds later, starting on the infant's head and face and spreading throughout the body in around 3minutes [48].

Lev-inducedStevensJohnsonsyndrome

A female patient with congenital heart disease who was 2.25 years old and had a pulmonary arterysling, ventricular septal defect, patent ductus arteriosus, and cleft mitral valve had hypothermic openheart surgery. On the seventh day following her surgery, she experienced cardiorespiratory arrest. Tracheal cannulation and ventilator-assisted respiration were used to treat her. On the ninth day following her surgery, she started having seizures, therefore she was given 5mg/kg/day of phenobarbital. On the 32 nd day following surgery, 10mg/kg/day of oxcarbazepine (OXC) was introduced due to her deteriorating condition and poorly managed seizures. On the 34th day, shestarted to develop rashes on her torso, and her body temperature rose to 37(8 8C. (i.e., two days after OXC was administered). On the 35th day, an erythematous maculopapular rash without exudates that turned pale under pressure appeared on her. The medication was changed to LEV (20mg/kg/day) due to OXC allergy.On the 32nd day following surgery,oxcarbazepine (OXC),10mg/kg/day, was administered due to her deteriorating condition and poorly controlled seizures. Onthe 34th day, her torso started to develop rashes, & her body temperature rose to 37(8 8C. (i.e., twodays after OXC was administered). On the 35th day, she began to get an erythematous maculopapular rash without exudates on her body that turned pale when touched. Due to OXC allergies, LEV (20mg/kg/day) was substituted for the original medication. On the 41st day, the LEV dosage was raised to 30mg/kg/daydue to the seizures'increased frequency. On the ninth day following LEV administration, the rashes returned. Her body temperature rises to 40 ° c on the 50th day following surgery. The fever persisted, and she developed more rashes on her face, body, and all four limbs [49].

DISCUSSION

The European Medicines Agency (EMA) has approved LEV for use as a (i) monotherapy in thetreatment of partial-onset seizures with or without secondary generalization in patients from 16 years ofage with newly diagnosed epilepsy (ii) adjunctive therapy in the treatment of partial-onset seizures withor without secondary generalization in adults and children with epilepsy starting at 1 month of age (iii) treatment of myoclonic seizure. The causes of adverse reactions to levetiracetam are not yet thoroughly understood. Levetiracetam has often been associated with an increased incidence of URTI. Adversereactions were usually easily resolved by dose reduction or discontinuation [50-54]. Three particular aspects of the side effect profile of LEV have been categorized: Asthenia/somnolence, coordination difficulties, and behavioral abnormalities/psychiatric adverse reactions [53]. Behavioral adverse reactions are today ratedas the most important potential drawback of treatment with LEV. Behavioral adverse events occur more often in children and adolescents than in adults [54].

CONCLUSION

A revolutionary second-generation antiepileptic medication is called LEV. It is authorized for use as an adjunctive therapy in adults with partial, myoclonic, and generalized tonic-clonic seizures. It was demonstrated to be effective as a monotherapy in three multicenter studies and as an adjuvant therapy in five multicenter trials. According to the findings of this research, LEV is just as effective in monotherapy as previous AEDs. LEV has a low protein binding capacity, little hepatic metabolism, and a twice-daily dosage schedule. The drug's adverse reaction profile, with the exception of psychiatric indications, is far better than that of previousAEDs.These manifestations, however, are discovered to be connected to the individuals'prior psychiatric histories. Levetiracetam's behavioural adverse effect profile has been studied and established in numerous controlled trials using sizable randomised cohorts. Upon initiating therapy with Levetiracetam, close clinical monitoring is advised in order to spot any potential side effects, especially in high-risk patients

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