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AN OVERVIEW OF THE RARE AND LIFE-THREATENING ADVERSE EFFECTS OF LEVETIRACETAM

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ABSTRACT

Background: Epilepsy is a central nervous system (neurological) disorder in which brain activity becomes abnormal, causing seizures or periods of unusual behavior, sensations, and sometimes loss of awareness. Anti-epileptic drugs (AEDs) are the main type of treatment for most people with epilepsy. Levetiracetam is one of the newer second-generation antiepileptic drugs with multiple mechanisms of action. It is a broad-spectrum antiepileptic drug that was approved by the United States Food and Drug Administration in 1999 and marketed worldwide since 2000. It approved as a treatment of partial seizures; other indications include adjunctive treatment of myoclonic seizures associated with juvenile myoclonic epilepsy and primary generalized tonic-clonic seizures associated with generalized epilepsy. Overall, most of people with epilepsy discontinue their drug due to rare and life-threatening adverse effects. **Method:** This review paper was prepared by referring research and review article from various sites like Pubmed, Google Scholar, Science Direct, Seizure Journal, Elsevier, Medscape, WHO Pharma Newsletter, Research Gate, Springer Link, Online library Wiley. The search was made using keywords like Levetiracetam, Keppra, Mechanism of action, Adverse events(neurobehavioural, renal, hepatic, dermatological, haematological, respiratory). **Observation:** Newer anti-epileptics are being favored in many clinical settings for seizure prophylaxis due to their good safety profile. Levetiracetam has become one of the most commonly used antiepileptic in current practice for treatment as well as prophylaxis against

seizures. Though safe and free of major side effects when comparing to older AED, it is however prudent to note that there are reports of serious adverse effects following levetiracetam, ranging from headache to organ failure. Common side effects include dizziness, somnolence, weakness, fatigue, irritability and headache. Rare but potentially serious adverse events include hypersensitivity reactions, rash and cognitive effects including suicidal ideation and behavior. It is advisable to keep the patient informed of such possible side effects with the use of newer AED like levetiracetam.

KEYWORDS: Levetiracetam, Keppra, Adverse events.

INTRODUCTION

Epilepsy is a common chronic disorder that requires long-term antiepileptic drug therapy.[1] Approximately one half of patients fail the initial antiepileptic drug and about 35% are refractory to medical therapy, highlighting the continued need for more effective and better tolerated drug.[1] The treatment of epilepsy will depend on appropriate classification of the seizure type and the epileptic syndrome, then the choice of an antiepileptic drug (AED) that is most appropriate for the seizure type and epileptic syndrome and also the safest and most appropriate for the patient's particular medical background.[1] The treatment of epilepsy should always begin with monotherapy, using a low initial dose and titrating slowly.[1] The older AEDs were generally approved for marketing and even used as first-line agents without undergoing the rigorous clinical trials now required of the newer antiepileptic drugs.[1] Among the more than sixteen marketed antiepileptic drugs approximately one half are older agents marketed before 1980, while the rest were marketed after 1990.[2] Levetiracetam (LEV) is one of the newest AEDs, marketed worldwide only since 2000.[2]

Levetiracetam (lev-eh-teer-ASS-eh-tam) is the generic name (non-brand name) for the drug called Keppra (KEP-ruh).[3] Keppra is a widely used seizure medicine from UCB.[3] Keppra is available in many countries, but the name or look may be different.[3] Extended release tablets, liquid, oral formulations and injectable solutions are also available.[3] Levetiracetam is available as tablets of 250, 500, 750 and 1000 mg generically and under the brand name Keppra.[4] The recommended initial dose in adults is 500 mg twice daily with dose escalation based upon tolerance and effect to a maximum of 1500 mg twice daily or 3000 mg of extented release formulations once daily.[4] Dosing in children is based upon body weight.

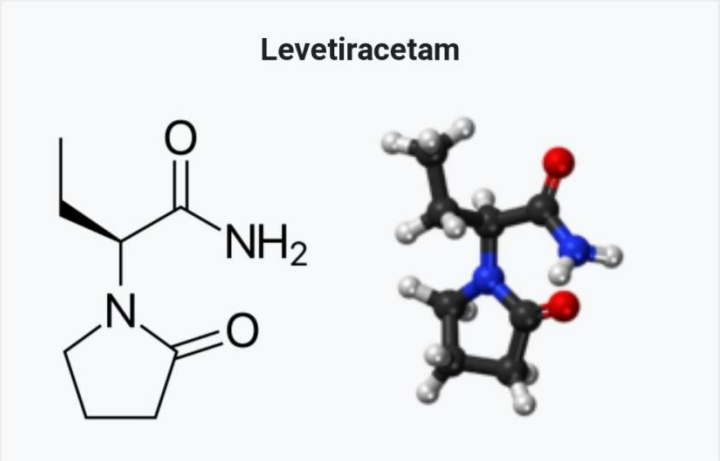

Figure 1 (a). Levetiracetam.

It is also used to treat Juvenile Myoclonic Epilepsy, Temporal Lobe Epilepsy Focal Impaired Awareness or Complex Partial Seizures, Myoclonic Seizures, Secondarily Generalized Seizures or Bilateral Tonic Clonic Seizure, Focal Aware or Simple Partial Seizure, Tonic-clonic Seizures.[4] The availability of an intravenous preparation is yet another advantage. Intravenous levetiracetam (IV LEV) is a second generation antiepileptic currently approved by the FDA as an adjunctive treatment in patients 16 years of age and older as an anticonvulsant when oral therapy is not tolerated.[5]

MECHANISM OF ACTION

Levetiracetam is an (S)-enantiomer of the ethyl analogue of piracetam, in the class of nootropic drugs which are considered to be "pharmacologically safe".[6] It is structurally unrelated to any other antiepileptic class and has a novel mechanism of action. The intravenous formulation was approved in 2006.[7] Its pharmacokinetic advantages include rapid and almost complete absorption, minimal insignificant binding to plasma protein, absence of enzyme induction, absence of interactions with other drugs, and partial metabolism outside the liver.[7]

The exact mechanism by which levetiracetam acts to treat epilepsy is unknown. Levetiracetam does not exhibit pharmacologic actions similar to that of classical anticonvulsants.[8] It does not inhibit voltage-dependent Na+ channels, does not affect GABAergic transmission, and does not bind to GABAergic or glutamatergic receptors.[8] However, the drug binds to SV2A[9], a synaptic vesicle glycoprotein, and inhibits presynaptic calcium channels, reducing neurotransmitter release and acting as a neuromodulator.[10] This protein has been related to modulation of synaptic vesicle exocytosis and neurotransmitter

release.[11] Animal models show that the affinity for SV2A is associated with protection against seizures making it an important target for new AEDs.[12] In vitro studies demonstrated oppositional activity to negative modulators of gamma-aminobutyric acid (GABA)-gated currents despite lack of binding affinity to GABA receptors.[13,14]

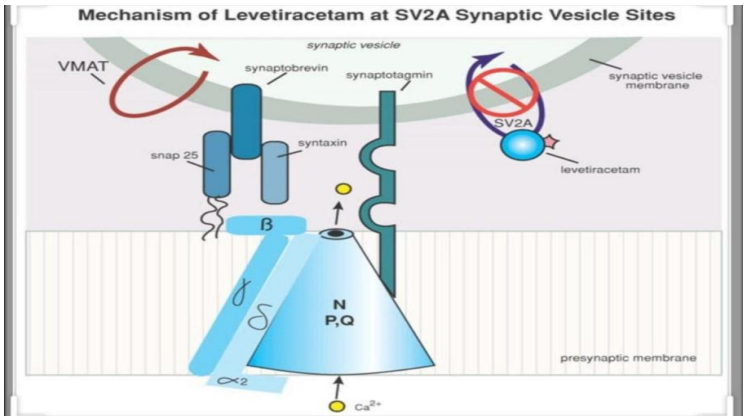

Figure 1(b): Mechanism of Levetiracetam at SV2A Synaptic Vesicle Sites.

The present review summarizes our understanding of the evidence on the adverse effects of levetiracetam and informs clinicians of the risks and provides a clearer picture of the underpinning evidence base. This will, in turn, allow clinicians to discuss with their patients the relative benefits and harms of a drug.

ADVERSE EFFECTS

a) NEUROBEHAVIORAL EFFECTS

As pharmacological treatments for epilepsy evolve, there is general consensus that newer AED's have less cognitive side effects in comparison with their older counterparts.[15] Among newer AED's and epilepsy patients, potential risks for neurobehavioral changes have been reported with Levetiracetem (LEV).[15] Levetiracetem (LEV) has garnered interest as a treatment for patient with brain tumor related epilepsy.[15] Since LEV became available in an intravenous formulation, it has been increasingly utilized because it requires no loading dose and ongoing monitoring.[16] However, the evidence from epilepsy samples suggests that LEV treatment is associated with changes in emotional functions. Specifically, studies are suggestive of increased aggression and possibly suicidality, especially in individuals with premorbid depression or behavioral problem.[17-18]

Lynam et al.[19] conducted a retrospective analysis of 147 patients with newly diagnosed primary and metastatic brain tumor. 41 of patients were on LEV and most commonly

reported side effects include depression, fatigue and irritability. *Newton et al.*[20] conducted a retrospective chart review of 40 patients with brain tumors (34 primary brain tumors and 6 metastatic brain tumors) who received LEV as an add-on or monotherapy and were followed for 4 week. Somnolence was the most frequently reported side effects and other symptoms included dizziness, headache and paresthesia. *Rosati et al.*[21] conducted a prospective study with 176 newly diagnosed glioma patients. All patients diagnosed with epilepsy (47%) of the sample were initially treated with LEV. Two patients discontinued LEV during the study because of intolerable diarrhea, visual hallucinations with psychotic thoughts.

Dinapoli et al.[22] conducted a case series to evaluate LEV as a monotheapy for brain tumor related epilepsy in a sample of 18 patients that they followed for 6 months. The Mini Mental Status Examination (MMSE) was used as a measure of global cognitive functions[23]; the Karnofsky Performance Scale (KPS) and the Bartel Index (BI) were used to evaluate overall functioning.[24] 61% of the sample had side effects at the beginning of the trial including rash, somnolence, periarthritis, weight loss and liver toxicity,[25] At 6 months 22.2% had mild side effects including somnolence and restlessness.[26] LEV may even provide some cognitive benefit in selected populations. For eg: In patients with high grade glioma, LEV improved memory in those patients.[27-28]

20% to 30% of patients with epilepsy have associated mood disorders, and 2–7% may have frank psychosis.[29] Behavioral adverse effects are common with levetiracetam and are seen in 5–34% of children.[30] Most of these are mild and seldom need discontinuation of levetiracetam. Common adverse effects include aggression, excessive sleepiness, hyperactivity and depression.[30-31] Rapid titration and prior intellectual or learning disability were associated with higher incidence of adverse effects. Severe adverse effects like severe depression, psychosis, and suicidal tendencies are rare.[32-33] Concomitant use of pyridoxine has been described to ameliorate behavioral side-effects of levetiracetam by decreasing hyperactivity.

b) HEMATOLOGICAL EFFECTS

Hematological adverse effects of LEV are extremely rare and have been limited to isolated cases of thrombocytopenia, leukopenia, or anemia.[34,35,36] Three cases of pancytopenia with the use of LEV have been reported. The first case is that of a 76-year-old woman who had a seizure in the setting of an ischemic stroke and developed pancytopenia two days after initiation of LEV.[37] The second case is a 65-year-old woman who received LEV after

undergoing surgical removal of a meningioma and developed pancytopenia 9 days after initiation of treatment, with bone marrow aspiration showing medullary hypoplasia.[38] The third case is a 16-year-old young woman with a history of Lafora disease who experienced pancytopenia 4 days after initiation of LEV treatment and recovered with discontinuation of the medication.[39] The fact that these patients presented with different diagnoses suggests that LEV, rather than a complication of the underlying disease, was the cause of pancytopenia. In addition, no one concomitant medication was common to all reported cases, and none of these reports studied HLA typing as a potential predisposing factor. In these cases, all other causes of hematologic disturbance such as thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, and heparin-induced thrombocytopenia were ruled out. Other medications such as enoxaparin and pantoprazole with potential hematologic adverse effects were discontinued without improvement in blood counts. The patient's hemolysis profile and blood smear did not reveal any signs of hemolysis. Therefore, it was hypothesized that LEV induced pancytopenia in those patients through bone marrow suppression.

Clinicians should be aware that LEV can cause severe pancytopenia, and consider discontinuation of LEV in patients who develop pancytopenia with negative hemolysis profile. More recently[40] reported case of a LEV-induced pancytopenia.

The retrospective study was conducted by Kinshuk Sahaya[41] to estimate the gravity of LEV-induced thrombocytopenia in a-risk population, that is, inpatients. In that analysis, they screened 758 patients on LEV in between June 2005 and December 2008. Twenty-nine patients with thrombocytopenia were identified in this population. A single possible case of LEV-induced thrombocytopenia could be identified after analyzing these patient’s records. In the remaining 28 patients they identified other possible etiologies of thrombocytopenia without evidence of strong association with LEV administration. They used the Naranjo scale to assess the probability of LEV causing thrombocytopenia. Then, a score of >9 is labeled as definite adverse drug reaction, whereas a score of 5–8 is labeled probable and 0–4 as possible adverse drug reaction. A comparison of that patient with previously reported cases and back-calculated Naranjo scale. This reported case was remarkable for the immune-compromised state of the patient. Although he had several risk factors for thrombocytopenia and had baseline leucopenia, it is notable that all those factors were present for a relatively long time. He had been stable prior to the initiation of LEV. Although his platelet count had

fluctuated a priori, it had never reached the level as that on LEV. He responded well to the discontinuation of LEV, and his counts improved within a few days. Although the most common adverse effects of this drug are minor, serious adverse effects such as thrombocytopenia have been reported.[42-43] Noticed within a few days to a few weeks, thrombocytopenia is suggested to be immune mediated and reversible on discontinuation of the LEV.

c) DERMATOLOGICAL EFFECTS

Levetiracetam is a widely used anti-epileptic drug. Rash, acanthosis, hyper pigmentation, purpura, and ulceration were major reactions.[44] To the best of my knowledge, this is the first report of skin hyperpigmentation as a side effect of levetiracetam in the literature.[45]

A 54-year-old female, known case of epilepsy (partial, complex partial with secondary generalization) following herpes simplex virus encephalitis two years ago. She was started on carbamazepine which was gradually increased to a dose of 1,200 mg per day without complete control of seizure frequency. One-year ago, levetiracetam was added to achieve a better control with success and complete remission of her seizures. She was kept on 1,000 mg of levetiracetam twice daily. She noticed a change in the color of her skin that started diffusely six months following the addition of levetiracetam. Her skin became dark all over her body including face, arms, trunk, and legs. She was not on any medication that can cause hyperpigmentation such as oral contraceptives or non-steroidal anti-inflammatory drugs. Her examination showed generalized hyperpigmentation with Fitzpatrick skin type IV. A skin biopsy showed mild epidermal acanthosis with hyperpigmentation of the basal layer. In addition, there was upper dermal fibroplasia and pigmentary incontinence. Work up for systemic disorders causing hyperpigmentation including thyroid function tests, electrolytes, serum cortisol, and renal function tests were unremarkable. Modification of the treatment was done with the addition of pregabalin in gradually increasing doses and gradual decrease in levetiracetam dose until complete discontinuation. In a follow-up visit to the clinic six months later, her skin hyperpigmentation improved significantly, and the patient was satisfied and continued to be seizure free.

Melanocyte-stimulating hormone is produced by the anterior pituitary gland and is responsible for stimulating the formation of the melanin and its dissemination to the epidermis.[46] The color of the skin is determined by the amount of melanin pigment that is produced within the melanocytes, which are found in the basal layer of the epidermis.[46] The

three basic types of melanin are eumelanin, pheomelanin, and neuromelanin.[47] The most abundant type is eumelanin, which is responsible for the brown and black pigmentation of human skin. Adrenocortico-tropic hormone is physiologically more important than melanocyte-stimulating hormone in determining the amount of melanin in the skin.[48] Cutaneous side effects are commonly associated with antiepileptic drugs such as carbamazepine, phenobarbitone, phenytoin, and lamotrigine.[48] These side effects may be mild such as maculopapular rash or more severe and life-threatening such as drug reaction eosinophilia and systemic symptoms. These cutaneous manifestations may appear within a few hours to weeks of the initiation of the anti-epileptic drug.

Fitzpatrick skin typing test is a classification scale for the color of the skin that estimates the response to ultraviolet light by different skin types.[49] It is composed of six categories ranging from pale white (type I) to deeply pigmented dark brown or black (type VI). Our patient had Fitzpatrick skin type IV. This type appears light brown that burns minimally and always tans well.[49-50] Fitzpatrick skin type IV may be prone to an overactive production of melanin after exposure to sunlight or receiving hormonal therapy, which may be an additional factor behind the development of hyperpigmentation as a side effect of levetiracetam.

Hyperpigmentation is an acquired darkening of the skin, mucous membranes, or nails that may result from sun damage, infections, autoimmune diseases, contact dermatitis, photosensitivity, or allergic reactions. Another possibility of hyperpigmentation is the formation of a stable drug-melanin complex which prevents melanin clearance in the dermal macrophages. Synthesis of other pigments such as lipofuscin under the direct influence of the drug with subsequent deposition may cause hyperpigmentation. Medications are the cause of skin hyperpigmentation in around 10–20% of the patients with the classic triggers being chemotherapeutics, oral contraceptives, non-steroidal anti-inflammatory drugs, and a variety of drugs such as amiodarone and chloroquine.[51] Additionally, the deposition of iron as a result of drug-induced damage to dermal vessels may lead to hyperpigmentation.[51,52]

Hair loss is one of the most important adverse reactions in patients on levetiracetam treatment.[53] Telogen effluvium (TE) is a form of non-scarring alopecia which presents as a diffuse hair loss. There are some known causes for TE, such as hormonal changes, stress and medications. Here is a case study presented by Vajiheh Aghamollaii[53] on patients who developed TE after consuming levetiracetam.

The first case is a 16 year old female who presented with falling attacks and jerky hand movements. Her EEG was abnormally compatible with myoclonic epilepsy syndrome and she was on topiramate 25 mg twice a day. Due to incomplete seizure control, lamotrigine was started for her and topiramate was tapered down. At the next follow up visits, she complained of experiencing generalized tonic-clonic seizures (GTCs) so levetiracetam 750 mg daily was added. Due to continuing GTC attacks lamotrigine was tapered down and discontinued as it was suspected to be the cause. After one year, while being on 1500 mg daily of levetiracetam, she complained of significant hair loss. Her hair loss had a diffuse pattern without any cicatricial lesion. After ruling out the common causes of hair loss, levetiracetam induced TE was proposed as the reason for her hair loss and zinc sulfate capsule 220 mg twice daily was started. Meanwhile, levetiracetam dose was increased to 1750 mg daily in this patient to achieve desirable seizure control. At the follow up visit, two months later, her hair condition had improved.

Second case is a 10-year-old female diagnosed with a typical absence seizure who had been treated with ethosuximide and valproic acid. She had a history of Steven-Johnson syndrome with both drugs. Topiramate and even carbamazepine, phenytoin and phenobarbital had been tried for her in the past. Carbamazepine and phenytoin had caused severe allergic skin reaction and phenobarbital and topiramate had shown no efficacy. She presented to our clinic taking topiramate 50mg BD with her absence attacks remaining uncontrolled. We started levetiracetam 125mg twice a day. Two months after the dose was increased to 1250mg a day, she started to experience profound hair loss. She was diagnosed with drug-induced TE as the other possible causes of hair loss were ruled out. Because of her history of drug reaction and that her attacks were only 50% controlled, levetiracetam was continued and zinc sulfate capsule 220 mg twice daily was added to her treatment. Two months later her hair loss improved.

After establishing the diagnosis of drug-induced TE the simplest way to treat it is to switch to another medication as TE often resolves with the cessation of the causing agent. However, if switching to another medication could not be achieved immediately, the clinician may lower the dose to minimum effective dose.

Calabrò et al.[54], have reported an abnormal zinc level in a patient with levetiracetam-induced TE which was normalized after changing the drug to topiramate. Zou et al.[55], have reported zinc supplementation to be effective for the treatment of levetiracetam induced TE

in 5 patients. One of the proposed mechanisms for levetiracetam seizure prevention is by an antagonizing zinc function in GABA- ergic receptors.[56] And all patients reported improvement in their hair condition by withdrawal of levetiracetam and treated successfully with zinc supplementation. Recently, there have been an increased number of reports on levetiracetam (LEV) induced cutaneous adverse drug reactions (CADRs), they include angioedema, Stevens Johnson syndrome, drug reaction eosinophilia and systemic symptoms, toxic epidermal necrolysis, hair loss, morbilliform rash, and maculopapular exanthema.

d) RESPIRATORY EFFECTS

Levetiracetam is widely regarded as a benign antiepileptic drug, compared to older antiepileptic medication.[57]

Here a case reported by Aisling Fagan[57] and Jonathan Fuld on eosinophilic pneumonia due to levetiracetam use in a non-smoking woman aged 59 years with no previous respiratory history. This patient presented with exertional breathlessness and marked desaturation on exertion. She displayed ‘reverse bat-wing’ infiltrates on her chest radiograph and peripheral eosinophilia on a complete blood count. Her symptoms, radiology and peripheral eosinophilia resolved completely with cessation of levetiracetam. This is the first report of isolated eosinophilic pneumonia due to levetiracetam.

Scott D Newsome and Lanny Y[58] reported the first case of diffuse interstitial lung disease by levetiracetam. Here the patient was a 9-year-old girl who was admitted to the pediatric intensive care unit for aspiration pneumonia. She has a history of epilepsy, cerebral palsy, mental retardation, asthma, and repeated hospitalizations for presumed aspiration pneumonia, which was resolved with conventional medical treatment. She has been on low-dose levetiracetam for her epilepsy over the past 2 years, and the dosage was increased just prior to admission. However, this time, with conventional treatment, the patient's aspiration pneumonia did not improve, which led to a lung biopsy. The biopsy demonstrated a diffuse interstitial process of relatively recent onset, with features consistent with diffuse lung disease. Levetiracetam was implicated in the pathogenesis of interstitial pneumonitis. The patient improved clinically after the discontinuation of levetiracetam and with the treatment of steroids.

Identifying and reporting a causative agent is crucially important, as cessation of the drug is essential for resolution of the syndrome.

e) HEPATIC EFFECTS

Drug-induced liver injury owing to antiepileptic drugs (AED) is well recognized.[59] It has been reported to occur more commonly with phenytoin and carbamazepine, and very rarely with valproate.[59] Levetiracetam has been linked to rare cases of clinically apparent drug induced liver disease also serum aminotransferase and alkaline phosphatase elevations during treatment.[60]

LEV has been considered to have an excellent safety profile with minimal hepatic side effects. However, a rare case of acute liver failure due to levetiracetam reported by Sharanya Jayashsnkar.[61] A 55-year-old male patient presenting with sudden onset dizziness, slurring of speech and headache was operated for posterior fossa cerebellar hematoma. His post-surgical period was complicated by development of gross icterus and his liver function test revealed total bilirubin of 9.4 mg/dl (normal, 0.1mg/dl), direct 2.0 mg/dl (normal, 0-0.35mg/dl); aspartate aminotransaminase/serum glutamic-oxaloacetic transaminase (AST/SGOT) of 911 IU/L; (normal, 10–40 IU/L); alanine aminotransferase/serum glutamic-pyruvic transaminase (ALT/SGPT)of 926 IU/L (normal, 10–40 IU/L); alkaline phosphatase (ALP) of 298; (normal, 40–112 U/L); International Normalized ratio (INR) of 1.09 (normal, <1.1). Complete blood counts were done to rule out sepsis and were normal. Ultrasound of the abdomen and peripheral smear (for identifying features of obstructive jaundice as well as portal hypertension and ruling out hemolysis for raised bilirubin respectively) were normal. So, a possibility of drug induced liver injury causing acute hepatic failure was considered. Since none of the drugs prescribed were commonly implicated to have hepatotoxic effects. Then, considered the possibility of levetiracetam and stopped the drug. Prophylactic hepatic encephalopathy regimen was also prescribed with strict monitoring of urine output, Glasgow coma scale (GCS), watching for seizures and features of upper gastrointestinal bleeding. From the second day of stoppage of the drug, the patient had dramatic improvement in liver functions and sensorium. In this case, the patient's hepatic function rapidly normalized following the stoppage of only levetiracetam from prescribed drug lists. Therefore, sufficiently concluded that levetiracetam caused hepatotoxicity.

Tan et al.[62] reported incidence of fulminant liver failure owing to levetiracetam. Syed and Adams[63] also reported a case of liver failure following prophylactic levetiracetam usage in a patient with head injury. *Sethi et al*.[64] reported a post-traumatic head injury patient who developed asymptomatic elevation of hepatic enzymes following levetiracetam usage.

Though rare, it is important to keep this rare but life-threatening complication of levetiracetam, as it can have profound effects on the timely and corrective management of the patient.

f) MUSCULAR EFFECTS

Rhabdomyolysis has been documented as a rare adverse effect of levetiracetam, and until now, only six cases have been reported.[65,66,67,68] Three of them were pediatric patients and the other three patients were in the late 20s. Rhabdomyolysis is a condition that is characterized by the destruction of skeletal muscle and the spillage of its contents into the bloodstream.

Case reported by Vaibhav Rastogi[68], in a 42-year-old male who was brought to the hospital with a complaint of generalized tonic-clonic seizures and urinary incontinence. His symptoms were caused by hyponatremia. Levetiracetam was started for seizure prevention along with management for hyponatremia. His creatine phosphokinase levels increased on the third day of admission to 30,000 U/L. Four days after the discontinuation of levetiracetam and with the institution of supportive therapy, the patient's rhabdomyolysis was resolved.

Hisanao Akiyama[69] presented a case report of suspected levetiracetam-induced rhabdomyolysis in a 29-year-old woman. She was hospitalized for generalized tonic–clonic seizure which developed during the EEG, and after this episode, she was started on intravenous phenytoin 250 mg daily. She had not experienced any seizures since starting intravenous phenytoin. A single dose of phenytoin 250 mg was given on hospital day 2, and intravenous medication was discontinued the same day (total phenytoin dose, 500 mg over 2 days). Levetiracetam 1000 mg daily and VPA 800 mg daily were started from hospital day 3. She developed myalgia, particularly backache, and weakness in both lower limbs after starting levetiracetam and VPA on hospital day 4. She was discharged because of improved clinical symptoms and drug adherence was good after discharge. However, myalgia and weakness were gradually aggravated, and she revisited the hospital after 3 days. A blood test revealed hyperCKemia of 2410 IU/L and a low blood VPA concentration of 33.6 μg/mL, and levetiracetam was immediately withdrawn. Sodium valproate 800 mg daily was continued. Withdrawal of levetiracetam immediately improved the myalgia and weakness, and hyperCKemia improved rapidly to a normal level; CK was 59 IU/L 28 days after discharge.

Based on the clinical course the patient was diagnosed as having rhabdomyolysis induced by levetiracetam without the measurement of serum myoglobin levels.

Regarding the drug interaction between levetiracetam and phenytoin or VPA, it has been reported that levetiracetam does not influence the serum concentration or pharmacokinetics of phenytoin or VPA.[70] Therefore, the possibility of rhabdomyolysis being induced by phenytoin or VPA is low. Also that patient started to experience myalgia and weakness in both lower limbs, as well as hyperCKemia, immediately after being started on levetiracetam.

According to medical interview forms, the serum concentration (i.e., Cmax) of levetiracetam peaks 2–3 h after administration and reaches a steady state 3 days after administration when a repeat dose of levetiracetam should be given.[70] These pharmacokinetics coincide with the onset of clinical symptoms or hyperCKemia. Since her signs and symptoms improved quickly once levetiracetam was withdrawn, the adverse effects were likely due to this drug alone.

Brigo et al[71], in their review, suggested that seizures usually cause a slight elevation of CPK (< 180 U/L) and the peaks are noted at 36-40 hours . In this patient, the CPK elevations were significantly higher (> 30,000 U/L) and were noted at 72 hours after admission. A review by Kashiura et al[72] noted a correlation between higher sodium correction rates (> 1 mEq/L/hour) and rhabdomyolysis. However, the sodium correction rate in this case report was 8-10 mEq/L/24 hours, which equates to <0.5 mEq/L/hour, which makes it very less likely to have rhabdomyolysis as a result of serum sodium correction.

Drastic elevations in the levels of CPK after the initiation of levetiracetam and a decrease in CPK levels after the withdrawal of the drug indicates that it was likely levetiracetam that caused the rhabdomyolysis. Clinicians should pay attention to the possible development of rhabdomyolysis during the treatment with levetiracetam.

g) RENAL EFFECTS

Levetiracetam is a widely used drug that has been reported to be generally tolerable and effective; however, it has the potential to negatively affect renal function. As per the case reported by Danielle C Spengler et al[73] in a healthy 23-year-old female patient who developed acute kidney injury one day after the initiation of levetiracetam therapy for new-onset seizures. Based on the time course of rise in serum creatinine in the patient and the

exclusion of other causes, this case suggests that levetiracetam use contributed to the acute kidney injury.

Another case report by Katrina Chau[74] on a 69-year-old woman with a background of early stage chronic lymphocytic leukaemia (CLL) was noted to have episodes of phrase repetition and instances of memory loss over 1 year. An electroencephalogram showed changes consistent with temporal lobe epilepsy. A magnetic resonance imaging showed mild deep white matter small vessel ischaemic changes with a small old infarct of the right caudate nucleus. She commenced on carbamazepine. Six weeks later, she developed generalized erythematous macular rash and was admitted to hospital for wet dressings. A skin biopsy confirmed a lichenoid drug reaction and serological markers of vasculitis were negative. At this time, the patient had normal renal function as assessed by a serum creatinine of 49 mmol/L (0.55 mg/dL) and the absence of pyuria, haematuria (by urinary microscopy) or albuminuria on a spot urine assessment. Carbamazepine was discontinued and the patient was commenced on levetiracetam 500 mg twice a day and discharged home. And she developed haemodialysis-requiring acute renal failure after commencement of treatment with levetiracetam, which was shown to be granulomatous interstitial nephritis by renal biopsy. Granulomatous interstitial nephritis (GIN) is an uncommon cause of renal failure, which may be caused by drugs. She made a complete recovery with cessation of levetiracetam and treatment with steroids. Although tubulointerstitial nephritis is relatively common, GIN is rare, accounting for ~1% of diagnoses in native renal biopsies.[75,76]

Two cases reported with an increasing creatinine value in connection to levetiracetam start, followed by a reduction to normal after by a reduction to normal after withdrawal of levetiracetam[77]:

Case 1: A 21-year-old male received levetiracetam 250 mg per day at the start of the month (exact time not given). On the 24th, the dose was increased to 500 mg per day and clobazam was added to the regimen. Two days thereafter, a five-fold increase in the creatinine was observed along with an abnormal creatine phosphokinase (CPK). Creatinine continued to increase during two more days reaching a 10-fold increase together with an increased CPK. After that levetiracetam was discontinued and replaced with lamotrigine (clobazam was continued). Patient recovered.

Case 2: A 73-year-old male presented at hospital with convulsions and started with levetiracetam, at which time creatinine was normal. Patient had a long-time treatment history of gliclazide, losartan and aspirin. The day after levetiracetam started, the creatinine had almost doubled. Two days later the creatinine was still elevated. Renal echography was normal. An allergic nephritis was suspected. Levetiracetam, gliclazide and aspirin (unclear if also losartan) was stopped and the next day the creatinine had decreased and was normal five days thereafter. Patient started with carbamazepine and re-started losartan and gliclazide.

Levetiracetam has high oral bioavailability and is excreted predominantly in the urine (93% after 48 h).[78] It's s elimination is directly dependent on creatinine clearance so an dose adjustment is required in renal impairment.[78] Potential consequences of therapy should be considered when deciding whether or not to prescribe this medication, and renal function should be monitored during treatment.

h) IN PREGNANCY AND BREASTFEEDING

Limited data are available on safety in pregnancy. In the analysis of the UK Epilepsy and Pregnancy Registry, 3 of 117 exposed pregnancies had a major congenital malformation, but all three were also exposed to other AEDs.[79] Four infants exposed to LEV monotherapy had a low birth rate, but the mean birth weight for infants exposed to LEV was within the normal range.[79] There were also no minor malformations in the LEV monotherapy group which included 39 monotherapy exposures. Other smaller reports also did not identify any LEV-related malformations.[80,81] Thus, preliminary data seemed favorable, but additional reports are needed for definitive assessment of LEV safety during pregnancy.

LEV is extensively transferred from mother into breast milk. However, breast fed infants had very low LEV serum concentrations, suggesting that breastfeeding should not be contraindicated.[82,83]

Adverse effects of levetiracetam are enlisted in the table given below

Table 1: Adverse effects of Levetiracetam.

Neurobehavioral effect	Aggression, depression, suicidal tendency, fatigue, irritability, somnolence, dizziness, headache, paresthesis, visual hallucination, psychotic thought, restlessness, excessive sleepiness.
Hematological effect	Thrombocytopenia, leucopenia, anaemia, pancytopenia
Dermatological effects	Rash, acanthosis, hyperpigmentation, purpura, ulceration, telogen, alopecia, Stevens-Johnson syndrome,

	angioderma, drug reaction eosnophilia.
Respiratory effects	Eosnophilia, Pneumonia, Diffuse interstitial lung disease, Interstitial neumonitis.
Hepatic effects	Acute liver failure, SGOT elevation, SGPT elevation.
Muscular effects	Rhahdomyolysis. hyperCKemia
Renal effects	Acute renal failure, Interstitial nephritis, Urinary tract sterosis, Hydronephrosis acidosis, Nephritis interstitial pallor.

CONCLUSION

Levetiracetam(LEV) is an antiepileptic drug with multiple mechanisms of action that correlates with its broad spectrum of activity. It inhibits neuronal hyper-synchronization, most likely by binding to synaptic vesicle protein 2a (SV2A) located in presynaptic membranes; this is a mechanism of action related to its antiepileptic activity. The present review is designed to provide an objective summary of the evidence base for adverse effects of levetiracetam use. The adverse effects of levetiracetam include aggression, depression, fatigue, irritability, somnolence, weight loss, periarthritis, eosinophilic pneumonia, diffuse interstitial lung disease, rash, hyperpigmentation, purpura, ulceration, telogen effluvium, pancytopenia, anaemia, thrombocytopenia, leukopenia, acute kidney injury, granulomatous interstitial nephritis, nausea, rhabdomyolysis. This review informs clinicians about the risks and provides a clearer picture of the underpinning evidence base. This will, in turn, allow clinicians to discuss with their patients the relative benefits and harms of a drug.

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