Journal of Acute Disease

journal homepage: www.jadweb.org

doi: 10.4103/2221-6189.221287

Eslicarbazepine acetate: A therapeutic agent of paramount importance in acute anticonvulsant therapy

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ARTICLE INFO

Article history:
Received 11 August 2017
Revision 20 August 2017
Accepted 2 September 2017
Available online 1 November 2017

Keywords:
Eslicarbazepine acetate
Partial-onset seizures
Epilepsy
Antiepileptic drugs
Drug interactions

ABSTRACT

Eslicarbazepine acetate (ESL) is a new, once daily, orally administered, third generation antiepileptic drug which is indicated in the treatment of partial-onset seizures. ESL is known to exert it's anticonvulsant effect by blocking the voltage-gated sodium channels. Several clinical trials and pharmacological studies have revealed that seizure control was better with ESL monotherapy (1 200 or 1 600 mg once daily) following a switch from other antiepileptic drugs in comparison with pseudo-placebo patients. The studies have indicated the ESL to be well tolerated and produced only mild to moderate emergent adverse events with the therapy. Being a dibenzazepine family member, structure and chemistry of ESL resembles more or less to carbamazepine and oxcarbazepine. ESL differs structurally from carbamazepine and oxcarbazepine at the 10, 11 position of dibenazepine nucleus. This molecular variation results in differences in metabolism and thus helps to prevent the formation of toxic epoxide metabolites. ESL following oral administration is rapidly metabolised to active metabolite namely S-licarbazepine which is responsible for its pharmacological activity. ESL exhibits acceptable pharmacokinetic profile and shows insignificant drug-drug interactions. In phase III clinical program, ESL was found to be efficacious and well tolerated in adult patients with partial onset seizures previously not controlled with treatment with one or two other antiepileptic drugs.

1. Introduction

Over the last few decades, antiepileptic drugs (AEDs) have made a considerable impact in the treatment and management of epilepsy[1,2]. Although, a large number of AEDs are available for the treatment of epilepsy, yet nearly 30% of patients have scanty seizure control[3]. Approximately 50 million people of all ages are affected by epilepsy worldwide[4] and it is estimated that 2.3 million adults (1%) in USA population suffers from this neurological disease. Epilepsy is a chronic non-communicable disorder of the brain which is characterized by recurring episodes of seizures. The seizures are produced due to abnormal excessive or synchronous neuronal activity in the brain[5,6]. The disease requires a long-term treatment which necessitates the development of well tolerated novel AEDs with fewer side effects, high efficacy and having a simplified dose

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How to cite this article: Farah Iram, Shah Alam Khan, Aftab Ahmad, Anees A. Siddiqui, Asif Husain. Eslicarbazepine acetate: A therapeutic agent of paramount importance in acute and chronic anticonvulsant therapy. J Acute Dis 2017; 6(6): 245-254.

regimen[7-9].

Eslicarbazepine acetate (ESL) is one of the most prominent AEDs developed recently by the Bial, a Portuguese pharmaceutical company. However, in early 2009, a Japanese company Eisai bought the marketing rights in Europe[10]. In April 2009, the drug was approved for use by the European Union under the trade names Zebinix™ and Exalief™[11,12] and as Aptiom™ in 2013 by the US Food and Drug Administration (FDA)[13].

ESL is a third generation AED whose clinical use is limited to partial-onset and generalized tonic-clonic seizures. It is a single-enantiomer member that belongs to the long-established family of the first generation dibenz[b,f]azepine AED like carbamazepine (CBZ) and second generation oxcarbazepine (OXC)[14]. ESL is a prodrug that is activated to Eslicarbazepine (S-licarbazepine), an active metabolite of OXC[15-17]. Both ESL and eslicarbazepine stabilize the inactivated state of voltage-gated sodium channels. It not only prevents the return activated state but also sustain repetitive neuronal firing[18-20]. ESL protects the development of seizures and have exhibited analgesic effects in preclinical models of epilepsy and nonclinical models of pain respectively[21-25].

ESL acts as a voltage-gated sodium channel blocker[26-28]. Constructively, it does not amend fast inactivation of voltage-gated sodium channel like CBZ, but alter the kinetics and voltage dependence of slow inactivation[29]. ESL is known for its improved tolerability profile as it provides a stable concentration of S-licarbazepine in CSF after administration and simplified dose regimen with a once-daily oral administration which leads to improved patient compliance[30-31]. This review article highlights the chemical, pharmacological, pharmacodynamic and pharmacokinetic profile of ESL as a mono or adjunct therapy in epilepsy.

2. Dosage and administration

2.1. Dosage for partial-onset seizures

The starting treatment dose is 400 mg orally once daily (OD) for first seven days and then recommended maintenance dose is 800-1 200 mg orally OD. Though, high maintenance dose of 1 200 mg is beneficial to some patients but leads to an increase in adverse reactions (ADRs). Generally, a dose of 1 200 mg daily is initiated for those patients who can tolerate 800 mg daily for at least one week. For some patients, treatment may be initiated at 800 mg OD, if the need for additional seizure reduction outweighs an increased risk of adverse reactions during initiation[32-34].

2.2. Dosage adjustment with other AEDs for partial-onset seizures

ESL should not be used along with OXC and CBZ as an adjunctive therapy because of the serious adverse reactions. In case of the patients taking other enzyme-inducing AEDs such as phenobarbital, phenytoin, and primidone, a higher dose adjustment is required[35,36].

2.3. Dosage adjustment of ESL in renal impairment patients

No dose adjustment of ESL is needed if creatinine clearance is $\geqslant$50 mL/min. In case of patients having creatinine clearance $<$ 50 mL/min, the starting dose is 200 mg orally OD which is increased to the recommended maintenance dose of 400 mg orally OD after two weeks[33,37].

2.4. Dosage adjustment in hepatic impairment patients

Patients suffering from mild to moderate hepatic impairment do not need a dose adjustment. No study has been conducted to investigate the use of ESL in severe hepatic impairment patients, hence in absence of clinical data, use of ESL in these patients should be avoided[28,34,38].

2.5. Dosage adjustment in pregnancy and lactation

There are no clinical trials which document the effect of ESL in pregnant women. However, some animal studies have suggested that ESL may be teratogenic in humans[28,39]. ESL is excreted into breast milk and is not recommended in breast feeding mothers. CBZ is usually a choice of AED as it is compatible with breast-feeding according to The American Academy of Pediatrics (TAAP)[40].

3. Chemistry

Chemically, ESL ($C_{17}H_{16}N_2O_3$; molecular weight 296.32) is (S)-5 carbamoyl-10, 11-dihydro-5H-dibenzo[b,f]azepin-10-yl acetate[41]. It is a white to off-white, odourless crystalline solid. ESL, CBZ and OXC share a common chemical moiety *i.e.* Dibenzazepine nucleus with a 5-carboxamide substituent. But ESL is structurally different at the 10, 11-position. Unlike CBZ, ESL is not metabolized into the CBZ 10, 11-epoxide, an active and potentially toxic compound. As a result, ESL has very low enzyme-inducing activity[42]. ESL has a solubility of <1 mg/mL in aqueous buffer solutions at different pH values and at physiologic conditions it remains non-ionisable. The ESL ester moiety is chemically hydrolyzed at low and high pH (1.2 and 10, respectively) to yield eslicarbazepine. Eslicarbazepine has a water solubility of 4.2 mg/mL, which is >10-fold higher than the aqueous solubility of ESL, CBZ and OXC[43]. At physiologic pH of 7.4 at 25 ℃, the log *P* value (n-octanol/water partition coefficient) is 8.8. According to the biopharmaceutic classification system (BCS) which categorizes drugs according to their water solubility and capability to pass across membranes, ESL belongs to BCS class Ⅱ *i.e.*, a highly permeable-poorly soluble drug[44,45].

4. Mechanism of action

Voltage-gated sodium channel (VGSC) is the target site of ESL. VGSC is responsible for generation and propagation of the epileptic discharge. VGSC have three states *viz.* deactivated state, a state of depolarization and inactivated state. In VGSC, ESL interacts with neurotoxin site][[46,47]. It showed more affinity for inactivated state in comparison to a deactivated state which results in highly selective blockage of the rapid repetitive firing of neurons in *in–vitro* studies[48-50]. ESL proved to be efficacious in the amygdala-kindled rat model and various other animal models against pro-convulsant agents such as metrazole, bicuculline, 4-amino-pyridine, latruncullin, and picrotoxin[51,52].

5. Pharmacokinetics

ESL is known to exhibit linear and dose-proportional (400-1 200 mg/day) pharmacokinetics in both healthy subjects and patients. ESL half life was found to be 13-20 h in patients. One dose a day, give steady-state plasma concentrations after 4-5 d[27,28,53].

5.1. Absorption

ESL after oral administration is mainly undetectable with 0.01% systemic exposure. Plasma concentration (C_{max}) of ESL is achieved at 14 h of the post-dose peak. Total of 90% of the dose of ESL is recovered in urine that consequently results in high bioavailability (>90%). T_{max} and volume of distribution (V_d) of ESL are 1-4 h and 61 L, respectively. ESL shows 20 mL/min, 80-120 mL/min of clearance and glomerular filtration rate, respectively[53,54].

5.2. Distribution

ESL shows fewer plasma proteins binding (about <40%) which is not concentration dependent. Warfarin, diazepam, digoxin, phenytoin, or tolbutamide does not influence plasma proteins binding of ESL in *in–vitro* studies and vice versa[27].

5.3. Metabolism

Once ESL is administrated orally, it undergoes major hepatic and minor intestinal metabolism. The hydrolytic metabolism of ESL produces an active metabolite eslicarbazepine (91%). It also results in minor active metabolites R-licarbazepine (5%) and OXC (1%). Initially, ESL is metabolised to eslicarbazepine and then consequently by oxidation a minor chiral inversion takes place to (R)-licarbazepine (Figure 1)[55-57]. ESL in *in–vitro* studies in human liver microsomes had no clinically significant inhibitory effect on the activity of CYP1A2, CYP2A6, CYP2B6, CYP2D6, CYP2E1, and CYP3A4[58-60]. Although, it exhibits a modest inhibitory effect on CYP2C19. In human hepatic microsomes, ESL exhibits mild activation of UGT1A1- mediated glucuronidation. ESL in fresh human hepatocytes had no induction of enzymes involved in glucuronidation and sulfation of 7-hydroxy-coumarin[61].

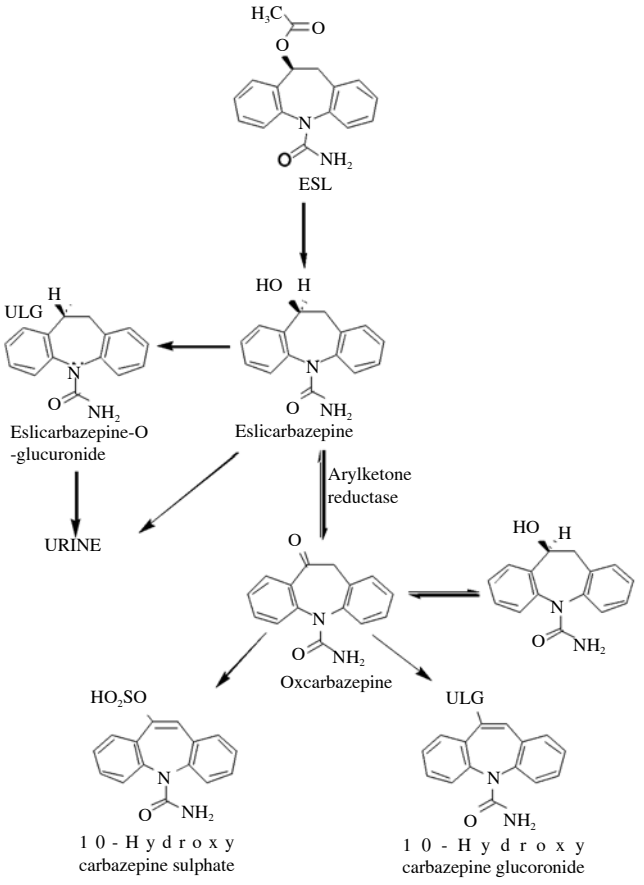

Figure 1. Metabolic pathways of ESL and OXC to eslicarbazepine and (R)-licarbazepine.

5.4. Excretion

The unchanged and glucuronide conjugated forms of ESL metabolites amounting to more than 90% of total metabolites are excreted in urine from the systemic circulation. The metabolites are excreted 2/3 in the unchanged form and 1/3 as a glucuronide conjugate. Total of 10% of the other minor metabolites are also excreted in the urine. The lower renal clearance rate of ESL in comparison to the glomerular filtration rate (20 mL/min < 80-120 mL/min) in healthy subjects is indicative of renal tubular reabsorption[62-64].

5.5. Specific populations (Geriatrics, gender and race)

The pharmacokinetic of ESL in elderly subjects is found to be unaffected with creatinine clearance of >60 mL/min in comparison to the subjects of age 18-40 years. Therefore, in geriatrics, no ESL dose adjustment is required. Pharmacokinetics was unaffected in healthy subjects' studies in term of gender. A clinical study involving Caucasian (n=849), Black (n=53), Asian (n=65) and other (n=51) population did not find any relevant effect of race on the pharmacokinetics of ESL.

ESL metabolites are mainly eliminated by renal excretion. A slightly slower elimination rate was observed in renal impairment patients when compared to healthy subjects. The elimination rate in renal impairment patients and healthy subjects were noted to be 10.2 mL/min and 17. 3 mL/min, respectively. However, dose adjustment is required in the patients with creatinine clearance below 50 mL/min[65-67].

5.6. Hepatic impairment

After multiple oral doses of ESL in healthy subjects, pharmacokinetics was evaluated on the basis of 7-9 points on the Child-Pugh assessment. No relevant effect of ESL clearance was observed in mild or moderate hepatic failure patients hence these patients don't require any dose adjustment[56,68,69].

6. Safety and tolerability

Safety and tolerability of ESL were evaluated by several studies in various diverse regions. Commonly reported adverse events includes hyponatraemia (114), convulsion (48), dizziness (29), fatigue (25), blood sodium decreased (21), vertigo (18) and rash (17)[70-74]. Rogin *et al*[75] performed a study of pooled analysis on the adult patients (n=825) with refractory partial onset seizures to evaluate the tolerability of ESL as an adjuvant therapy. They were given OD dose of ESL 800 mg (n=415) or 1 200 mg (n=410) while 426 patients received placebo only. Apart from blurred vision, all treatment showed a dose response relationship. Commonly occurred adverse events were found as:

Dizziness: 19.8% (800 mg), 28.3% (1 200 mg), 9.4 % (placebo); Somnolence: 12.5% (800 mg), 14.9% (1 200 mg), 9.4 % (placebo); Headache: 12.5% (800 mg), 14.9% (1 200 mg), 9.4 % (placebo).

Krauss *et al*[76] accomplished a pooled analysis to evaluate the effects of starting dose and dose titration scheme in ESL treatment patients. It was observed that ESL 800 mg 'without-titration' group and the ESL 800 mg 'with-titration' group varies a lot in treatment-emergent adverse events in the second week of treatment. The patients who do not go dose titration showed more adverse events. Similarly, 800 mg initiated dose of ESL showed more adverse events in comparison to 400 mg dose. Authors further reported that 1 200 mg dose exhibits more rashes as compared to 800 mg dose. Whereas, when patient initiated with 800 mg dose the rashes were not found to be high in comparison to 400 mg dose[76].

Costa *et al*[77] conducted a phase Ⅲ, multicentre open-label non controlled study. This study involved 72 patients who were treated with one or two AEDs with age ⩾65 years and had at least two partial onset seizures during two month baseline period (treated with 1-2 AEDs). Based on dose-individual response, the dose was maintained (400-1 200 mg) for 26 wk. Dizziness, somnolence, fatigue, convulsion and hyponatraemia were the commonly observed adverse events and were of mild to moderate intensity[77].

Several other studies were conducted to evaluate the safety and tolerability of ESL. Dizziness, nausea, somnolence and hyponatraemia were the commonly noted adverse events. A total of 2.7%-6.6% patient who were given ESL showed adverse events in these studies[78-80].

7. Toxicology

Some of the important studies conducted to investigate the toxicological profile of ESL are summarized in Table 1.

Table 1

Toxicology study of ESL.

Type of study	Experiment	Conclusion
Carcinogenesis	The two-year carcinogenicity study in mice. ESL was administered orally at doses of 100 mg/kg/day, 250 mg/kg/day and 600 mg/kg/day.	It was observed that at dose 250 mg/kg/day, 600 mg/kg/day in female and 600 mg/kg/day in male increased the hepatocellular adenomas and carcinomas. This dose was not related to the enhancement of tumours[81].
Mutagenesis	*In vitro* Ames assay was performed in mammalian cells.	ESL was found to be nonmutagenic in the *in–vitro* assay. It was also not clastogenic in human peripheral blood lymphocytes and in *in–vivo* mouse micronucleus assay[27].
Impairment of fertility	ESL was orally administered at the dose of 150 mg/kg/day, 350 mg/kg/day and 650 mg/kg/day to male and female mice. The dosing was done prior to and throughout the mating period further, it was continued till gestation day 6 in the female.	At all doses, it enhanced the embryo lethality[81].

8. Drug interaction

8.1. Human liver microsomes

ESL does not have any effect on CYP isoforms—CYP1A2, CYP2A6, CYP2B6, CYP2D6 and CYP2E1, CYP3A4, and CYP4A9/11[82]. ESL have minimal or no inhibitory effects on human liver microsomes and on some enzymes like UGT1A1, UGT1A6 and the epoxide hydrolase[83]. CYP2C9-mediated 4-hydroxylation of tolbutamide is moderately affected by ESL. Bialer *et al*[56] illustrated that ESL in fresh human hepatocyctes does not induce phase Ⅱ hepatic enzymes, CYP1A2, and CYP3A4, responsible for glucuronidation and sulfation[56]. Interestingly, ESL was shown to inhibit CYP2C19 at therapeutic concentration[84]. Incubation of 14C ESL with other AEDs (acetazolamide, clobazam, clonazepam, gabapentin, lamotrigine, phenobarbital, primidone and valproic acid) does not inhibit ESL metabolism[85].

8.2. Population pharmacokinetics studies

In ESL phase Ⅲ clinical studies, epileptic patients were administered concomitantly with other AED such as CBZ (n=526),

lamotrigine (n=203), and valproic acid (n=209). The pooled population pharmacokinetic analysis concludes that oral clearance of topiramate CBZ and lamotrigine get enhanced by 15%, 14% and 12% respectively. The clinical significance of this enhancement in oral clearance was not observed, hence the study does not recommend dose adjustment. Also, ESL does not affect the oral clearance of clobazam, gabapentin, levetiracetam, phenobarbital, phenytoin and valproic acid[86].

8.3. Interactions with other AEDs

8.3.1. Phenytoin, phenobarbital, and carbamazepine

A study reported that the co-administration of ESL (1 200 mg/day) and phenytoin (300 mg/day) in healthy patients (n=16) for 27 d caused enhancement in AUC and C_{max} by 30%-35% which is probably due to the inhibition of CYP2C19 by ESL. The geometric mean ratio was 117%-146% BIAL. If ESL is concomitantly administered with phenytoin, the dose needs to be decreased. ESL oral clearance is enhanced if the patient is administered phenytoin, phenobarbital, and CBZ. If ESL is concomitantly administered with CBZ, it increases the probability of adverse events as compared to the ESL concomitantly administered with other AEDs[83,87].

8.3.2. Lamotrigine

Both ESL and lamotrigine are metabolised by glucuronidation pathway. A study carried out in 16 healthy subjects in which ESL and lamotrigine were co-administered for duration of 19 d. The AUC, C_{max} for ESL and lamotrigine were noted to be 95%, 96% and 88%, 86%, respectively. The data indicated that there was no substantial pharmacokinetic interaction between ESL and lamotrigine in the healthy subject and therefore their co-administration does not require dose adjustment[88].

8.3.3. Topiramate

Concomitant administration of ESL and Topiramate have no relevant change in ESL plasma exposure but Topiramate plasma exposure decreases by 18%, and the reason for this decline plasma concentration is the enzyme induction[89,90].

8.3.4. Other AEDs

Apart from above mentioned drugs Clobazam, gabapentine, levetiracetam, topiramate and valproic acid do not exhibit any significant affects on ESL plasma exposure (BIAL-data on file). Therefore no dose adjustment is recommended for any of these AEDs[89].

8.4. Interactions with other drugs

8.4.1. Oral contraceptives

A study involving 20 healthy females reported that ESL lowers and alters the effectiveness of oral contraceptives if ESL and oral contraceptives are used concurrently. Therefore a woman on ESL treatment is recommended to consider other contraception methods[91-93].

8.4.2. Warfarin

Concomitant use of ESL and warfarin leads to a significant decrease in (S)-warfarin (potent enantiomer) plasma exposure level. However, no significant effects were noted on (R)-warfarin. The (S)-warfarin C_{max} and AUC were noted to be 81% and 77% respectively[94-96].

8.4.3. Simvastatin

Published data recommend adjusting and increasing the dose of simvastatin whenever simvastatin is used concomitantly with ESL. The simvastatin undergoes CYP3A4-mediated oxidative metabolism. Therefore, CYP3A4 induction by ESL is the reason behind this pharmacokinetic interaction which requires elevated simvastatin dose[97].

8.4.4. Metformin

A study by Rocha *et al*[98] demonstrated that ESL had no clinical significance on metformin pharmacokinetic. The metformin plasma exposure was also found to be unaffected by ESL. A two way cross over, randomized open label study was performed in the healthy patient (n=20). After pre-treatment with ESL (1 200 mg/day), single dose metformin (850 mg) was administrated. The metformin C_{max} and AUC were found to be 88% and 95% respectively and hence no significant effects of ESL on metformin was observed[98].

8.4.5. Digoxin

A two-way crossover, randomized on healthy patients (n=12) showed that ESL does not have any clinically significant effect on digoxin pharmacokinetics; therefore no dose adjustment is recommended[99].

9. Contraindications

ESL is contraindicated in some dermatologic reactions such as Stevens-Johnson Syndrome[26,28] and therefore use of ESL should be discontinued. ESL is also contraindicated in drug reaction with eosinophilia and in symptoms of multiorgan hypersensitivity. The multiorgan hypersensitivity is characterised by fever, rash, lymphadenopathy, eosinophilia and other organ failure. If alternative etiology for symptoms was unable to develop then ESL should be discontinued. Rarer report of anaphylactic reactions and angioedema are also reported[100,101].

10. Adverse reactions

10.1. Suicidal behaviour and ideation

ESL was found to augment depression of central nervous system (CNS), consequently increasing the risk of suicidal thoughts, behaviour and indication of depression. ESL administration may also cause mood swings in some patients[67,101,102].

10.2. Serious dermatologic reactions

ESL may lead to Stevens-Johnson syndrome. It causes serious or sometimes fatal dermatologic reactions. It may also lead to toxic epidermal necrolysis[68,103].

10.3. Drug reaction with eosinophilia and systemic symptoms/ Multiorgan hypersensitivity

ESL administration may cause Drug Reaction with Eosinophilia and Systemic Symptoms. It is known as Multiorgan Hypersensitivity which may be fatal or life-threatening. It is characterised by fever, rash, lymphadenopathy, hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis and viral infection. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately[103,104].

10.4. Anaphylactic Reactions and Angioedema

ESL administration infrequently causes anaphylactic reactions. Laryngeal edema caused by anaphylaxis and angioedema can be fatal. It is suggested that ESL should be discontinued if a patient is found to have any of these conditions[67,104].

10.5. Hyponatremia

ESL may cause hyponatremia. In a controlled epilepsy trial more percentage of ESL treated patients experienced lower sodium values in comparison to the placebo-treated patients. The effects arose in first eight weeks of treatment. All effects were found to be dose-related. Hyponatremia due to ESL may lead to serious and life threatening complications which include seizures, nausea, vomiting, dehydration, severe gait instability and injury. Serious cases required hospitalization. Hyponatremia further causes hypochloremia. The dose of ESL should be reduced or discontinued depending on the patient's severity[69,105].

10.6. Neurological adverse reactions

10.6.1. Dizziness

Dizziness, ataxia, vertigo, balance disorder, gait disturbance, nystagmus and abnormal coordination were caused by the administration of ESL. A controlled epilepsy trial performed at the doses of 800 mg and 1 200 mg/day showed 26% and 38% of these events respectively when compared to 12% of placebo patients. It was found that events were more often serious in ESL treated patients than in placebo patients (2%, 0%). Increased risks of these events have been found in titration period and in geriatrics patients as compared to maintenance period and younger ones[68,104,106].

10.6.2. Somnolence and fatigue

Dose dependent increases in somnolence and fatigue-related adverse reactions like fatigue, asthenia, malaise, hypersomnia, sedation, and lethargy was observed after ESL administration. The controlled epilepsy trials revealed that these events were reported in placebo patients (13%), randomized patients with 800 mg/day (16%) and 1 200 mg/day (28%). The event was found to be serious in 0.3% of patients and caused discontinuation in 3% patients[68,104,105].

10.6.3. Cognitive dysfunction

Cognitive dysfunction including memory impairment, disturbance in attention, amnesia, state of confusion, aphasia, speech disorder, slowness of thought, disorientation and psychomotor retardation are increased by ESL therapy a in dose dependent manner. The controlled epilepsy trials revealed the placebo patients (1%), 800 mg/day ESL (4%) and 1200 mg/day ESL patients (7%) showed these events. The drug administration caused seriousness and discontinuation in 0.2% and 1.0% of the patients[69,102,103].

10.6.4. Visual changes

Diplopia, blurred vision, and impaired vision are some of the dose dependent events caused by ESL. Total of 16% randomized patient who were administered ESL in controlled epilepsy trials showed these events when compared to 6% of placebo patients. About 0.7% and 4% of ESL treated patient show seriousness and discontinuation respectively. Titration period (compared to the maintenance period) and geriatric patients (compared to younger adults) illustrate high risk of these events[102, 105].

10.7. Withdrawal of AEDs

ESL may enhance the risk of high seizure frequency and status epilepticus with concomitant use of other AEDs. So it is recommended to withdraw the other AEDs to avoid adverse events[69, 106].

10.8. Drug induced liver injury

ESL administration leads to hepatic effects which are more than three times mild to moderate in elevation of the transaminases. It was suggested to have regular baseline evaluations of liver function tests (LFTs). It has been recommended to discontinue ESL in jaundice and other liver injuries[67,107].

10.9. Abnormal thyroid function tests

ESL administration lowers the serum T3 and T4 (free and total) values in a dose dependent manner[106,108].

11. Overdosage

ESL overdose leads to symptoms like hyponatremia, dizziness, nausea, vomiting, somnolence, euphoria, oral paraesthesia, ataxia, walking difficulties, and diplopia. Unfortunately, there is no specific antidote for the overdose of ESL. Symptomatic and supportive

treatment is recommended for overdose toxicity. The overdose of ESL may be overcome by the removal of the drug by gastric lavage and/or inactivation by administering activated charcoal (adsorbant). Based on patients clinical situation, haemodialysis may be recommended and partial clearance of ESL may be achieved by standard haemodialysis procedures[109-111].

12. Conclusion

ESL, a third generation, single enantiomeric dibenzazepine family member is limited to partial-onset and generalized tonic-clonic seizures. In the diverse model of species, ESL undergoes extensive first pass metabolism to its major active metabolite eslicarbazepine. ESL is found to be effective as adjunctive therapy in adult patients with refractory partial-onset seizures. The most promising dose of ESL is between 800 and 1 200 mg. ESL monotherapy patients experienced a fall in seizure frequency when compared with baseline. When ESL is used as a monotherapy the relatively elevated completion rate and the adverse events profile at doses of 1 200 and 1 600 mg once daily demonstrate that ESL is efficacious and well tolerated. ESL not only confirmed a therapeutic effect as the add-on treatment for partial-onset seizures in adults but also sustained efficacy during long term study. ESL has minimal adverse effects like dizziness, somnolence, headache, nausea and vomiting. The drug has a distinct mechanism of action, posology and pharmacokinetic profile as compared to other existing AEDs. It exhibits linear pharmacokinetics in both genders with moderate liver impairment. It requires dose adjustment in renal impairment patients because it is eliminated primarily by renal excretion. ESL is the most acceptable AED as it has least drug-drug interactions at pharmacodnamic and pharmacokinetic level. Phenobarbital, phenytoin, and carbamazepine may induce ESL clearance and oral contraceptive decreases plasma exposure in a dose-dependent manner thus it is recommended to be used with precautions in female.

Conflict of interest statement

We declare that we have no conflict of interest.

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