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Preliminary Evaluation of the Antiepileptic Activity of Lacosamide in Libyan Epileptic Center.

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Abstract: Lacosamidewas recently approved as an antiepileptic drug by the United Statesand European Union. Lacosamideis used as an adjunctive therapy in the treatment of intractable partial-onset seizures in patients 16-17 years of age and older. Lacosamide introduced to Ali Askar Hospital, Tripoli-Libya, in tablet (50-100mg)and syrup dosage forms (10mg/ml).This study was performedon 61 patients (between the years of 2013 to 2015).The purpose of this study was to evaluate the safety and efficacy of oral lacosamideadministration as a concomitant therapy with multiple antiepileptic drugs (AEDs) with intractable epilepsy.Seizure frequency for patients with intractable partial epilepsy were recorded and compared to the seizure frequency after adding lacosamide to their prior treatment regimen. 74 % had reduction in seizure frequency with lacosamide and (5%) of seizure freedom. The non-responders to lacosamide were13%. While another 13% get worse with this drug. Complex partial seizures recorded the highest ratio in this study according to the type of seizures. In conclusion, adjunctive lacosamide was safe, efficacious, well tolerated and dramatically reduced seizures in patients with intractable epilepsy who had failed by otherAEDs. However, epilepsy still can be controlled but not totally cured.

Keywords: Epilepsy, Antiepileptic drugs,Lacosamide, Partial seizures, Seizure free.

1 Introduction

Many considerations and therapeutic advances should be taken in the classification, diagnosis, and treatment of epilepsy. The first step in evaluation of the person with epilepsy is determining whether the seizures are partial or generalized in onset; this determination will guide further evaluation and is mandatory in choosing an antiepileptic drug (AED). With new AEDs approved for use in epilepsy by the US Food and Drug Administration since 1993, the choice of AED has become more complex and it is impossible to predict whether a patient will respond favorably to a drug based on clinical features or clinical laboratory results [2]. AEDs have many different mechanisms of action, but there does not seem to be a strong base of evidence to demonstrate that AED choice should be based on mechanism of action. Clinical trials of the new AED lacosamide suggests that combining this AED with another AED that has minimal or no activity at the sodium channel may lead to better tolerability and efficacy [12].
Thus, treatment of epilepsy often imposes an exposure to various antiepileptic drugs (AEDs) and requires long-term commitment and compliance from the patient [1]. A significant proportion of patients with epilepsy remain medically intractable. For those patients with medically refractory epilepsy, combined administration of AEDs or the use of new AEDs is an appropriate therapeutic option.

Lacosamide is an antiepileptic drug that was approved by the European Commission (2008) and the US FDA in 2008 as an adjunctive therapy in the treatment of partial onset seizures in patients≥16 years of age and older [2].Lacosamide, (R)-2-acetamido-N-benzyl-3-methoxypropionamide, is an amino acid with a novel anticonvulsant activity [3,4]. Lacosamide is available for oral and intravenous use. Lacosamide has a linear pharmacokinetic profile with high oral bioavailability [**Table 1**]. Studies in healthy volunteers demonstrated that lacosamide is rapidly and completely absorbed [6, 7].Peak serum concentrations occur at 1-2 hours after oral intake, and the elimination half-life of lacosamide is about 13 hours [5,8].The pharmacokinetics of both oral and intravenous lacosamide are dose-proportional (up to 800 mg).

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Animal studies showed that lacosamide exhibits two novel mechanisms of action; it selectively enhances slow inactivation of voltage-gated sodium channels without affecting fast inactivation, which may normalize neuronal firing thresholds [9,10] results in the stabilization of hyperexcitable neuronal membranes. In preclinical experiments, lacosamide has also been shown to bind to collapsin response mediator protein-2 (CRMP-2), which is involved in neuronal differentiation, regulation of gene expression, polarization and axonal outgrowth [9,11]. However, the precise mechanisms by which lacosamide exerts its antiepileptic effect in humans are not fully understood. Nevertheless, the role of CRMP-2 binding in seizure control is also unknown until now, but it may be a factor in the disease modifying potential of lacosamide [12]. The strength and limitation of lacosamide for patients of epilepsy has been practically taken in consideration(**Table 2**).

Since there is no any previous studies that are conducted on patients attending inthe Epileptic Centers in Libya, this preliminary study was carried out to evaluate the effectiveness, efficiency and safety of this drug.

Aim The purpose of this study is to evaluate the safety and efficacy of oral lacosamide administration as an adjunctive therapy with multiple AEDs for the reduction of the number of seizures in patients with intractable epilepsy (Epilepsy-unit at Ali Omar Asker Hospital-Libya).

2 Methods

A retrospective study was performed on 61 patients with intractable epilepsy who received Lacosamide at epilepsy-unit during a period of 2013 to 2015. Lacosamide(Vimpat)®introduced to the epilepsy-unit,Ali Omar Askar hospital on April 2013 in tablet and syrup dosage forms (50-100mg and 10mg/ml, respectively). The general strategy is to increase the medication dose until either the seizures are controlled, or until dose-limiting side effects appear.

Data were obtained from epilepsy-unit medical records, doctors and the hospital pharmacy record. Efficacy was evaluated by comparing seizure frequency of patients with intractable partial epilepsy on their prior antiepileptic drugs to the seizure frequency after adding lacosamide to their treatment regimen. Gender, ages, and types of epilepsy are recorded in all 61 patients. Mean changes in seizure frequency, its % reduction, % increase, % freedom and those who are donot respond to the treatment and side effects were calculated.

The primary assessment of efficacy was based on the change in seizure frequency [16]. Secondary efficacy parameters included percent change in seizure frequency, achievement of seizure-free status and proportion of seizure-free days [16].

3 Results

Seizures were reduced in 74% (Fig.1),while increased by 13% inpatients post administration of lacosamide(Fig. 2).Epilepsy is usually controlled, but not cured. However, lacosamide recorded 5% of seizure freedom (Fig. 3). Thirteen percentage of patients were not responding to lacosamide (Fig. 4). No differences were found between male and female in the cases recorded (gender independent). Complex Partial Seizures recorded the highest ratio in this study.In all patients receiving lacosamide, dizziness (18%), vision disturbances (13%), headache (10%), confusion (8%), drowsiness(7%), nausea (5%), were the most common adverse effects (Fig. 5&6).Not all patientsperformed clinical lab investigations before and during lacosamide therapy (Fig.7).Complex Partial Seizures recorded the highest ratio in this study according to the type of seizures (Fig. 8).

4 Discussion

The treatment goal for a patient with epilepsy is eliminating seizures while at the same time avoiding adverse events. Lacosamideas a new anticonvulsant has a favorable pharmacokinetic profile and a proposed novel mechanism of action, with common adverse effects. This study found that the adjunctive therapy withlacosamide was safe, efficacious, and well tolerated since it significantly reduces seizures in patients with intractable epilepsy who had failed by multiple anticonvulsants. These findings suggest a positive effect on quality of life with adjunctive lacosamide therapy added into the treatment paradigm. The general strategy which is followed in the epilepsy unit in Libya is to increase the medication dose until either the seizures are controlled, or until dose-limiting side effects appear. However, it is not possible to predict who will suffer from side effects or at what dose the side effects will appear.Thus, cautionshould be applied when interpreting any of such observations.

Results from many clinical studies also demonstrate that lacosamide is well tolerated and effective in controlling partial-onset seizures as adjunctive therapy. Lacosamide expands treatment options for patients with partial epilepsy and may provide significant benefit to patients with refractory seizures. Clinical study also supports the safety of an intravenous lacosamide infusion duration as short as 15 min for short-term (2-5 days) replacement for patients temporarily unable to take oral lacosamide [13]. There was no significant relationship between lacosamide high doses and the presence of side effects during 12 months of use [14,18]. lacosamide with simultaneous tapering of traditional sodium channel AEDs had marked reduction in CNS-related adverse events compared with patients treated [14].

Few trials assessing the efficacy of various AEDs, and none of them provide evidence of a clear first choice drug. Adverse effect profiles of the new generation of AEDs

generally show better tolerability, but the choice of AED must be individualized because the adverse effect profiles of the newer AEDs differ widely. One area where the new AEDs consistently outperform the older AEDs is pharmacokinetic profile. Three new AEDs have no hepatic metabolism or protein binding, and others have minimal drug-drug interactions [19]. Ultimately, selection of an appropriate agent involves matching a patient to a medication, or combination of medications, with the best record of efficacy while avoiding issues of tolerability and unwanted drug interactions (specifically tied to the needs of a given patient). Despite major advances in AED development, approximately one-third of people with epilepsy will have incomplete control of seizures no matter which AED is used alone or in combination, emphasizing the need for more effective AEDs [20]. Patients with medication-resistant epilepsy may be candidates for epilepsy surgery, a highly effective treatment that is underutilized in this population.

Table 1. Main properties of lacosamide.

Indications	Adjunctive therapy for partial seizures (≥16 years)
Approval status	Approved by both EMEA, FDA
Mode of action	Selective enhancement of slow inactivation of voltage-gated sodium channels
Starting dose	100 mg/day
Therapeutic dose	200–400 mg/day
Half-life (h)	13
Time to C_{max} (h)	1–4
Oral bioavailability (%)	~100
Protein binding (%)	<15

EMEA, European Medicines Agency; FDA, Food and Drug Administration (U.S.) [12]

Table 2. Practical considerations of lacosamide for patients with epilepsy.

Strength of lacosamide	**Limitation of lacosamide**
• Novel mechanism of action. • Clean pharmacokinetics. • Rapid onset of action. • Low drug interactions. • Available intravenous solution. • No interaction with oral contraceptives. • Low incidence of sedation, rash or weight gain.	• High incidence of dizziness. • Required dose adjustment in patients with renal and hepatic impairment. • Potential PR prolongation on EKG. • Unknown efficacy and safety in children.

EKG, electrocardiogram; PR refers to PR interval in the EKG measurements[12].

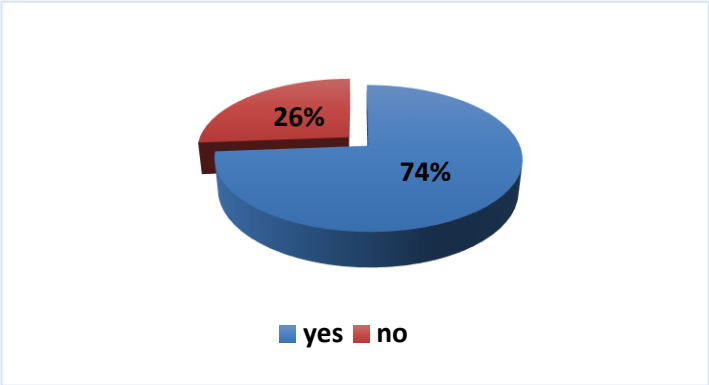

Figure 1. Percentage of seizure reduction by Lacosamide

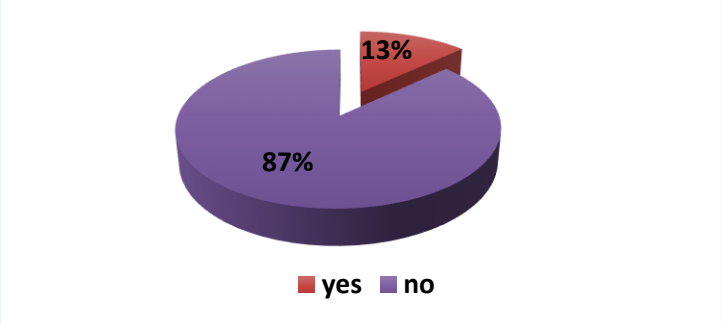

Figure 2. Percentage of increase in seizure by Lacosamide.

Figure 3. Percentage of freedom by Lacosamide

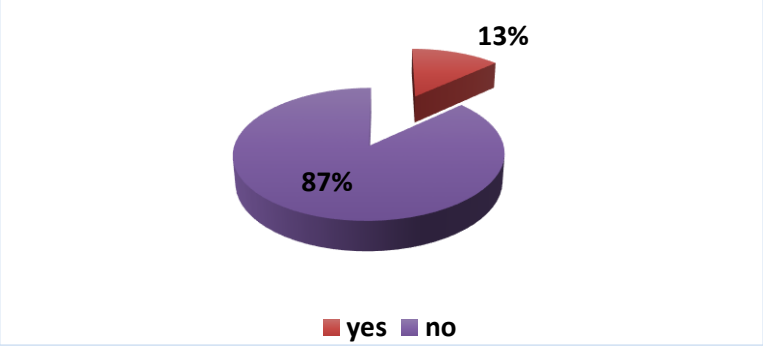

Figure 4. Percentage of patientsnot respond to Lacosamide

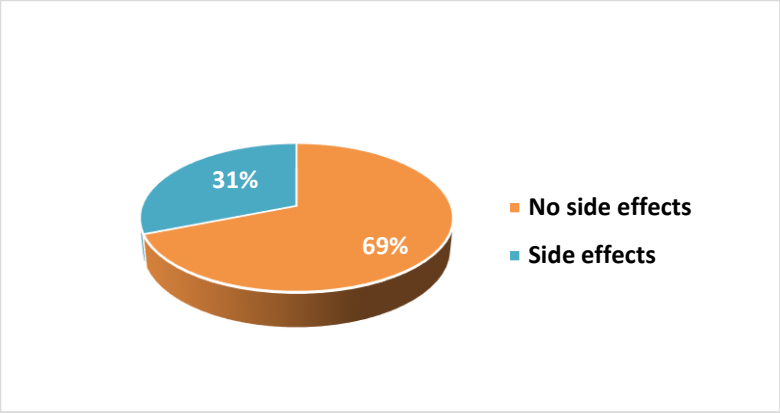

Figure 5. Percentage of side effects in patientstreated with Lacosamide.

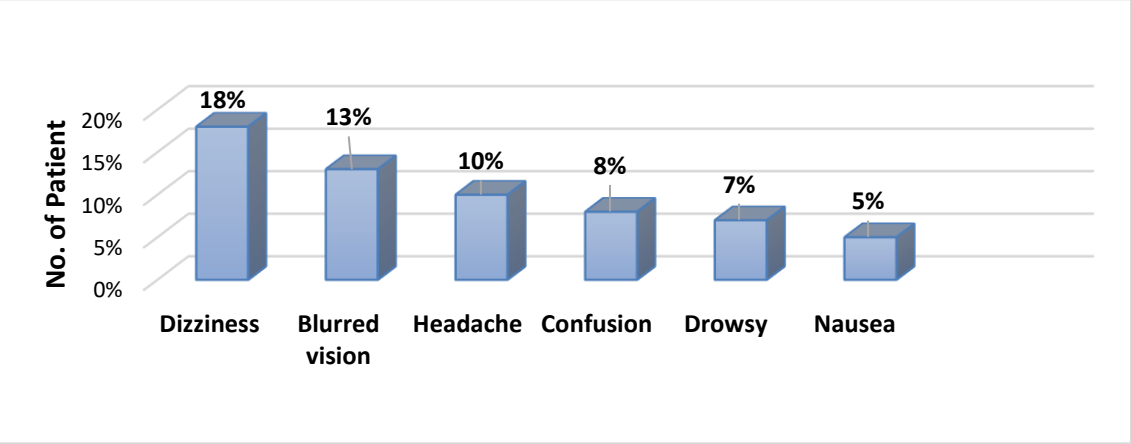

Figure 6. Side effects of Lacosamide

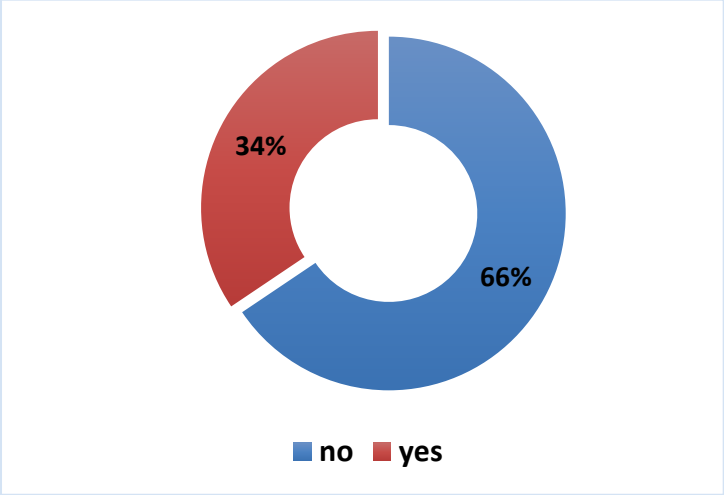

Figure 7. Percentage of patients performed clinical lab

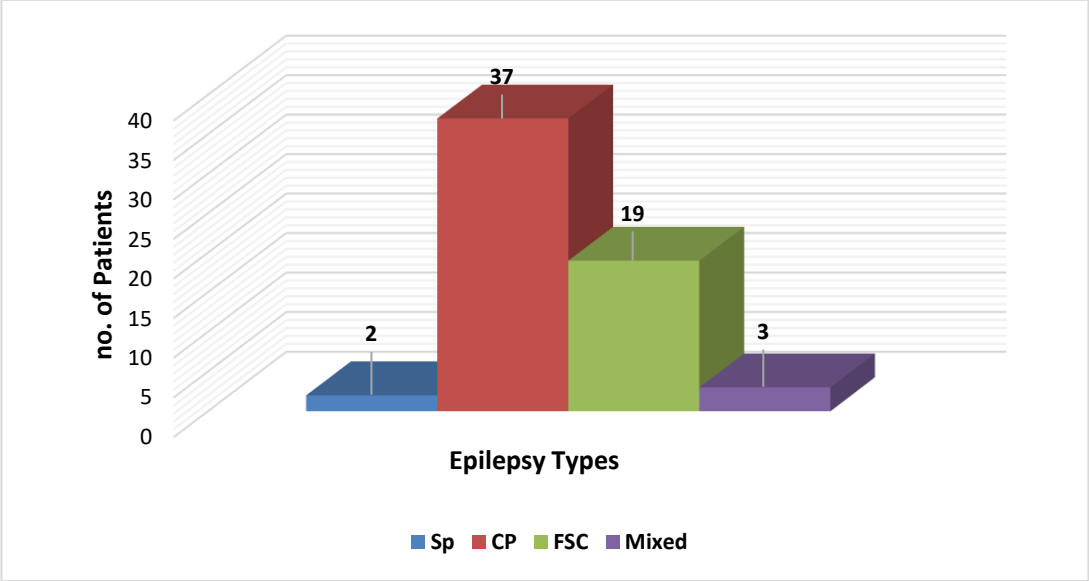

Figure 8. Types of Epilepsy recorded.

*Sp:Simple partial seizure CP: Complex partial seizure, FSC: Focal secondary generalized seizure, Mixed:Simple and Complex partial seizure.

5 Conclusions

lacosamide significantly reduced seizure frequency in patients with uncontrolled partial-onset seizures. Along with favorable pharmacokinetic and tolerability profiles, these results support further development of lacosamide as an AED.

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