Briveracetam and Seletracetam – two new third-generation antiepileptic drugs

Briweracetam i Seletracetam – dwa nowe leki przeciwpadaczkowe trzeciej generacji

Magdalena Chrościńska-Krawczyk[1,2], Mirosław Jasiński[1,3]

[1]Department of Neurology, Medical University of Lublin
[2]Department of Pathophysiology, Medical University of Lublin
[3]Department of Neurological Nursing, Faculty of Nursing and Health Sciences, Medical University in Lublin

STRESZCZENIE

Jednym z najczęściej występujących zaburzeń neurologicznych jest padaczka, charakteryzująca się nawracającymi napadami drgawkowymi. Chorobą tą dotkniętych jest ok. 50 mln. osób na całym świecie, co stanowi 1–3% populacji. Padaczka zaburza funkcjonowanie społeczne oraz stwarza problemy natury psychologicznej u dotkniętych nią osób. Pomimo dużego postępu w badaniach klinicznych i doświadczalnych terapia prowadząca do długotrwałych remisji jest nieskuteczna w 30% przypadków. Możliwymi przyczynami oporności na leki przeciwpadaczkowe mogą być podłoże genetyczne, choroby towarzyszące oraz substancje osłabiające działanie leków przeciwpadaczkowych, np. kofeina i aminofilina. Obecnie dostępnych jest ok. 20 nowych, należących do trzeciej generacji, leków przeciwpadaczkowych. Prawdopodobnie najlepszą opcją terapeutyczną dla osób cierpiących z powodu padaczki lekoopornej jest odpowiednia, uwzględniająca interakcje pomiędzy lekami, kombinacja dwóch lub więcej leków przeciwpadaczkowych. Opracowanie dotyczy mechanizmów działania, profilu farmakokinetycznego oraz interakcji nowych leków trzeciej generacji: briveracetamu (BRI) {(2S)-2-[(4R)-2-oxo-propylpyrrolidinyl]-butanamide} oraz seletracetamu (SEL) [pochodna (S)-_-etyl-2-oxo-pyrrolidonowego acetamidu]. Są one pochodnymi lewetiracetamu (LEV) posiadającymi 10-krotnie większe powinowactwo do białka SV2A niż lewetiracetam.

Słowa kluczowe: leki przeciwpadaczkowe, Briweracetam, Seletracetam, Lewetiracetam, padaczka

ABSTRACT

One of the most common neurological disorders is epilepsy characterised by recurrent spontaneous seizures. It is estimated that over 50 millions of people in the whole world have the disease, which means app. 1-3% population. Epilepsy not only affects the brain itself but also influences the social, vocational and psychological functioning. Despite much progress in understanding the pathophysiological processes underlying seizures, there are still about 30% of epilepsy patients that are not seizure free. There are many possible causes of this state: genetic, disease-related and drug related factors, applied substances which reduce anticonvulsant effect of antiepileptic drugs (AEDs), for example: caffeine and aminophylline. Currently there are about 20 novel AEDs which belong to the third-generation AEDs category. Probably the best therapeutic option for patients suffering from drug resistant epilepsy is the combined administration of two or more AEDs or the application of novel AEDs. This review summarizes the information on the mechanisms of action, pharmacokinetic profiles and drug interactions of novel, third-generation, antiepileptic drugs: briveracetam (BRI) {(2S)-2-[(4R)-2-oxo-propylpyrrolidinyl]-butanamide} and seletracetam (SEL) [derivative of (S)-_-ethyl-2-oxo-pyrrolidine acetamide]. They are derivatives of levetiracetam (LEV) and they have 10-fold greater affinity for SV2A protein than does levetiracetam.

Key words: Antiepileptic drugs, Brivaracetam, Seletracetam, Levetiracetam, Epilepsy

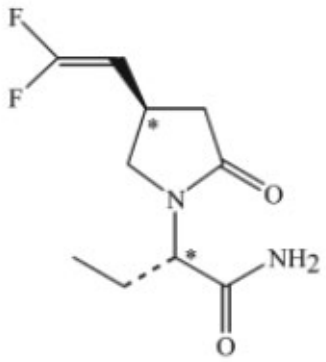
INTRODUCTION

Epilepsy is one of the most common neurological disease. Almost 1 million people in the world suffer from this disorder characterised by recurrent spontaneous seizures, resulting from excessive, uncontrolled electrical activity in the brain [1]. Epilepsy not only affects the brain itself but also influences social, vocational and psychological functioning. Drugs treating epilepsy have been available since 1857 when bromides salts were recognized as having antiseizure activity. Next, two drugs –phenobarbital and phenytoin became available in the first 50 years of the twentieth century. 16 new AEDs were discovered between 1946 and 1978. In 1993 the second wave of new drugs began [2]. Currently there are about 20 novel AEDs, which belong to the third-generation AEDs category [3], among the other are: SEL and BRI. They are derivatives of LEV substituted at the 4-position on the 2-pyrrolidinone ring [3,4] .They have 10-fold greater affinity for SV2A [4]. The other third-generation AEDs are: carabersat (CRB), carisbamate(CBM), DP-valproid acid (DP-VPA), eslicarbazepine acetate (ESL), fluorofelbamate (FFBM), fosphenytoin (FPHT), ganaxolon (GNX), lacosamide (LCM), losigamone (LSG), pregabaline (PGB), remacemide hydrochloride (RMC), retigabine (RTG), rufinamide (RUF), safinamide (SAF), soretolide

(SRT), stripentol (STP), talampanel (TLP) and valrocemide (VLR).). Probably the best therapeutic option for patients suffering from drug resistant epilepsy is the combined administration of two or more AEDs or the application of novel AEDs [3,5,6,]. Despite the progress in understanding the pathophysiological processes underlying seizures, there are still about 30% of epilepsy patients that are not seizure free [3]. There are many possible causes of this state: genetic, disease-related and drug related factors, applied substances which reduce anticonvulsant effect of AEDs, for example: caffeine and aminophylline.

The aim of this review is to summarize our knowledge about two novel, third-generation AEDs: seletracetam (SEL) and brivaracetam (BRI).

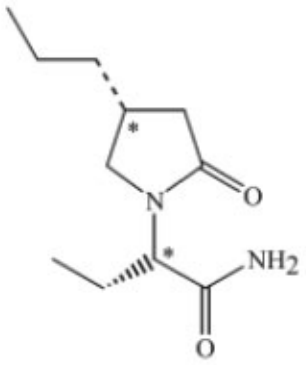
SELETRACETAM



Seletracetam (ucb 44212)

Seletracetam (SEL) [derivative of (S)-_-ethyl-2-oxo-pyrrolidine acetamide] is a new, third generation antiepileptic drug. It is a structural analogue of levetiracetam but seletracetam has 10-fold greater affinity for SV2A than does levetiracetam [3,7-10]. SV2A is a protein component of synaptic vesicles that is structurally similar to 12-transmembrane domain transporters [10]. The role of SV2A is not well known but this protein probably assists with the coordination of synaptic vesicle exocytosis and neurotransmitter release [11,3]. There is no clear mechanism how drugs bind to SV2A and lead to anticonvulsant effect [12]. The research have shown that there is a correlation between the binding affinity of seletracetam for SV2A and the degree of seizure protection afforded by these analogues in animal models [13,14]. Seletracetam reduces high-voltage activated calcium currents, but has no effect on voltage-dependent potassium or sodium currents. Also, this drug does not transform the low –voltage activated T-type calcium currents. [7,3]. This analogue of levetiracetam does not show anticonvulsant activity in acute seizure models (MES and PTZ tests) but is effective against hippocampal kindled rats and secondarily generalized motor seizures [7]. Seletracetam also protects against clonic convulsions in audiogenic seizure- prone mice and spike--wave discharges in the GAERS rats [7,3], and is 10-fold more potent than LEV in the corneal kindling [7]. Matagne et al. (2005) in their experiments have observed that SEL reduced the amplitude and number of population spikes in model in which high K^+-low Ca^+ perfusion fluid induces epileptiform field potentials in CA3 area of rat hippocampal slices [11]. Hamann et al.(2008) have demonstrated that, SEL shows antidystonic efficacy compared to levetiracetam in paroxysmal dystonia in the dt^{sz} mutant hamster [15]. The data has shown that SEL is rapidly and nearly completely absorbed from the gut [7,13,3]. Less than 10% is bound to protein. C max reaching is eliminated by metabolism and excretion in the urine, as unchanged drug (25-30%) and as an inactive carboxylic acid metabolite (55-60%). The major metabolic pathway consists of hydrolisis of the acetamide group to form the carboxylic acid metabolite [3]. Seletracetam's plasma half-life is approximately 8 h. Metabolite concentration are about ten-fold lower than those of the parent compound. The current data has shown, that SEL introduces no significant cardiopulmonary, CNS or respiratory tract effects [11]. SEL has a low ability for interaction with other drugs or of other drugs with SEL[3,11].

BRIVARACETAM



Brivaracetam (ucb 34714)

Brivaracetam (BRI) {(2S)-2-[(4R)-2-oxo-4-propylpyrrolidinyl]-butanamide}, like seletracetam, is a novel, third generation antiepileptic drug. It is a high –affinity synaptic vesicle, protein 2A (SV2A) ligand and is a 10-fold higher affinity for SV2A than LEV. [11,3]. In contrast to LEV, BRI has inhibitory activity on voltage – dependent sodium channels [11]. The recent data in corneally kind has shown that brivaracetam is more efficacious and potent than LEV in seizure modeily generalized motor seizures, secondarily generalized motor seizures in corneally kondled mice and clonic convulsions in audiogenic seizure- susceptible mice [8,11,16]. This drug does not show anticonvulsant activity in acute seizure models (maximal electroshock- induced seizure (MES) and pentetrazole test [3]. BRI induces suppression of both motor seizure severity and after discharge duration in amygdala – kindled rats, as well as spike – and--wave discharges in the Genetic Absence Epilepsy Rat from Stasbourg (GAERS) [13]. The ED50 of BRI was 1,2 mg/kg, in corneally kondled mice, 2,4 mg/kg in genetically sound--sensitive mice, and 2,6 mg/kg i.p. in GAERS [16]. There

were also studies of the anticonvulsant properties of BRI in an animal model of acute, partially drug- resistant self-sustaining status epilepticus (SSSE), which was induced by perforant path stimulation (PPS) in adult male rats. This data has shown that BRI shortened the cumulative duration of active seizures in a dose-dependent manner [11]. This drug also demonstrated potent and nearly complete seizure suppression in a rat model of acute, partially drug-resistant , self-sustaining status epilepticus induced by perforant path stimulation [17] Another results have demonstrated activity of this drug in the experimental models of neuropatic pain and essential tremor [12,18]. BRI is rapidly and almost completely absorbed after oral administration over 2 h [13]. Approximately 20% of the drug is bound to plasma proteins [3,19]. Breveracetam's renal clearance is low (0,06 mL/min/kg) and it is eliminated by hepatic metabolism. The major metabolic pathways of BRI include hydrolysis of the acetamide groups and CYP2C8 (microsomal liver cytochrome) – mediated hydroxylation [3,4]. The briveracetam's half-life elimination is about 8 h and does not depend on dose [13]. Approximately 95% of dose is recovered in urine within 72 h. [3,4,13,19]. The results of the studies have suggested that no dose adjustments due to drug interactions are required. Another studies have shown that pharmacokinetic profile of BRI in renally impaired and elderly patients is similar to that in healthy subjects. In patients with hepatic impairment was observed an increase in exposure to BRI by up to 50-60% in severely impaired subjects, and the tolerability profile of this drug in these population studies was similar to that observed in healthy people [11]. Otoul et al. (2007) in their studies monitored plasma concentrations of concomitant AEDs. They have shown that BRI did not modified the steady-state plasma concetrations of carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, topiramate or valproid acid in this population. BRI increases plasma concentrations of carbamazepine-10,11- epoxide but decreases plasma concentrations of phenytoin [20]. The other data has shown interaction between BRI and the estrogen and progestin components of a low-dose oral contraceptive and there was not any impact on suppression of ovulation [3,21].

Kastelejin-Nolst Trenite et al. studies (2007) has shown, that BRI in doses 10,20,40 or 80 mg applied in patients with photosensitive epilepsy suppresses generalized photoparoxysmal electroencephalographic (EEG) responses [22]. This drug is also being tested in patients suffering from partial- onset seizures and as an add-on treatment in patients (16-65 years) with refractory partial-onset seizures. BRI in doses 5-150 mg/day were well tolerated in patients with uncontrolled partial-onset seizures. The most frequent side effects with an incidence of >5% are: nausea, vomiting, fatigue, nasopharyngitis, anorexia, convulsion, dizziness, headache, somnolence and insomnia [23]. In the double-blind, placebo-controlled, phase IIb Van Paesschen et al. studies of adjunctive BRV (50 and 150 mg/day) in adults with uncontrolled partial-onset seizures, the primary efficacy analysis did not reach statistical significance; however, statistically significant differences compared with placebo were observed on several secondary efficacy outcomes. BRV was well tolerated [24].

The development of third-generation AEDs (e.g. BRI and SEL) gives hope for 30% of patients with drug resistant epilepsy. These drugs have better tolerability, less drug interactions, milder adverse effects and improved pharmacokinetic characteristics compared to the first-and second-generation AEDs.

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Adres do korespondencji:

Klinika Neurologii Dziecięcej Uniwersytetu Medycznego w Lublinie, ul. Chodźki 2, 20–093 Lublin, e-mail: madziachr@poczta.wp.pl