New antiepileptic drugs – an overview

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Abstract

The last ten years of the 20th century is called in neuroscience "decade of the brain". This period has brought many new antiepileptic drugs (AEDs) to the practising physician. New AEDs include: vigabatrin, lamotrigine, topiramate, tiagabine, gabapentin, oxcarbazepine, levetiracetam and zonisamide (not registered in Poland). The development of these drugs was under the current epilepsy theory (balance-disturbances between inhibitory and excitatory neurotransmitters in the brain). Mechanism of action of the new AEDs is due to increase of the GABA-system activity and/or reaction with ion-channels events in neurons.

The aim of the study was an overview of the current literature on the new AEDs in the treatment of seizures and epileptic syndromes. Data from literature show that the new AEDs are better tolerated, have fewer drug interactions and seem to affect cognitive functions to a lesser degree compared to the conventional drugs. Most of them are recommended to an add-on therapy of partial seizures with/without second generalization, although there are more evidences on efficacy of new AEDs in monotherapy. The new AEDs seemed to be similar to the conventional drugs in efficacy, but superior in tolerability. New AEDs with more selective activity and lower toxicity have been significant improved the quality of life in the epileptic patients. Numerous chemical compounds with potential antiepileptic activity are in experimental and clinical development.

Key words: epilepsy, new antiepileptic drugs.

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The last ten years of 20th century is called in neuroscience "decade of the brain". This period has brought many advances to the treatment of neurological disabilities, including epilepsy. A number of new antiepileptic drugs (AEDs) have been licensed for the treatment of seizures. The new AEDs include: vigabatrin, lamotrigine, topiramate, tiagabine, gabapentin, oxcarbazepine, levetiracetam and zonisamide (not registered in Poland). The need of marketing new drugs was refractory epilepsy and severe side-effects of classical AEDs. Although most epileptics become seizure-free with traditional therapy, 30% of them will continue to have seizures despite the use of AEDs either alone or in combination [1]. The development of new AEDs have been based under the current epilepsy theory, where seizures resulting from alteration of the balance between neuronal excitation and inhibition [2]. Mechanisms of action of the currently marketed AEDs are more selective according to the classical AEDs and include modulation of voltage-dependent ion-channels, enhancement of inhibitory neurotransmission and attenuation of excitatory transmission in the brain [3]. Only levetiracetam has a novel mechanism of action (binding to the specific protein on the synaptic plasma membrane). The majority of the new AEDs after experimental and clinical studies was initially licensed to the treatment of refractory partial-onset seizures as add-on therapy to the classical AEDs. Few of the new AEDs have been evaluated in monotherapy, including severe epileptic syndromes as infantile spasms or Lennox-Gastaut syndrome (LGS). The results of yet experiences with new AEDs are very promising.

The aim of this work was a short overview of the current literature and results of our studies on the new AEDs in the treatment of seizures and epileptic syndroms.

1. Gabapentin

Gabapentin (GBP) was the second (after felbamate-not described in this paper) new antiepileptic agent approved to the market as adjunctive therapy for partial seizures (PS). Although GBP is structurally related to the predominant inhibitory neurotransmitter in the CNS – GABA, there are no significant

evidences that GBP directly interact with GABA-system and its precise mechanism of action is still unknown [4]. Possible mechanisms of action of GBP include sodium- and calcium-channels blockade. A numerous studies on GBP as adjunctive therapy of PS demonstrated significant reduction in seizure frequency from baseline [i.e. 5]. Results of trial comparing efficacy of GBP and carbamazepine (CBZ) in monotherapy in patients with refractory partial epilepsy suggesting equivalent efficacy of both drugs, but GBP had any severe adverse effects [6]. GBP is contraindicated in the treatment of primary generalized seizures (PGS) and can make worse progress and produce myoclonic jerks [7]. The ability of rapid introduction for the patient, wide margin of safety with good tolerability and no significant drug interaction are important advantages of GBP.

2. Vigabatrin

Vigabatrin (VGB) is an irreversible inhibitor of GABA-transaminase which exerts its antiepileptic effect by increasing the level of the neurotransmitter GABA. Except for use in infantile spasms, where it is recommended as monotherapy [8], VGB is used mainly as a second line antiepileptic drug in refractory PS. As an add-on agent, VGB is well-tolerated and can be of long-term benefit in a substantial proportion of patients with intractable partial epilepsy [9]. VGB has been compared with CBZ in few monotherapy trials. The largest study recruited 459 patients who were randomised to VGB or CBZ, and was of 52 weeks duration [10]. The results showed no significant difference between drugs for the primary end point time to treatment failure, or for the outcome time to 6 month remission. However, confidence intervals around these estimates failed to meet the authors' generous definition of equivalence. Patients taking VGB had significantly earlier first seizures post-randomization, and were significantly more likely to have VGB withdrawn due to lack of therapeutic effect, whereas CBZ was significantly more likely to be withdrawn because of side effects. Results of a prospective trial from our Department indicate that VGB seems to be safe and an effective antiepileptic drug as primary monotherapy for epilepsy in children with similar proportion of side effects as CBZ [11]. VGB similar as GBP is contraindicated in PGS (excluding infantile spasms – drug of 1st choice). This drug can trigger absence – and myoclonic seizures. The most severe toxic effects occurred during VGB-therapy are visual field abnormalities, which are reversible but need periodic control [12]. The commonest psychiatric manifestation of VGB-treatment, occurred even at 16% of patients, is depression [13].

3. Lamotrigine

Lamotrigine (LTG) is a broad-spectrum agent effective in partial, absence, myoclonic and tonic-clonic seizures [14]. LTG exhibits its antiepileptic effect by blockade of sodium-channels and to a lesser degree, calcium-channels [15]. A numerous clinical trials have shown LTG's efficacy as add-on therapy in PS and PGS (including LGS). In opposite to the majority of new AEDs, LTG can be used as monotherapy in PS with/without second generalization [16]. Rash is the main problem encountered by patients starting LTG and this lead to cessation of therapy [13]. There have been reports of LTG-associated Stevens-Johnson syndrome and toxic epidermal necrolysis. Severe rashes occur more often with rapid titration and in children [17]. The risk of skin rash is higher when LTG is coadministered with valproic acid, which inhibits the metabolism of LTG. LTG is one of the most effective new AEDs, which therapeutic spectrum is similar to valproate, but high risk of severe side-effects needs slow titration schedule, especially in concomitant therapy with valproate.

4. Tiagabine

Tiagabine (TGB) similar as VGB has selective mechanism of action on GABA-system in the CNS. TGB blocks uptake of GABA into neurons and glial cells [18]. TGB is narrow-spectrum agent effective only in PS with/without secondary generalization [19] and is licensed as add-on therapy in refractory partial epilepsy. Much clinical data show that TGB is efficacious and well tolerated [19,20]. Most often occurred side-effects of TGB are dizziness and drowsiness. There are rare reports on the non-convulsive epileptic status observed during the treatment with TGB [i.e. 21].

5. Topiramate

Topiramate (TPM) has generally been considered to be a highly effective new AED. TPM is licensed as adjunctive treatment in adults and children 2 years or older with PS, PGS, and seizures associated with LGS [16]. TPM has multiple mechanisms of action, including inhibition of sodium and calcium currents, blockade of the glutamate receptors and facilitation of GABA effects at the GABA-A receptor [3]. Retrospective studies comparing efficacy and tolerability of few new AEDs have showed that psychiatric side-effects (including depression and hallucinations with psychotic symptoms) were a significant problem with TPM leading to its withdrawal. Cognitive side-effects and weight loss were also reported by a high percentage of the patients taking TPM [13]. In the same study much as 40% of the patients had to withdraw of TPM due to side-effects. Other clinically relevant adverse effect of TPM is nephrolithiasis, with a reported incidence of 1.5% [22]. Despite of risk of above mentioned side-effects TPM offers high efficacy in the treatment of almost all seizures types.

6. Oxcarbazepine

Oxcarbazepine (OXC) is an analogue of carbamazepine. It is reduced to its active metabolite, 10-11-dihydro-10-hydroxycarbamazepine (HCBZ). The metabolic pathway of OXC does not include formation of an epoxide compound. The exact mechanism of action of OXC remains unknown, but it is believed to involve blockade of sodium-channels [16,23]. The clinical efficacy and tolerability of OXC have been demonstrated in numerous trials in adults and in children. Results of these trials have showed similar efficacy of OXC (as adjunctive therapy and as monotherapy) in the treatment of PS [16,23]. Compared with older AEDs (especially with CBZ), OXC appears to have lower incidence of side-effects [23]. The most common adverse effects are usually related to the CNS (dizziness, ataxia, nystagmus) and gastrointestinal system (nausea, vomiting). Other side-effect observed during OXC-therapy is hyponatremia. The decrease in sodium levels is related to the OXC dose. Most patients experiencing OXC-associated hyponatremia are asymptomatic [23], although there are reported severe case of hyponatremia result-

ing in coma [24]. OXC does not induce its own metabolism or hepatic enzymes and does not interact with other antiepileptic drugs [16].

7. Levetiracetam

Levetiracetam (LEV) is an analogue of piracetam, a widely used nootropic agent [25]. LEV has novel mechanism of action involving an interaction with a novel binding site on the synaptic plasma membrane recently discovered to be the Synaptic Vesicle protein 2A [26]. LEV is high-effective as add-on treatment of PS in adults [27] and in children [28]. There are much trials confirming its efficacy in generalized epilepsies [i.e. 29] and LGS [29,30]. Preliminary data suggest effectiveness of LEV as monotherapy in patients with new onset seizures [31]. Side-effects of LEV-therapy are mild and rarely necessitating discontinuation of the drug [32].

New targets in epilepsy treatment

The search for antiepileptic agents with more selective activity and lower toxicity continues to be an area of intensive investigation in neuroscience. There are many chemical compounds have been tested as antiepileptic agents. The drugs in most advanced development (including clinical studies) are: atipamezole, BIA-2-093, fluorofelbamate, NPS 1776, pregabalin, retigabine, safinamide, stiripentol, talampanel, ucb 34714 and valrocemide. Part of them is chemical derivative from marketed AEDs, the other representing new structural classes of compounds, for which the precise mechanism of action in epilepsy is still unknown. First clinical trials with these compounds are very promising [33].

The development of new AEDs has expanded therapy options and offered advantages to the patient. Although clinical trials show that new AEDs are not efficacious when compare to the classical drugs, their better tolerability and fewer drug interactions have significant improved the quality of life of epileptic patients. Comparative, long-term and open further trials should be done to assess long-term efficacy and comparative features of the new AEDs.

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