Newer Anti-Epileptic Drugs in Children

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Summary

The introduction of new anti-epileptic drugs (AED) provides more options for treatment of children with epilepsy. We review indications, safety and tolerability of ten new AEDs (lamotrigine, oxcarbazepine, vigabatrin, levetiracetam, topiramate, zonisamide, felbamate, rufinamide, gabapentin and perampanel). We also make a short review of the most recent new AEDs not yet approved in pediatrics. Many issues specific for children are not addressed during the development of new AEDs, like the impact on the developing brain. New AEDs are usually approved as adjunctive therapy based on adult clinical trial. In pediatrics, the choice of a new AED for children depends on many factors including age, cognitive development, epileptic syndrome and its etiology, as well as concomitant medication.

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Key words: Newer anti-epileptic drug, childhood epilepsies, side effects

Neuere Antiepileptika für Kinder

Die Entwicklung neuer Antiepileptika (AE) hat breite therapeutische Möglichkeiten in der Epilepsiebehandlung pädiatrischer Patienten eröffnet. In diesem Beitrag werden zehn AE der neuen Generation vorgestellt (lamotrigine, oxcarbazepine, vigabatrin, levetiracetam, topiramate, zonisamide, felbamate, rufinamide, gabapentine, und perampanel), gefolgt von einer kurzer Zusammenfassung zweier für Kinder noch nicht anerkannten Medikamente. Auch wenn die neuen AE einige Besserungen in der Neuro-Pädiatrie hervorbringen konnten, werden leider spezifische Probleme, insbesondere die Folgen auf die Gehirnentwicklung, vor und bei der Vermarktung nicht untersucht. Die neuen AE sind generell als „add-on"-Mittel zugelassen, meistens nach Studien an Erwachsenen. Beim pädiatrischen Patienten ist die Wahl eines AE vom Alter, der kognitiven Entwicklung, dem epileptischen Syndrom, den Ko-Medikationen, und der unterliegenden Ätiologie der Epilepsie abhängig.

Schlüsselwörter: Neuere Antiepileptika, Epilepsien des Kindesalters, Nebenwirkungen

Nouveaux médicaments antiépileptiques pour les enfants

Le développement d'anti-épileptiques (AE) de nouvelle génération a fourni de nouvelles options thérapeutiques dans la prise en charge des épilepsies de l'enfant. Dans cet article, dix AE de nouvelle génération sont passés en revue (lamotrigine, oxcarbazepine, vigabatrin, levetiracetam, topiramate, zonisamide, felbamate, rufinamide, gabapentine et perampanel) en plus d'un court résumé des plus récentes drogues, non encore approuvés en pédiatrie. Malgré des avancées significatives, de nombreux problèmes spécifiques à l'enfant ne sont pas pris en compte lors du développement de ces drogues, comme l'impact sur le cerveau en développement. Les nouveaux AE sont habituellement approuvé en complément à d'autres AE, basé sur des essais cliniques adultes. En pédiatrie, le choix d'un nouvel AE dépend de différents facteurs incluant l'âge, le développement cognitif, le syndrome épileptique, les co-médications, et l'etiologie sous-jacente de l'épilepsie.

Mots clés : Nouveaux antiépileptiques, épilepsies de l'enfance, effets indésirables

Nuovi medicamenti antiepilettici per i bambini

Lo sviluppo dei medicamenti antiepilettici (AE) delle nuova generazione ha permesso di espandere le possibilità terapeutiche in neuropediatria. Dieci nuovi AE approvati per l'uso pediatrico (lamotrigina, oxcarbazepina, vigabatrina, levetiracetam, topiramato, zonisamide, felbamato, rufinamide, gabapentina e perampanel), oltra a due sostanze non ancora ammesse in questa fascia d'età, saranno passati in rassegna in questo contributo. Purtroppo, durante l'iter che porta alla messa sul mercato dei farmaci antiepilettici, l'industria ha poco interesse per aspetti molto importanti, particolarmente quelli che riguardano lo sviluppo del cervello nel'in-

fanzia. I nuovi AE sono generalmente approvati quali "add-on" in base a studi condotti sugli adulti. Nell'ambito pediatrico, la scelta del medicamento dipende da diversi fattori, quali l'età, lo sviluppo cognitivo, la sindrome epilettica, la sua eziologia, e la co-medicazione.

Parole chiave: Nuovi antiepilettici, epilessie dell'infanzia, effetti indesiderati

Introduction

Epilepsy is a common pediatric neurologic disorder, affecting 0.5 to 1% of all children [1]. The failure rate of a first anti-epileptic drug (AED) with a newly diagnosed epilepsy remains high, around 20% to 40%. This has been attributed to poor effectiveness and/or high frequency of adverse effects, and stimulated the search for new drugs [2, 3]. Although there is poor evidence that the newer AEDs are more effective than the older ones [4] they are usually better tolerated, have fewer interactions with other drugs, need less serum level checks and some may potentially have some neuroprotective effects [5]. These features are obvious advantages, but evidence-based data on their effectiveness and safety in children are often lacking. Hence, their use often depends on the clinician's experience [1].

We review here 10 new AEDs, i.e. lamotrigine, oxcarbazepine, vigabatrin, levetiracetam, topiramate, zonisamide, felbamate, rufinamide, gabapentin and perampanel. We focus on their use in pediatric epileptic syndromes (**Table**) and briefly review the most recent AEDs not yet approved in pediatrics.

Lamotrigine

Lamotrigine (LTG) prolongs the slow inactivation of voltage-gated sodium channels and blocks NMDA receptors [3]. It acts on generalized and focal seizures. It was initially indicated as an adjunctive therapy in Lennox-Gastaut syndrome (LGS) (Class I evidence). Since then, its efficacy was demonstrated in infantile spasms (IS), absence epilepsy (Class II evidence), epilepsy with myoclono-atonic seizures (MAE), juvenile myoclonic epilepsy (JME) and idiopathic epilepsy [7]. It has, pharmacodynamically, a synergic effect with valproic acid (VPA) in myoclonic and absence epilepsy [8]. LTG is well tolerated and may be efficacious for focal seizures in patients as young as 1 month old [9].

The clearance of LTG is increased by carbamazepine (CBZ) and phenytoin (PHT) and decreased by VPA [3]. Besides common side effects like dizziness, somnolence, headache or ataxia, severe immune-allergic skin reaction like Stevens-Johnson syndrome can occur more commonly in children. A rapid titration or the simultaneous use of VPA are risk factors [10, 11]. Worsening of myoclonic seizures was reported in JME and Dravet syndrome (DS) but is not an absolute contraindication in these syndromes [4, 12].

Oxcarbazepine

Oxcarbazepine (OXC) is a keto derivative of CBZ. It blocks voltage-gated sodium channels. Potassium conduction potentiation, inhibition of calcium channels and inhibition of NMDA receptors are additional described mechanisms [3, 4]. It is indicated in adjunctive therapy for focal seizures in children ≥ 2 years of age and in monotherapy in children ≥ 4 years of age (Class I evidence) [13]. OXC was shown to be equivalent to CBZ and PHT in its efficacy with a higher tolerability (Class I and II evidences) [14-16].

Acting on different liver cytochromes, OXC may decrease phenobarbital (PB) and PHT levels [3]. Side effects include somnolence, ataxia, diplopia, tremor, dizziness and gastro intestinal disturbances. CBZ-induced severe cutaneous adverse reactions, like Stevens-Johnson syndrome, have been associated with HLA-B*1502 in Asian populations. About 25-33% of patients with a hypersensitivity reaction to CBZ also have an allergic reaction to OXC [17]. Expert opinion recommend HLA-testing in patients from Southeast Asia before initiating OXC. For patients who test positive for B*1502, OXC should be avoided [18].

Hyponatremia is a well-known side effect of OXC due to its effects on anti-diuretic hormone, distal convoluted tubule in the kidney and vasopressin. It is usually asymptomatic and rare in children. Natremia returns to normal levels with dose reduction, drug discontinuation or fluid restriction [7, 17, 19]. OXC can worsen myoclonic and absence epilepsy.

Vigabatrin

Vigabatrin (VGB) is an inhibitor of GABA-aminotransferase increasing GABA levels in the central nervous system [20]. Its main indication in children is in IS. Its efficacy was demonstrated whatever the cause of the IS [21], but especially in tuberous sclerosis complex (TSC), with more than 90% of good responders [4, 22]. It can also be used as an adjunctive therapy in focal and generalized seizures [4, 20]. It has no major drug interaction.

The most serious potential side effect is an irreversible visual field constriction (VFC) [23]. In an observational cohort study of children with IS, the authors showed VFC diagnosed by electro-retinogram (ERG) in 5.3% of children after 6 months of VGB-exposure and 13.3% after 12 months [24]. The occurrence of VFC was not influenced by age at initiation of VGB, gender, or dosage. Authors recommend minimizing VGB treatment to 6 months to reduce the prevalence of VFC in children with IS [25]. When VGB is the only efficient

Table: Use of newer anti-epileptic drugs in pediatric epilepsy syndromes: preferred treatment options based on expert consensus [6]

Syndrome	AED	Dose	Treatment line
Infantile Spasms	VGB	50 to 150 mg/kg/d	1st (TSC)
	TPM	1 to 10 mg/kg/d	2nd-3rd
	LTG	1 to 7.5 mg/kg/d	2nd-3rd
Dravet Syndrome	TPM	1 to 7-8 mg/kg/d	1st-2nd
	LEV	20 to 50 mg/kg/d	2nd-3rd
Epilepsy with Myoclonic Atonic Seizures	LTG	1 to 7.5 mg/kg/d	2nd-3rd
	TPM	1 to 7-8 mg/kg/d	2nd-3rd
	LEV	20 to 50 mg/kg/d	1st-2nd
Lennox-Gastaut Syndrome	RUF	10 to 45 mg/kg/d	1st-2nd
	TPM	1 to 7-8 mg/kg/d	1st-2nd
	FBM	15 to 45 mg/kg/d	2nd-3rd
	LTG	1 to 7.5 mg/kg/d	2nd-3rd
Idiopathic and Non Idiopathic Focal Epilepsies	LEV	20 to 50 mg/kg/d	1st-2nd
	OXC	8 to 45 mg/kg/d	1st-2nd
	TPM	1 to 7-8 mg/kg/d	2nd-3rd
	GBP	10 to 90 mg/kg/d	1st-2nd
Genetic (Idiopathic) Generalized Epilepsies			
Childhood Absence Epilepsy	LTG	1 to 7.5 mg/kg/d	2nd-3rd
Epilepsy with Myoclonic Absence	LTG	1 to 7.5 mg/kg/d	2nd-3rd
Epilepsy with Tonic Clonic Seizures Alone	LTG	1 to 7.5 mg/kg/d	1st-2nd
	TPM	1 to 7-8 mg/kg/d	1st-2nd
	ZNS	1-2 to 5-8 mg/kg/d	1st-2nd
Juvenile Myoclonic Epilepsy	LTG	1 to 7.5 mg/kg/d	1st-2nd
	LEV	20 to 50 mg/kg/d	1st-2nd
	TPM	1 to 7-8 mg/kg/d	1st-2nd
	ZNS	1-2 to 5-8 mg/kg/d	1st-2nd

Legend: AED: anti epileptic drug, VGB: vigabatrin, TPM: topiramate, LTG: lamotrigine, LEV: levetiracetam, RUF: rufinamide, FBM: felbamate, OXC: oxcarbamazepine, GBP: gabapentin, ZNS: zonisamide, TSC: Tuberous Sclerosis Complex

drug, like it can be the case in TSC, an ophthalmologic examination is recommended 3 months after initiation, then every 3 months. In children ≤ 5-6 years, an ERG should be considered; since this test requires sedation, risks and benefits should be evaluated for each infant [20, 26]. If seizures are not controlled within 4 weeks for IS and 3 months for focal seizures, VGB should be discontinued and an ophthalmological examination performed 3-6 months after VGB discontinuation [26].

Common side effects like weight gain, behavioral changes, headaches, sleep disturbances, drowsiness and ataxia are reported. VGB may exacerbate myoclonic seizures [20]. Abnormal signal on T2 and diffusion weighted imaging localized in basal ganglia, brainstem and dentate nucleus, were noticed on the brain MRIs of one third of infants treated by VGB for IS. They are related to younger ages and higher doses. The mechanism remains unclear [24]. Children are asymptomatic and signal abnormalities are reversible after drug discontinuation [27].

Levetiracetam

Levetiracetam (LEV) is a pyrrolidine derivative, structurally similar to the piracetam. Its exact mechanism of action is unknown. Its binding to synaptic vesicle protein 2A may play a role. Inhibition of voltage-gated calcium channels and reduction of GABA and glycin-mediated are postulated [4, 28]. Its major metabolic pathway is independent on any liver CYP450 isoenzymes and it has a low plasma proteins bounding, therefore interactions with other drugs are very unlikely [29].

LEV is indicated as an adjunctive treatment for focal seizures in children >4 years old (Class III evidence) [30] and myoclonic seizures in JME (Class IV evidence) [7]. There are growing evidences of its broad-spectrum action on generalized and focal seizures [28]. High dose IV LEV (40-60mg/kg) has been shown to be effective in childhood refractory status epilepticus. It offers an interesting alternative to benzodiazepine especially in children with severe encephalopathy and/or cerebral palsy at higher risk of cardio-respiratory failure [31, 32].

LEV is well-tolerated [28]. A major side effect is behavorial change with aggressiveness, obsessive or psychotic behavior [33]. These signs usually manifest in children with pre-existing cognitive or behavioral/emotional disorders. Their incidence is higher in children [29].

Topiramate

Topiramate (TPM) is a sulfamate-substitued monosaccharide. Its exact mechanism is unknown. It may inhibit voltage-gated sodium and calcium channels, potentiate GABA-mediated chloride currents, block glutamate-mediated excitatory transmission, and inhibit carbonic anhydrase enzymes [3, 4].

Current indications are as an adjunctive therapy for children of 2-12 years of age with focal seizures or idiopathic generalized tonic-clonic seizures (Class I evidence) [7]. It has also shown efficacy in IS, LGS (Class IV evidence) [34], JME (Class IV evidence) and refractory focal seizures (Class I evidence) [35-37]. It decreases the frequency of status epilepticus in DS.

TPM levels can be decreased by PHT and CBZ [3]. TPM can cause nephrolithiasis and metabolic acidosis, usually asymptomatic but requiring caution in patients with renal failure. Hyperthermia due to hypohydrosis is a risk with febrile illnesses or hot weather. Somnolence, paresthesia, nystagmus, glaucoma, anorexia and weight loss were reported. TPM may reduce expressive language or verbal fluency; this side effect can be difficult to ascertain in children with developmental delay/intellectual disability. A drug discontinuation should be considered if there is any doubt [37].

Zonisamide

Zonisamide (ZNS) is a sulfonamide derivative. The proposed mechanisms of action are inhibition of sodium and T-type calcium channels and inhibition of potassium-evoked glutamate synaptic transmission. It also acts on the dopamine and serotonin transmission facilitation and is a weak carbonic anhydrase inhibitor [3]. ZNS is approved for patients >16 years as an add-on therapy for focal seizures. It has shown efficacy and safety in children [38, 39]. It has a good effect in JME (Class IV evidence), absence or myoclonic epilepsies [40, 41]. It can be effective and safe at high dose in IS [42].

ZNS is metabolized by the CYP450 3A4, hence levels are decreased by enzyme inducers like PHT, PB and CBZ [4, 40]. ZNS is well-tolerated; side effects are similar to TPM. Cases with Stevens-Johnson syndrome were reported [40].

Rufinamide

Rufinamide (RUF) is a triazole derivative with a novel chemical structure. Its mechanism of action is unknown; a prolongation of the inactivation phase of voltage-gated sodium channels is postulated [3]. RUF was approved as an adjunctive therapy for tonic/atonic seizures in LGS in children ≥ 4 years [43, 44]. A favorable safety and tolerability profile of RUF for children with intractable epilepsy was shown [45, 46]. Kluger et al. report good effect of RUF in MAE [47]. A retrospective European multicenter study evaluated the efficacy and tolerability of RUF in DS. The retention rate decreased from 45% after 6 months of treatment to 15% after 34 months. RUF was stopped due to seizure aggravation in about 30% of patients and side effects in 10%. Therefore the authors state that RUF does not seem to be a suitable option for long-term treatment in DS [48].

A lower maximal daily dose of RUF is required in case of concomitant use of VPA. It is of special importance in children weighing less than 30kg who may have larger interindividual pharmacokinetic variability [45, 47]. Common side effects, like fatigue, somnolence, ataxia, dizziness, vomiting and headaches, can be reduced by slow titration (every 5-7 days) and subside with maintenance dosing [47]. A hypersensitivity syndrome was reported in children ≤ 12 years of age. They all recovered quickly after drug discontinuation [45].

Felbamate

Felbamate (FBM) is a dicarbamate. Suggested mechanisms of action are: sodium channels antagonism, inhibition of voltage-gated calcium channels and NMDA receptors and potentiation of GABAergic activity [4, 49]. It was the first drug to be tested in a placebo-controlled trial in children with LGS [50] where it was approved for adjunctive therapy (Class I evidence) [51]. There is Class III evidence for its use in IS, absence seizures, JME and Landau-Kleffner syndrome. FBM may be effective in MAE (Class IV evidence) [49].

FBM is a CYP2C19 inhibitor; hence PHT, PB, VPA and OXC levels are increased [7]. Common adverse effects like anorexia, gastro-intestinal complaints, sleep disturbances and gait abnormality were reported. FBM is related to rare but serious, not dose-related, potentially fatal hepatotoxicity and aplastic anemia. A slow drug titration may reduce this risk. Blood cell counts and hepatic enzymes' levels should be performed before the initiation of FBM and monitored regularly [52].

Gabapentin

Gabapentin (GBP) mimicks the structure of GABA and increases the seizure threshold. Its exact mechanism of action is unknown. GBP binds to an auxiliary subunit of voltage-gated calcium channels [4]. It has a short elimination half-time, so it is preferably divided into 3 or 4 doses per day [7]. It is approved as an adjunctive therapy for treatment of focal seizures in children ≥12 years [4]. There is Class I evidence of its efficacy and tolerability in newly diagnosed focal epilepsy and refractory focal epilepsy [14, 34]. One class III double blind trial showed its efficacy in benign rolandic epilepsy [6].

GBP is usually well-tolerated with common side effects including behavioral changes, weight gain, dizziness, somnolence and fatigue. Ataxia, nystagmus and choreoathetosis have been reported [7].

Perampanel

Perampanel (PER) is a non-competitive selective AMPA receptor antagonist acting on post-synaptic glutamate transmission [53]. PER was recently approved by the European Medicines Agency and FDA for adjunctive treatment of children ≥ 12 years of age with focal epilepsy [54, 55]. Double blind drug trials showed a responder rate between 15 and 38%, 2 to 5% of patients being seizure free at 3 months. Long-term safety study showed good tolerability during up to 3 years of exposure [56]. Its long half-life allows a single daily dose.

PER is primarily metabolized via tCYP450, hence, CYP450 inhibitors/inducers may affect their levels. PER could induce liver enzymes and interact with concomitant AEDs like PHT, PB or RUF [57]. Adverse events include dizziness, somnolence, irritability, headache and ataxia [58]. One case of drug reaction with eosinophilia and systemic symptoms was reported [59].

Lacosamide, Brivaracetam

No pediatric studies are available for these drugs. However, they offer interesting perspectives for pediatric use. The following summaries are based on adult studies.

Lacosamide (LCM)

LCM is a functionalized amino acid molecule thought to inactivate voltage-gated sodium channels and interact with the Collapsing-Response Mediator Protein 2 (CRMP-2) involved in neuronal differentiation, polarization and axonal outgrowth [60]. LCM have been FDA-approved for the adjunctive treatment of focal epilepsy [61-63]. Case reports suggest an efficacy in refractory status epilepticus [64, 65]. The effect of LCM on CRMP-2 was postulated to be responsible for neuroprotective effects in animal models. Of particular concern for children is the possible impact of LCM on normal brain development in very young children, given the known interaction with CRMP-2 highly expressed during early development in the CNS [60, 66].

Brivaracetam (BRV)

This (S)-isomer of LEV appears to have a low side effect profile and a potent broad spectrum of action which makes it appealing for use in children [67].

Conclusion

The introduction of a new AED is always welcomed with enthusiasm. In the pediatric population, they are usually first approved as add-on therapies based on adult clinical trials. These extrapolated data do not allow addressing specific pediatric issues. Drug doses often differ from the adult and must be adjusted according to age and weight at diagnosis and at follow-up. Side effects are potentially different in the developing child with possible impact on cognition. Drug and dosage forms are often not suited to pediatric use especially in infancy and neonates. The choice of an appropriate AED requires not only knowledge of pharmacokinetics according to age, drug interactions and best formulation for children but also of the age-related epileptic syndromes, underlying etiology and co-existing medical problems/and cognitive disorders.

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