Journal of Al Azhar University-Gaza *(Natural Sciences)*, **2013, 15** : **1-30**

(Review Article)

New antiepileptic drugs in children with epilepsy

Mohammed K. El-Habil

E-mail: dr.habil1@hotmail.com

Received 27/11/2012 Accepted 10/9/2013

Abstract: *Over the past two decades, eleven new antiepileptic drugs (AEDs) have been introduced into the market that expanded treatment options for children with epilepsy. These novel AEDs offer equal efficacy with improved tolerability, pharmacokinetic properties including less drug interactions, and side effect profiles compared with old drugs. However, despite the wide therapeutic range of old and new AEDs, more than 25% of epileptic patients remain refractory to treatment and thus there is a substantial need to develop more effective drugs that block epileptogenesis, resulting in complete cure of epilepsy. With many new medications available, the clinician treating children with epilepsy must be well versed with the application of these drugs to their patient population. This article will review the mechanisms of action, indications, pharmacokinetics, dosing, and safety profiles of the new AEDs in children with epilepsy. Also, the principles of AED selection for children will be discussed.*

Keywords*: Antiepileptic drugs, Epilepsy, Children*

Introduction

Prior to 1990, six major antiepileptic drugs (AEDs) were available for the treatment of all forms of epilepsy. These included carbamazepine, phenobarbital, phenytoin, primidone, valproic acid, and ethosuximide (French et al. 2004). Approximately 70% of patients with epilepsy will become seizure-free using these old antiepileptic drugs . For the remaining 30%, recurrent seizures as well as intolerable adverse effects can have significant impact on quality of life. This incomplete therapeutic outcome has stimulated intensive research for novel antiepileptic drugs (LaRoche & Helmers 2004).

Over the past two decades, eleven new AEDs (felbamate, fosphenytoin, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, vigabatrin, and zonisamide) have been introduced into the market that expanded treatment options for children

with epilepsy (Figure 1) , (Donner & Snead 2006). These novel AEDs offer equal efficacy with improved tolerability, pharmacokinetic properties including less drug interactions, and side effect profiles compared with old drugs. However, despite the wide therapeutic range of old and new AEDs, more than 25% of epilepsy patients remain refractory to these drugs and thus there is a substantial need to develop more effective drugs that block epileptogenesis, resulting in complete cure of epilepsy (Donner & Snead 2006, Bialer 2006). In addition, some authors thought that the increased availability of treatment options implies that drug choice in patients with epilepsy is more complicated than in the past, and there is a concern that inadequate knowledge of indications, contraindications, and mode of use of the newer drugs could result in some patients receiving suboptimal treatment or being exposed to undue risks from side effects and drug interactions (Emblio 2002). Therefore, with many new medications available, the clinician treating children with epilepsy must be well versed with the application of these drugs to their patient population. In this article the drugs are reviewed in alphabetical order.

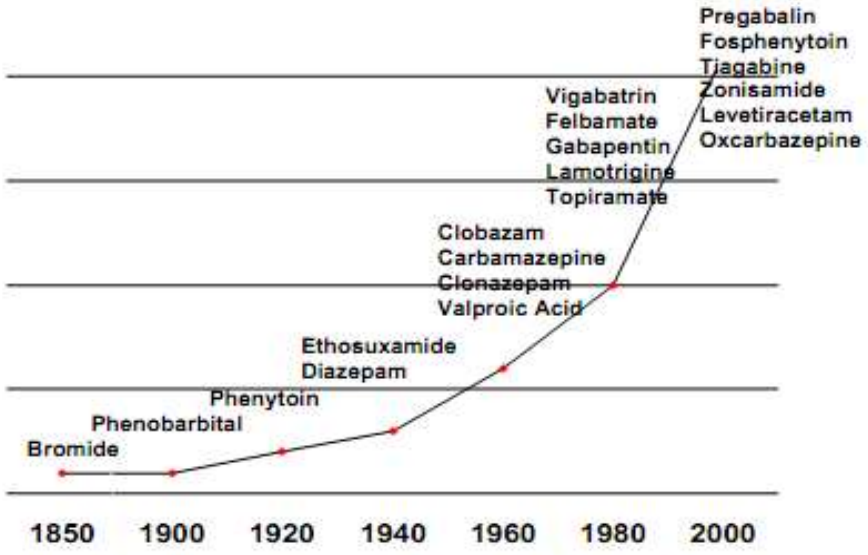

Figure 1. *History of antiepileptic drugs development, from Donner E.J. and Snead O.S . New Generation Anticonvulsants for the Treatment of Epilepsy in Children. The American Society for Experimental NeuroTherapeutics, Inc. Vol. 3, 170–180, April 2006. All rights reserved.*

General aspects of epilepsy in children

An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure (Fisher et al. 2005).

Not only epilepsy is common in childhood, it is also different from epilepsy in adults. In children, dysgenetic lesions of the brain, specific pediatric epilepsy syndromes (including age-related like infantile spasm and genetic syndromes), and factors related to pregnancy, labor, and delivery figure prominently and express themselves differently (Wallace & Farrell 2004).

Comorbid cognitive and behavioral conditions are very common in children with epilepsy. While it is difficult to differentiate the effects of seizures, AED treatment, and underlying neuropathology on the cognitive profiles of children with epilepsy, there is no doubt that those children are at risk for learning difficulties. Furthermore, conditions such as attention deficit and hyperactivity disorder, autism, and mental retardation are common in children with epilepsy . These conditions may complicate the initial diagnosis of epilepsy in children and often require consideration when selecting an AED (Donner & Snead 2006).

Principles of AED selection for children with epilepsy

The primary goal of treatment is to achieve a complete seizure control with less adverse effects (Tomson 2007), which is accomplished in more than 60% of patients who are treated with antiepileptic drugs (AEDs). In many patients with epilepsy, monotherapy is a possible and preferred treatment. However, if the patient has a more severe form of epilepsy, polytherapy is needed. As many as 30–50% of the patients with epilepsy may not be adequately treated with a single AED, and two or more drugs may be needed (Kwan & Brodie 2000).

Initiating treatment with an antiepileptic drug is a major event in the life of a patient. Therapy is long term, usually for at least 3 years and, depending on circumstances, sometimes for life. A full explanation of all the implications must be given to the parents of epileptic children. Antiepileptic treatment will fail unless the patient/parents fully understands the importance of regular therapy and the objectives of treatment (Singhi & Mitra 1997, Dhillon & Sander 2003).

AED that is most suitable for the patient's seizure type should be introduced slowly, starting with small dose, as too rapid titration may induce side effects that will lose the patient's confidence (Wallace 1992, Dhillon & Sander 2003). There is no single optimum dose of any AED that suits all patients. The required dose varies from patient to patient, and from drug to drug, so it needs to be individualized (Dhillon & Sander 2003, Tomson 2007). Most specialists would prefer patients to remain on the same brand of medication, as absorption may differ between similar formulations from various manufacturers (Pellock 1994).

Pharmacokinetics are unique in children. Drug clearance is highest in neonates, up to four times that of adults. Drug clearance then declines with age, reaching adult values in adolescence. This can result in the need for more frequent monitoring of drug levels and alterations in dose in children (Donner & Snead 2006).

The judicious use of therapeutic drug monitoring (TDM) can improve the control of seizures particularly in patients on therapy with old antiepileptic drugs (AEDs). Overall; however, the usefulness of TDM of newer AEDs seems to be limited and its indiscriminate use is not justified. Exceptions are represented with individualization of treatment in selected cases in a particular clinical setting such as renal failure, dialysis, ascertainment of non-compliance, drug interaction, and toxicity. These drugs are usually effective over a wide range of serum concentrations but with substantial interindividual variation in response. Any particular individual may have good clinical response at concentrations outside the reference range for AED. Therefore, the dose should never be adjusted up and down to keep blood level in the therapeutic range in patients who become seizure free. Based on current data, TDM is not a substitute for clinical judgment, and the dose should be titrated to the optimal control of the patient. It is the patient who is being treated, not the serum drug concentration (Pellock & Willmore 1991, Mattson 1995, johannessen et al. 2003).

Discontinuation of AED(s) must be based on knowledge about natural history of the particular epilepsy and the possibility of remission. In general, 70% of children with seizures, who become seizure free for two or more years while on AED will remain so after withdrawal (Gherpelli 1992). Therefore, withdrawal of AED therapy is recommended after two years seizure free interval. The standard practice in most epilepsy centers is to taper off AED(s) over a period of 3-6 months. However, no correlation has been found between seizure recurrence and the taper period (Mattson 1995, Serra et al. 2005) .

1. Felbamate (FELBATOL®)

Felbamate (FBM) was the first new antiepileptic drug to gain FDA approval in 1993 and is chemically unrelated to any of the other antiepileptic drugs (Wagner 1994). Several mechanisms of action have been identified, including sodium channel blockade, calcium channel blockade, and antagonism of N-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors (LaRoche & Helmers 2004).

Although felbamate has a broad spectrum activity against a variety of refractory seizures types, its primary indication in children is currently restricted to the adjunctive treatment of Lennox–Gastaut syndrome (LGS) and partial seizures, because of its lifethreatening idiosyncratic adverse effects, as aplastic anemia and hepatic failure, observed postmarketing (wagner 1994 , pelloc 2006 , Hwang & Kim 2008). The incidence of aplastic anemia with felbamate may be as high as 1:8000 (Pellock & Brodie 1997, Kaufman et al. 1997). Hepatotoxicity was also reported at a slightly lower incidence of 1 in 10000, which parallels the risk with valproate therapy (LaRoche & Helmers 2004). Felbamate remains on the market in the United States but with a black box warning for aplastic anemia and hepatic failure and is not considered a first-line anticonvulsant medication (Donner & Snead 2006). Rather, this drug is restricted to only the most intractable patients with epilepsy and can be administered only by a neurologist and it is recommended to monitor hematologic function frequently (LaRoche & Helmers 2004). Common adverse effects include anorexia, weight loss, insomnia, and ataxia, are reversible after discontinuation or dose reduction (LaRoche & Helmers 2004).

Oral felbamate is at least 90% absorbed, and peak concentrations are reached in 2-6 hours (Tmax) with a bioavailability of > 90% . The half life of the medication in general is 14 to 23 hours (Ward & Shumaker 1990, wagner 1994). Its Vd is 0.76 L/kg in adults and 0.91 L/kg in children. Protein binding is approximately 25% (Kelley et al. 1997). The drug is eliminated partly by renal excretion and also by oxidative metabolism (Thompson et al. 1999). Formation of a reactive metabolite, atropaldehyde, has been hypothesized as the toxic intermediate resulting in both liver failure and aplastic anemia (Patsalos et al. 2008). Impaired renal function is associated with higher serum felbamate concentrations and longer half-life values (27–34 hours), (Johanssen et al. 2003).

Felbamate is an inhibitor of the cytochrome P450 (CYP) isoenzyme 2C19, and of β-oxidation. Concomitant medications will often need

to be reduced upon initiation of felbamate (Linda et al. 2004). FBM can increase the serum levels of other AEDs, such as phenytoin, phenobarbital, valproic acid (VPA), and carbamazepine-10,11-epoxide by up to 20–50% (Graves 1993). However, the metabolism of felbamate is inducible and its clearance can be doubled by phenytoin and increased by 40% by carbamazepine and phenobarbital so that serum felbamate concentrations are decreased (Wagner et al. 1991, Howard et al. 1992). Felbamate clearance is reduced by valproic acid (20%), (Ward et al. 1991) and possibly by gabapentin (37%) resulting in increased serum felbamate concentrations (Hussein et al. 1996).

Felbamate is typically started at 15 mg/kg/day divided three times/day (maximum 1,200 mg/day) for one week, then increased to 30 mg/kg/day divided three times/day (maximum 2,400 mg/day) the second week. Then increased to 45 mg/kg/day divided three times/day (maximum 3,600 mg/day). Further adjustments in dose may be made based on clinical response and toxicity. In children, a higher dose of up to 90 mg/kg/day may be required for complete seizure control (Hwang & Kim 2008). Felbamate is supplied as 400 and 600 mg tablets and in an oral suspension of 600 mg/5 mL (Linda et al. 2004 , Donner & Snead 2006). In patients treated with therapeutic doses, serum felbamate concentrations in the order of 30–60 mg/L have been reported (Faught et al. 1993).

2. Fosphenytoin (CEREBYX®)

Fosphenytoin is a phosphorylated prodrug of phenytoin, approved in 1996, which was developed to avoid the adverse effects associated with the parenteral administration of phenytoin, i.e., local pain after intravenous administration and more serious adverse effects such as cardiovascular complications (Donner & Snead 2006). Fosphenytoin and phenytoin are both classified as hydantoins. The anticonvulsant properties of fosphenytoin are fully attributed to phenytoin, which acts at the voltage-gated sodium channel (Boucher 1996).

In comparison with phenytoin preparations, which have a pH value of 11, fosphenytoin has a pH value of only 8.6, which decreases the risk of cardiovascular and cutaneous side effects. The near-neutral pH value of fosphenytoin allows effective intravenous (IV) or intramuscular (IM) administration (Takeoka 1998). Fosphenytoin is a highly water soluble, phosphate ester of phenytoin, that has no known pharmacologic activity before its conversion to phenytoin (Boucher 1996). It is rapidly and completely converted to phenytoin by phosphatases present in the liver, red blood cells, and many other tissues (Browne 1997). Every 1.5 mg of

fosphenytoin yields 1 mg of phenytoin (Donner & Snead 2006). Morton (1998) found that fosphenytoin was converted to phenytoin within 8.3 minutes (range, 2.5-18.5 minutes). In addition, no significant difference in conversion rates was noted between young and old patients.

The absorption rate appears to be the rate-limiting step in the conversion of fosphenytoin to phenytoin after intramuscular administration . Bioavailability of phenytoin derived from both intravenous and intramuscular fosphenytoin is essentially 100% (Boucher 1996). Fosphenytoin is extensively bound (95-99%) to albumin in a saturable fashion. This leads to displacement of phenytoin (and increased phenytoin free faction) as a function of fosphenytoin concentration in plasma . The rapid achievement of effective concentrations after IV administration permits the use of fosphenytoin in emergency situations, such as status epilepticus (Fischer et al. 2003). Phenytoin derived from fosphenytoin is extensively metabolised in the liver and excreted in the urine. Direct renal excretion of fosphenytoin is low and clinically insignificant (Browne 1997).

Fosphenytoin is most commonly used in the treatment of status epilepticus, prophylaxis or treatment of seizures associated with neurosurgery or head injury, or as a substitute for oral phenytoin in children aged 5 years and over (Allen et al. 1995, Uthman et al. 1996, Rylance et al. 2008). Intravenous administration results in a reduced incidence of pain and burning at the infusion site compared with phenytoin and the tachyarrhythmia that has been associated with phenytoin has not been reported with fosphenytoin. For these reasons, fosphenytoin has become the standard of care in many institutions (Donner & Snead 2006).

The dose of fosphenytoin is expressed as phenytoin sodium equivalent (PE); fosphenytoin sodium 1.5 mg equals phenytoin sodium 1 mg. For children with status epilepticus, the dose of fosphenytoin by intravenous infusion is initially 20 mg(PE)/kg given at a rate of 2–3 mg/kg/minute, then 4–5 mg(PE)/kg daily in 1–4 divided doses given at a rate of 1–2 mg/kg/minute . For prophylaxis or treatment of seizures associated with neurosurgery or head injury, fosphenytoin is administrated by intravenous infusion at a rate of 1–2 mg(PE)/kg/minute, initially 10–15 mg(PE)/kg then 4–5 mg(PE)/kg daily in 1–4 divided doses. As a substitute for oral phenytoin, fosphenytoin can be given by intravenous infusion at a rate of 1–2 mg(PE)/kg/minute in the same dose and dosing frequency as oral phenytoin therapy (Rylance et al. 2008). Fosphenytoin is available in 75mg/ml vial of 10ml. With

therapeutic doses of fosphenytoin, serum concentrations of active phenytoin derivative are in the order of 10-20 mg/L (Takeoka 1998).

3. Gabapentin (NEURONTIN®)

Gabapentin (GBP) , a structural analogue of GABA with a cyclohexane ring inco-rporated, was approved for use in 1993. It is originally developed to treat plasticity and has been shown to have potent antiepileptic effects (Rose & Kam 2002, LaRoche & Helmers 2004). Interestingly, more than 80% of prescriptions for gabapentin are for off-label uses such as neuropathic pain, migraine headache, spasticity, and bipolar disorder (LaRoche & Helmers 2004).

Although it has a similar structure to that of GABA, it does not bind GABA receptors (Hwang & Kim 2008). Gabapentin appears to act by a novel mechanism to increase cerebrospinal fluid GABA levels and act on the alpha-2-delta-1 subunit of Ca^{+2} receptors (Linda et al. 2004).

GBP can be used as an adjunctive therapy for partial seizures with and without secondary generalization in patients older than 3 years (LaRoche & Helmers 2004). This drug was initially considered to be of low potency; however, this was related to the low doses used when the drug first became available. Clinical practice has demonstrated good efficacy against partial seizures at higher doses than originally proposed. However, higher dosing may be limited by saturable gastric absorption and three times per day dosing is usually required. A double-blinded, placebo-controlled study of gabapentin as add-on therapy in children with refractory partial seizures demonstrated superior efficacy in controlling partial seizures and secondarily generalized seizures compared with placebo with good tolerability, and these results have been replicated (Donner & Snead 2006). Also, there is evidence that GBP is effective as a monotherapy for newly diagnosed partial epilepsy (Donner & Snead 2006, Hwang & Kim 2008). It is easy to use as an add-on drug, or in children on chemotherapy or other medications for which drug interactions would not be tolerated, as well as in children with liver function impairment (Donner & Snead 2006). Gabapentin has not been shown to be effective in treatment of primary generalized seizures, and can worsen absence and myoclonic seizures (Linda et al. 2004).

Gabapentin is rapidly absorbed from the gastrointestinal tract by the L-amino acid transport system. Peak serum concentrations (Tmax) are attained 2 to 3 hours after a single dose. Bioavailability decreases with increasing dosage, probably because of saturation of the transporter's capacity (Vollmer et al. 1988). GBP has a few distinct pharmacokinetic properties: it is not bound to plasma proteins (Vd, 0.9 L/kg), a lack of any

significant pharmacokinetic interactions, it is 100% excreted via the kidney, and the absence of hepatic oxidation induction (Vollmer et al. 1988, Hwang & Kim 2008). Coadministration with antacids causes a decrease in bioavailability of gabapentin (LaRoche & Helmers 2004). The half-life is 5–9 h, and increases in the presence of impaired renal function (McLean 1995). The concentration-to-dose ratio increases with age (Arminjo et al. 2004). On a weight basis, 33% larger doses would be required in younger children (aged <5 years) to achieve the same exposure as older children (Johannessen et al. 2003).

Another attractive feature of gabapentin is the absence of serious or idiosyncratic adverse effects or organ toxicities (LaRoche & Helmers 2004). In the pediatric population, its use has been associated with behavioral changes, including aggression, irritability or hyperactivity (Linda et al. 2004). The most common side effects are sedation, somnolence, dizziness, fatigue, ataxia and gastrointestinal disturbance which usually is resolved within the first 2 weeks of therapy . A modest weight gain may occur (LaRoche & Helmers 2004, Linda et al. 2004, Donner & Snead 2006).

The dose of gabapentin is 10mg/kg on day 1, then 10mg/kg twice daily on day 2 , then 10mg/kg three times daily on day 3, increased according to response to usual dose of 20–60 mg/kg/day in three divided doses. Further dose adjustments up to 90 mg/kg/day were reported and may be necessary if seizure control is not obtained at lower dosages. Gabapentin is supplied as 100, 300, or 400mg capsules; 600 or 800 mg tablets; or in an oral suspension containing 250 mg/mL (Donner & Snead 2006, Hwang & Kim 2008, Rylance et al. 2008). Due to gabapentin's predominant renal clearance, dose adjustments may be necessary in patients with renal impairment or immature kidney function (Linda et al. 2004). The reference serum gabapentin concentrations are in the order of 2–20 mg/L (Patsalos et al. 2008).

4. Lamotrigine (LAMICTAL®)

Lamotrigine (LTG) is a broad-spectrum agent that was approved for use in 1994 as an adjunctive treatment in adults with partial-onset seizures (LaRoche & Helmers 2004). Later approval was granted for adjunctive therapy for partial seizures in children aged 2 years or older, as well as monotherapy in children with generalized seizures associated with Lennox–Gastaut syndrome and in adults with epilepsy when converting from valproic acid therapy (Donner & Snead 2006). Lamotrigine exhibits its antiepileptic effect primarily by blockade of sodium channels , facilitating the inhibition of glutamate release and inhibition of high-

voltage activation Ca^{+2} currents possibly through inhibition of presynaptic N-type Ca^{+2} channels (Gilliam & Gidal 2001, Hwang & Kim 2008).

LTG has a broad range of efficacy for diverse types of seizures: juvenile myoclonic epilepsy (JME), infantile spasms (IS), LGS, absence seizures and Rett syndrome (Hwang & Kim 2008). LTG is equivalent to VPA for patients with newly diagnosed childhood absence epilepsy although LTG requires a much slower titration period (Coppola et al. 2004). Moreover, Franz et al (2001) indicated that LTG was effective and well-tolerated as initial monotherapy for epilepsy in patients with tuberous sclerosis complex (TSC). They proposed that the usefulness of LTG in TSC may relate to an underlying defect of glutamatergic neurotransmission in partial epilepsy. Expert opinion in the USA has made consensus on the efficacy of LTG: it can be applied as a first-line agent for older children with myoclonic and generalized tonic–clonic seizures. For children with cryptogenic complex partial seizures, LTG is considered as a second monotherapy after an initial trial of CBZ or oxcarbazepine. It is also appropriately used for children with LGS, next to VPA or topiramate and is commonly used as the treatment of choice for children with absence seizures as well (Hwang & Kim 2008). Recently, Valencia et al (2009) have showed that LTG was effective and well-tolerated as monotherapy in children and adolescents for both focal and generalized epilepsies.

Lamotrigine is known to produce a skin rash in up to 5–10% of patients. These rashes have the potential to be severe and life-threatening requiring hospitalization and drug discontinuation, some progressing to Stevens-Johnson syndrome . Severe rash occurs more often in children; up to 1% incidence has been reported (Donner & Snead 2006). The risk of rash is related to the dose and the speed of titration. It usually occurs within the first 2–8 weeks after initiation, which necessitates low starting doses and slow titration. Other risk factors for development of serious rash are younger age and concomitant use of valproic acid (LaRoche & Helmers 2004, Donner & Snead 2006). Common dose-related adverse effects are dizziness, sedation, headache, diplopia, and ataxia (Hwang & Kim 2008).

Lamotrigine is absorbed rapidly and completely from the gastrointestinal tract (Tmax,1–3 hours, and bioavailability of approximately 98%). Absorption of lamotrigine is linearly related to dose and is unaffected by food. It is approximately 55% bound to plasma

proteins, and has a volume of distribution of about one L/kg (Johannessen et al. 2003).

Lamotrigine exhibits autoinduction that is complete within 2 weeks and can be associated with a 17% reduction in lamotrigine serum concentrations (Hussein & Posner 1997). Lamotrigine has a long half-life; 24 h, which permits once or twice per day dosing (Titlic et al. 2008). Only 10% of a given dose of LTG is excreted unchanged and the drug is almost exclusively metabolized via hepatic glucuronidation (Reimers et al. 2007) . LTG, therefore, has no significant effects on the metabolism of other antiepileptic drugs or oral contraceptives (LaRoche & Helmers 2004). However, oral contraceptives are associated with a 50% reduction of the mean steady-state plasma concentration of lamotrigine (Donner & Snead 2006). Hepatic enzyme inducers such as carbamazepine and phenytoin will decrease the half life of lamotrigine from 24 to 15 h, which may require dosing alterations. Furthermore, acetaminophen and rifampicin have been reported to accelerate the metabolism of lamotrigine (Johannessen et al. 2003). The most important interaction to note is that the half-life is very prolonged (60 h) when lamotrigine is used in combination with valproic acid (Donner & Snead 2006). This because lamotrigine metabolism is inhibited by valproate (Battino 2001). The elevated lamotrigine levels that occur when used in conjunction with valproic acid significantly increase the risk of skin rash and care must be taken when using these drugs in combination. To reduce the risk of severe skin rash, a long, slow titration of dose is required when used alone or in combination with other AEDs especially VPA (Donner & Snead 2006). Lamotrigine clearance is higher in children than in adults (Bartoli et al. 1997, Perucca 2006) , moderately reduced in the elderly (Perucca 2006) and may be increased by up to 300% during pregnancy (Patsalos et al. 2008).

The dose guidelines vary based on coadministration with valproate or an enzyme-inducing AED (EIAED) (eg, carbamazepine, phenytoin, phenobarbital, or primidone). In children 2–12 years of age on valproate, treatment can be initiated at 0.15 mg/kg/day in one or two divided doses for 2 weeks. The dose may be increased during week 3 by an additional 0.15 mg/kg/day given in two divided doses for the next 2 weeks. After week 4, the dose may be increased every 1–2 weeks by 0.15–0.3 mg/kg/day. Maintenance dose in children on valproate is typically 1–5 mg/kg/day . In children 2–12 years of age on an enzyme-inducing AED without valproate , treatment can be initiated at 0.6 mg/kg/day in one or two divided doses for 2 weeks. The dose may be increased during week 3

by an additional 0.6 mg/kg/day given in two divided doses for the next 2 weeks. After week 4, the dose may be increased every 1–2 weeks by 0.6–1.2 mg/kg/day. Maintenance dose in children on EIAEDs is typically 5–15 mg/kg/day. Lamotrigine is supplied as 25, 50, 100, and 200 mg tablets and 2, 5, and 25 mg chewable tablets (Linda et al. 2004, Donner & Snead 2006). With therapeutic doses, serum lamotrigine concentrations is in the order of 2.5–15 mg/L (Patsalos et al. 2008).

5. Levetiracetam (KEPPRA®)

Levetiracetam (LEV) was approved in 1999 for the adjunctive treatment of adults with partial-onset seizures (LaRoche & Helmers 2004). It is a pyrrolidine acetamide derivative and an analogue of piracetam . The exact antiepileptic mechanism of LEV is unknown. However, the drug binds to a synaptic vesicle protein, SV2A, which is believed to impede nerve conduction across synapses (Donner & Snead 2006, Elberry 2012).

Levetiracetam is rapidly absorbed after oral ingestion (Tmax, 1 hour), its bioavailability is essentially 100%. Serum levetiracetam concentrations increase linearly with dose, and it is not bound to plasma proteins. Its volume of distribution is 0.5 to 0.7 L/kg (Johannessen et al. 2003). The rate, but not the extent, of absorption is slowed in the presence of food (Patsalos et al. 2008). Although most of the drug is renally excreted unchanged (66%), the major metabolic pathway is enzymatic hydrolysis of the acetamide group to produce the inactive carboxylic acid metabolite (Pellock et al. 2001). Metabolism of levetiracetam is not dependent on liver CYP isoenzymes. Therefore, levetiracetam does not have significant pharmokinetic interactions and it is an easy addition to other drug therapies in individuals with multiple medical conditions or chronic illness (Linda et al. 2004). Renal function determines the rate of elimination of levetiracetam. The half-life is 16–18 h in neonates at birth, 5–7 h in children aged 6–12 years, 6–8 h in healthy adults, and 10–11 h in the elderly (Patsalos et al. 2008). However, the apparent clearance is 30–40%, higher in children than in adults (Pellock et al. 2001). Regarding renal failure, dose adjustments are necessary as elimination of levetiracetam is reduced in patients with renal dysfunction (Linda et al. 2004).

The broad-spectrum efficacy of levetiracetam as an adjunctive therapy and as monotherapy for generalized and partial childhood epilepsies and for some types of specific epileptic syndromes of infancy and childhood (such as juvenile myoclonic epilepsy, benign rolandic epilepsy, and Jeavon syndrome) has been demonstrated in previous

studies (Verrotti et al. 2010, Elberry 2012). Moreover, LEV can be used as an adjunctive therapy for children with refractory partial epilepsy (Glauser et al. 2002). Also, experimental evidence from animal models that levetiracetam is effective against absence seizures (Donner & Snead 2006). Recent study reported that IV levetiracetam can be used adjunctively or as monotherapy in children with status epilepticus and acute exacerbation of seizures (Kirmani et al. 2009).

Common adverse effects of levetiracetam in clinical trials included somnolence, asthenia, headache, and infection. The majority of adverse effects occurred in the first 4 weeks of therapy and did not appear to be dose related. The most significant adverse effects are behavioral, such as anxiety and agitation that were reported in up to 13% of the study cohort (LaRoche & Helmers 2004). Psychotic symptoms have also been reported in children (Donner & Snead 2006). Such behavioral changes and psychotic reactions seem to occur more frequently in younger patients (under 4 years of age). The onset of signs/symptoms usually occurs early, even during the titration phase, and in many cases, at a low dose (<20 mg/kg/day). These side effects appear to be reversible after discontinuation or dose adjustment of the drug (Verrotti et al. 2010).

The starting pediatric dose is 10-20 mg/kg/day in two divided doses, with a gradual increase by 10–20 mg/kg/day increments every 2 weeks to a maximum dose of 60 mg/kg/day in two divided doses. Levetiracetam is supplied as 250, 500, and 750 mg tablets, 100 mg/ml sugar free oral solution, and vial of 5ml contains 100mg/ml concentrate for intravenous infusion (Linda et al. 2004, Donner & Snead 2006, Elberry 2012). The reference range in patients treated with therapeutic doses is in the order of 12 to 46 mg/L (Leppik et al. 2002).

6. Oxcarbazepine (TRILEPTAL®)

Oxcarbazepine (OXC) was approved by the FDA in 2000 for use as monotherapy or adjunctive therapy for partial-onset seizures in patients aged 4 years or older. It is a keto analog of carbamazepine that was designed to have similar efficacy and fewer adverse effects due to the lack of formation of carbamazepine's toxic metabolite, carbamazepine-10,11-epoxide (Donner & Snead 2006). Like carbamazepine, oxcarbazepine and its active metabolite 10-monohydroxy derivative (MHD) block voltage-dependent sodium channels that limit high-frequency neuronal firing (LaRoche & Helmers 2004, Donner & Snead 2006).

Although oxcarbazepine has similarities to carbamazepine in its structure, efficacy, and adverse effect profiles, it has significant

differences in the pharmacokinetics and dose titration, and these two drugs are considered distinct therapeutic agents (Glauser 2001, Hwang & Kim 2008). OXC shows linear pharmacokinetics (Patsalos et al. 2008). It is rapidly absorbed after oral administration (Tmax, 1-2 hour), and food has no effect on the rate or extent of absorption (Glauser 2001, Johannessen et. al 2003). Oxcarbazepine undergoes rapid and almost complete metabolism by a presystemic 10-keto reduction to form two pharmacologically active enantiomers of MHD, which are equipotent in terms of anticonvulsant activity and are found in serum at concentrations much higher than those of the parent drug . MHD serum concentrations peak (Tmax,3–5 hours) somewhat later than the parent drug. MHD is 40% protein bound with a Vd of 0.75 L/kg (Patsalos et al. 2008). The half-life of both enantiomers is 7–12 h, and their elimination occurs primarily by glucuronidation. In children aged 2–6 years, a higher body weight of oxcarbazepine is required compared with older children and adults to obtain comparable serum MHD concentrations (Battino et al. 1995). The clearance of oxcarbazepine and MHD is reduced in patients with impaired renal function . Preliminary data suggest a pronounced increase in oxcarbazepine and MHD clearance in pregnancy (Patsalos et al. 2008).

The autoinduction seen with carbamazepine does not occur with oxcarbazepine (Donner & Snead 2006). CBZ, PHT, PB, and VPA can be associated with decreased serum levels of the active metabolite. However, OXC may increase the serum levels of PB and PHT (Bialer et al. 1999). In addition, oxcarbazepine enhances metabolism of oral lamotrigine, contraceptives and felodipine, resulting in lower serum levels (Johannessen et al 2003, LaRoche & Helmers 2004).

Dizziness, diplopia, nausea, somnolence and ataxia are well-known dose related adverse effects of OXC (Jarrar & Buchhalter 2003). Hyponatremia has been significantly reported in up to 2.5% patients, although it is rare in children. Serum sodium levels should be monitored when clinically indicated (Donner & Snead 2006). A serious skin rash can occur, which may evolve into Steven–Johnson syndrome or toxic epidermal necrolysis (Hwang & Kim 2008). A cross-hypersensitivity reaction between CBZ and OXC was reported (LaRoche & Helmers 2004).

Dosing in children starts at 10 mg/kg/day divided twice/day for 1 week, and is then increased by 10 mg/kg/day increments weekly to a target dose of 30–45 mg/kg/day divided twice/day. Patients may be directly switched from carbamazepine to oxcarbazepine using a ration of

1.5:1 oxcarbazepine : carbamazepine for doses up to 1500 mg/day of carbamazepine; i.e. the dose requirements are approximately 50% higher for oxcarbazepine, and 1:1 for higher daily doses (Linda et al. 2004, Donner & Snead 2006). Oxcarbazepine is supplied as 150, 300, and 600 mg tablets and in an oral suspension containing 300 mg/5 mL (Donner & Snead 2006). During therapeutic doses of oxcarbazepine, serum concentrations of active 10-monohydroxy derivative are in the order of 3–35 mg/L (Patsalos et al. 2008).

7. Pregabalin (LYRICA®)

Pregabalin is a newly developed antiepileptic drug that was approved in 2005 for adjuvant therapy of partial seizures in adults. It was previously approved for the treatment of neuropathic pain associated with diabetic peripheral neuropathy (Donner & Snead 2006).

This drug is a structural analog to GABA, but functionally unrelated. It readily crosses the blood-brain barrier, and binds potently to the alpha-2-delta subunit, an auxiliary protein associated with voltage-gated calcium channels in the central nervous system, attenuating depolarization-induced Ca+2 influx in nerve terminals . This process results in a reduction of the excitatory neurotransmitter, glutamate (Jan et al. 2009).

Pregabalin is stated to have very rapid absorption (Tmax, 1.3 h), with a bioavailability of >90% (Busch et al. 1998) that achieves steady-state serum levels within 48 h, which may prove to be a favorable pharmacokinetic property (Donner & Snead 2006, Patsalos et al. 2008). Pregabalin is not protein bound and its Vd is 0.4 L/kg (Dworkin et al. 2003). Within the clinically used dose range, serum pregabalin concentrations are linearly related to dosage . Pregabalin is not metabolized, does not induce or inhibit liver enzymes, and is primarily (98%) excreted unchanged in urine with a clearance similar to the glomerular filtration rate. The elimination half-life of pregabalin in serum is 4.6–6.8 h (Patsalos et al. 2008). Patients with impaired renal function show a reduced drug clearance and require a reduction in dose (Randinitis et al. 2003).

Studies indicated that pregabalin was more effective than placebo as add-on therapy in patients 12 years of age and older with refractory partial seizures with or without secondary generalization (Donner & Snead 2006). However, Jan et al (2009) prospectively studied the effect of pregabalin on children with intractable epilepsy, aged 4-15 years, over

a 6 month period. These children exhibited medically refractory epilepsy that had failed many antiepileptic drug trials, ranging from 4-8 drugs (mean, 5 drugs) and they were treated with pregabalin at a dose of 5-14 mg/kg/day (mean, 8.7 mg/kg/day) in two divided doses. Authors of this study have concluded that pregabalin, in the dose used, was a useful addition in the treatment of refractory childhood epilepsy.

Adverse effects are dose related, the commonest being somnolence, dizziness, and ataxia. Weight gain was seen in patients on the highest dose of 600 mg/day (Hamandi & Sander 2006).

Although the drug lacks international pediatric data, pregabalin can be used at a dose of 5-14 mg/kg/day in two divided doses for children older than 4 years, which is supported by previous study (Jan et al. 2009). Pregabalin is supplied in 25, 50, 75, 100, 200, 225, and 300 mg tablets (Donner & Snead 2006). The serum drug concentrations were in the range of 2.8 - 8.2 mg/L (Berry & Millington 2005).

8. Tiagabine (GABITRIL®)

Tiagabine (TGB) was approved in 1997 for adjunctive treatment of partial seizures in patients 12 years of age and older. TGB exerts its activity by selectively inhibiting the uptake of GABA by the transporter molecules, thus increasing the extracellular concentrations of GABA in the brain without increasing whole-brain GABA levels. This prolongs the inhibitory action in the cortex, and in particular the hippocampus (Pellock 2001).

Pediatric double-blind, placebo-controlled studies of TGB continue, but initial information suggests particular efficacy against epilepsy characterized by complex partial seizures. Efficacy in other types of epilepsy will require further studies (Pellock 2001, Linda et al. 2004). A pediatric study was conducted in Europe, focusing on dose-ranging management (Uldall et al. 2000). This single-blind study evaluated the tolerability, safety, and preliminary efficacy of ascending doses (0.25–1.50 mg/kg/day) of TGB add-on therapy in children older than 2 years, with different syndromes of refractory epilepsy. Fifty-two children aged 2–15 years were enrolled. Patients were followed over four months of treatment. TGB appeared to be more effective in localization-related syndromes than in generalized epilepsy syndromes in this study.

After oral ingestion, tiagabine is rapidly absorbed (Tmax, 0.5–2 h) with a bioavailability of 90–95% (Gustavson & Mengel 1995). Although food has no effect on the extent of absorption, the rate of absorption is

considerably slower in the presence of food. Tiagabine is highly protein bound (96%) and has a Vd of about 1.4 L/kg. Tiagabine shows linear pharmacokinetics and is almost entirely metabolized, predominantly by hepatic cytochrome P-450 system with <1% of a tiagabine dose excreted unchanged in urine (Patsalos et al. 2008). TGB does not induce or inhibit hepatic microsomal enzyme systems and therefore does not affect the concentration of other drugs. Its metabolism; however, is induced by AEDs such as barbiturates, carbamazepine, and phenytoin. The half-life is 5–8 h, which is reduced to 2–3 h in patients taking hepatic enzyme–inducing AEDs. The elimination of tiagabine is nearly doubled in children (Donner & Snead 2006). The metabolism of tiagabine is slower in patients with hepatic dysfunction, the half-life in these patients being 12–16 h (Lau et al. 1997).

The most common side effects of tiagabine are dose-related somnolence, confusion, ataxia, and dizziness (LaRoche & Helmers 2004).

Dosing in pediatric patients is started with 0.1 mg/kg/day for one week, and is then increased by 0.1 mg/kg/day weekly. Effective maintenance doses are between 0.25–1.5 mg/kg/day divided three times/day (Pellock 2001, Linda et al. 2004). However, in children 12 years of age and older, on an enzyme-inducing AED, the starting dose of tiagabine is 5 mg/day twice daily for one week then increased by 5-10 mg/week. Usual maintenance dose is 30-45 mg/day increased to a maximum dose of 56 mg/day (doses above 30mg daily are given in 3 divided doses) (Rylance et al. 2008). Significantly lower doses are recommended in patients not taking an inducing AED. Tiagabine is supplied as 5,10, and 15mg tablets (Linda et al. 2004, Donner & Snead 2006). With therapeutic dose, serum levels are between 20 and 100 microg/L (Bentué-Ferrer et al. 2010).

9. Topiramate (TOPAMAX®)

Topiramate (TPM), a sulphamate-substituted monosaccharide, which was originally synthesized as an oral hypoglycaemic, is another broad-spectrum agent approved in 1997 as adjunctive treatment for patients older than 2 years of age with primary generalized tonic–clonic seizures, partial-onset seizures, or seizures associated with Lennox–Gastaut syndrome. Topiramate is also used for migraine prophylaxis (LaRoche & Helmers 2004, Guerrini 2006, Donner & Snead 2006).

Although the exact mechanism of action of TPM remains unknown, multiple mechanisms have been hypothesized based on in

vitro studies, including voltage-sensitive sodium channel blockade, GABAa-mediated chloride current increment, glutamate-mediated neurotransmission inhibition and increase of potassium conductance (Guerrini 2006).

Following oral ingestion, the absorption of topiramate is rapid (Tmax, 2–4 h), with a bioavailability of 81–95% . While food coingestion delays topiramate absorption by about 2 h, the maximum serum concentrations attained are unaffected . The Vd of topiramate is 0.6–1 L/kg. Topiramate is only 15% bound to serum proteins, but it does have a high affinity/low capacity binding site on erythrocytes (Patsalos et al. 2008). There is a linear relationship between topiramate dose and serum concentration. This drug has a long half-life of 10–23 h and is given in one or two daily doses. Topiramate is excreted unchanged via the kidneys (Donner & Snead 2006). The clearance rates of TPM are inversely dependent on the age of the patient. It in children is approximately 50% greater than that in adults and decreases progressively with age until puberty, presumably due to age-dependent changes in the rate of drug metabolism. Therefore, the serum concentration is 33% lower in children at the same dose than in adults (Battino et al 2005, Hwang & Kim 2008). Since renal elimination predominates, the dose of topiramate should be reduced by 50% in patients with a creatinine clearance of <70 mL/min (Johannessen et al. 2003). The plasma concentration of topiramate is reduced by 50% by hepatic enzyme inducers such as phenytoin and carbamazepine (Donner & Snead 2006). However, topiramate exerts no significant effects on other antiepileptic drugs or on serum norethindrone levels but decreases serum estradiol levels by 30% and serum digoxin levels by 12% (LaRoche & Helmers 2004).

In Europe, TPM is indicated as monotherapy in adults and children aged six years and above with newly diagnosed epilepsy who have generalized tonic-clonic seizures or partial (focal) seizures with or without secondarily generalized seizures . It is also indicated as adjunctive therapy for epilepsy in children over two years of age and adults with either partial onset or generalized tonic-clonic seizures (Guerrini 2006). Additional indications include the add-on treatment of Lennox-Gastaut syndrome in children and adults, and as a first-line treatment for infantile spasm (Guerrini 2006, Donner & Snead 2006, Peltzer et al 2009). A recent open prospective trial demonstrated efficacy and tolerability of TPM in children younger than 2 years of age (Grosso et al. 2005).

Topiramate has not been associated with any life-threatening adverse events; however, there is a risk of serious hyperchloremic, nonanion gap metabolic acidosis (lowering of serum bicarbonate levels) for which measurement of baseline and periodic serum bicarbonate levels is recommended. Oligohidrosis and hyperthermia occurs most often in hot weather and has been reported in children (Donner & Snead 2006). Renal stones formation can occur with a reported incidence of 1.5%, possibly caused by its carbonyl anhydrase inhibitor activity (LaRoche & Helmers 2004, Faught 2007) . The most significant adverse effects in clinical use relate to cognitive dysfunction. In children, this may present as deterioration in school performance, reduced use of language, or reports of poor attention. Somnolence may contribute to this problem and may be reduced by starting at a low dose (1 mg/kg/day) and increasing slowly. Anorexia can also be a significant adverse effect of topiramate and may require discontinuation of the drug in small children with weight loss averaging 1 to 6 kg predominantly in the first 3months of therapy (LaRoche & Helmers 2004, Donner & Snead 2006, Hwang & Kim 2008).

TPM is usually initiated at 0.5-1.0 mg/kg/day at night, then increased by 1 mg/kg/day (divided twice/day) increments each week to be maintained in a range of 3–9 mg/kg/day. The maximum dose is 15 mg/kg/day divided into two doses (Rylance et al. 2008). Younger patients require higher doses of topiramate to achieve serum topiramate concentrations comparable to adults (Donner & Snead 2006). When coadministered with an EIAED, topiramate levels may be reduced by ≤50%, necessitating higher maintenance doses. Topiramate is supplied as 25, 50, 100, and 200 mg tablets and 15, 25 and 50 mg sprinkle capsules that may be swallowed whole or opened and sprinkled onto soft food (Linda et al. 2004, Donner & Snead 2006, Rylance et al. 2008). The reference range in patients treated with therapeutic doses is in the order of 12 to 46 mg/L (Johannessen et al. 2003).

10. Vigabatrin (SABRIL®)

Vigabatrin (VGB), a molecule first synthesized in 1974, was initially licensed in the UK and Ireland in 1989 and is available in more than 50 countries (Willmore et al. 2009, Tolman & Faulkner 2009). It was approved for use in the United States in 2009 as adjunctive therapy for adult patients with refractory complex partial seizures (rCPS) who have responded inadequately to several alternative treatments and as monotherapy for patients one month to 2 years of age with infantile

spasms (IS). Interestingly, vigabatrin is one of the most well-studied AEDs worldwide (Shields & Pellock 2011).

This drug is an irreversible inhibitor of GABA-transaminase. Structurally identical to GABA except for the addition of a vinyl group, vigabatrin was designed specifically to increase concentrations of GABA in the brain and thereby inhibit epileptogenic circuits and decrease seizure frequency (Grove et al. 1981, Shields & Pellock 2011).

Because vigabatrin is associated with peripheral visual field defects (pVFDs) as reported in 1997 (Eke et al. 1997), the Food and Drug Administration (FDA) withheld approval of vigabatrin until additional information on pVFDs could be gathered and analyzed (Shields & Pellock 2011). In 2009, vigabatrin was approved by the FDA in conjunction with a comprehensive Risk Evaluation and Mitigation Strategy (REMS) to decrease the risk of vigabatrin-associated vision loss while providing benefit–risk analyses for appropriate patient populations (Shields & Pellock 2011).

Vigabatrin is effective as monotherapy for patients one month to 2 years of age with infantile spasm. Response to therapy generally occurred within 2 weeks of starting vigabatrin. (Carmant 2011). Also, there are further studies in children with tuberous sclerosis, indicate that vigabatrin is particularly effective for infantile spasms in this population (Donner & Snead 2006). Additionally, Greiner et al (2012) indicated that vigabatrin was effective for refractory childhood partial-onset epilepsy.

The most significant adverse effect of vigabatrin is retinal toxicity in the form of permenant constriction of the visual field (Hammoudi et al. 2005). The prevalence of the VGB-induced peripheral VFD in children was 15% and in infants ranged from 15% to 31%. A bilateral nasal defect may be the first clinical indication and may progress to a concentric, bilateral field defect observed in many affected patients; central visual acuity is almost always preserved. The earliest finding of the first abnormal field examination in children and infants was after 11 and 3.1 months respectively (Willmore et al. 2009). Therefore, routine ophthalmologic screening is recommended in all children treated with vigabatrin. Infants are tested at baseline and at 3-month intervals for the first 18 months of treatment, and then every 6 months thereafter (Willmore et al. 2009). In fact, there is some evidence that children with infantile spasms on vigabatrin may have compromised visual function that predates vigabatrin therapy and may be more due to the infantile spasms than the drug (Hammoudi et al 2005).

Because response to treatment typically occurs much more rapidly (i.e., within 1–2 weeks for IS) than the onset of a vigabatrin-associated pVFD, the risk of developing pVFDs may be minimized by discontinuing vigabatrin early during the course of therapy for patients who experience inadequate clinical response (Shields & Pellock 2011).

Minor side effects include somnolence, headache, dizziness, fatigue, ataxia, tremor, weight gain, and hyperactivity are commonly noted (Hwang & Kim 2008). Psychotic disorders or hallucinations have occurred rarely (Willmore et al. 2009).

Vigabatrin is rapidly absorbed from the gastrointestinal tract (Tmax, 1–2 h) with a bioavailability of 60–80% . Food co-ingestion does not affect either the rate or the amount of vigabatrin absorbed . It is not protein bound and its Vd is 0.8 L/kg. Within the clinically used dose range, serum vigabatrin concentrations are linearly related to dosage. Vigabatrin is not metabolized and is not enzyme inducer or inhibitor. It is primarily excreted unchanged in urine (Patsalos et al. 2008). Patients with impaired renal function show a reduced drug clearance and require a reduction in dose. Because children have a higher vigabatrin clearance compared with adults, they require higher doses to attain comparable serum concentrations (Armijo et al. 1997). The half life is 5–11 h and the drug may be given once or twice daily (Donner & Snead 2006). Since vigabatrin acts by irreversibly inhibiting GABA-transaminase, the enzyme responsible for the metabolism of GABA, there is a clear dissociation between its concentration profile in serum and the duration of pharmacological effect, which is related to the regeneration time of the enzyme (Rey et al. 1992).

For refractory childhood partial-onset epilepsy the initial dose is 40 mg/kg daily in single or two divided doses, then adjusted according to body-weight over 2-3 weeks as the following: body-weight 10–15 kg, 0.5–1 g daily; body-weight 15–30 kg, 1–1.5 g daily; body-weight 30–50 kg, 1.5–3 g daily; body-weight over 50 kg, 2–3 g daily. For infantile spasms (West's syndrome), monotherapy, 50 mg/kg daily, adjusted according to response over 7 days; up to 150 mg/kg daily used with good tolerability (Rylance et al. 2008, Shields & Pellock 2011). Vigabatrin is supplied as 500 mg tablets or 500 mg sugar-free powder in sachet that should be dissolved in water immediately before taking (Donner & Snead 2006). The expected trough serum concentrations are in the range of 0.8–36 mg/L (Patsalos et al. 2008).

11. Zonisamide (ZONEGRAN®)

Zonisamide (ZNS) is a broad-spectrum anticonvulsant that has been available in the United States since 2000 but has had widespread clinical use in Japan and South Korea since 1989. It is a sulfonamide derivative that acts by blocking sodium as well as T-type calcium channels (LaRoche & Helmers 2004, Hwang & Kim 2008).

Following oral ingestion, zonisamide is rapidly (Tmax, 2–5 h) absorbed (Taylor et al. 1986). Food co-ingestion does not affect the absorption of zonisamide. Serum proein binding is 40–60% and its Vd is 1.5 L/kg. Zonisamide shows high affinity to be taken up by erythrocytes, with concentration exceeding those in serum four to nine fold, which can be attributed to high-affinity binding to carbonic anhydrase and other red cell protein components (Matsumoto et al. 1989). This drug undergoes hepatic metabolism via the cytochrome P450 system. Zonisamide has the advantage of a long half-life, averaging 60 to 70 hours, making once-daily dosing possible, and is reduced to 30 h with concomitant use of enzyme inducing AEDs. Zonisamide does not alter the metabolism of other AEDs (LaRoche & Helmers 2004, Donner & Snead 2006). Compared with adults, children require higher doses to attain comparable serum concentrations (Perucca 2006).

Globally, it is indicated for the treatment of partial seizures, and further reports have demonstrated its efficacy in generalized tonic–clonic seizures , particularly myoclonus . There has been extensive clinical trial and clinical practice experience with zonisamide therapy in Japanese children. Open-label data from pediatric clinical trials conducted in Japan suggest that zonisamide is well tolerated and effective against partial- and generalized-onset seizures in children (Glauser & Pellock 2002).

Somnolence, poor appetite, weight loss, headache, pruritus, and skin rash are commonly observed dose related adverse effects . Because zonisamide is a sulfonamide derivative, its use is contraindicated in patients with a known sulfonamide allergy. Moreover, zonisamide was reported to cause renal stones in an early study; however, this was not replicated in later trials. Hyperthermia and anhidrosis have also been reported in children (LaRoche & Helmers 2004, Hwang & Kim 2008).

The recommended starting dose in children is 2–4 mg/kg/day in one or two divided doses, increased by 1–2 mg/kg/day every 2 weeks intervals to a target maintenance dose of 4 to 8 mg/kg per day in one or two divided doses. The maximum dose of 12 mg/kg/day may be tolerable and necessary in selected patients. Plasma concentrations of zonisamide are reduced by approximately 50% when coadministered with EIAEDs;

therefore, dose adjustment may be necessary in such cases . Zonisamide is available in 25, 50, and 100 mg capsules (Mimaki 1998, Miura 2004). The formulation (capsule) makes administration in pediatric patients more challenging; however, the powder within the capsule can be reformulated for immediate use in liquids or soft foods (eg, apple sauce or pudding). A reference range of 10–40 mg/L has been suggested (Mimaki 1998).

Conclusion

The advent of the new antiepileptic drugs, from felbamate to zonisamide, raised hope to control epilepsy with fewer adverse effects and improved quality of life. Unfortunately, 20-30% of patients continue to experience refractory epilepsy despite the use of these new agents, and dose-related adverse effects and idiosyncratic reactions continue to be problematic. No available AED has been proven to block epileptogenesis, resulting in complete cure of epilepsy; rather, these medications are only anticonvulsant, providing only symptomatic relief from seizures. As the number of available , effective , but imperfect antiepileptic drugs increases, many challenges remain. These include: choosing the appropriate drug for the epileptic syndrome, assessing accurately the range of a drug's adverse effects in an individual patient, and considering carefully the drug's interaction in combination drug therapy. In considering drug combinations, with different mechanisms of drug action and favorable pharmacokinetic/pharmacodynamic interactions (an area requiring additional studies) are of importance. Clinicians caring for children who have epilepsy anticipate further advances in the pharmacogenetics and molecular pathophysiology of epilepsy, leading to individually tailored, effective, and safe therapy.

Acknowledgement

This article was reviewed by the scientific committee of Al-Rantisy specialized pediatric hospital; Dr. Mohamed I. Abunada M.D (Head of pediatric neurology department) , Dr. Ashraf S. Alewaity (Vice head of pediatric neurology department) and Dr. Mohammed M. Abu Selmiya (Palestinian board in pediatrics). I really appreciate their knowledge.

References

Allen FH Jr, Runge JW, Legarda S., et al. (1995). Safety, tolerance and pharmacokinetics of intravenous fosphenytoin (Cerebyx) in status epilepticus. Epilepsia .36(4):90.

Armijo JA, Cuadrado A, Bravo J, Arteaga R. (1997). Vigabatrin serum concentration to dosage ratio: influence of age and associated antiepileptic drugs. Ther Drug Monit . 19:491–498.

Armijo JA, Perna MA, Adin J, Vega-Gil N. (2004). Association between patient age and gabapentin serum concentration-to-dose ratio: a preliminary multivariate analysis. Ther Drug Monit . 26:633–637 .

Battino D, Estienne M, Avanzini G. (1995). Clinical pharmacokinetics of antiepileptic drugs in pediatri patients. Part II. Phenytoin, carbamazepine,sulthiame, lamotrigine, vigabatrin, oxcarbazepine and felbamate. Clin Pharmacokinet . 29:341–369.

Boucher BA. (1996). Fosphenytoin: A novel phenytoin prodrug. Pharmacotherapy. 16(5):777-791.

Browne TR. (1997). Fosphenytoin (Cerebyx). Clinical Neuropharmacology . 20 (1):1-12.

Bartoli A, Guerrini R, Belmonte A, Alessandri MG, Gatti G, Perucca E. (1997). The influence of dosage, age, and comedication on steady state plasma lamotrigine concentrations in epileptic children: a prospective study with preliminary assessment of correlations with clinical response. Ther Drug Monit . 19:252–260.

Busch JA, Strand JC, Posvar EL, Bockbrader HN, Radulovic LL. (1998). Pregabalin (CI-1008) single-dose pharmacokinetics and safety/tolerance in healthy subjects after oral administration of pregabalin solution or capsule doses. Epilepsia . 39(6):58.

Bialer M, Johannessen SI, Kupferberg HJ, Levy RH, Loiseau P, Perucca E. (1999). Progress report on new antiepileptic drugs: a summary of the fourth Eilat conference (EILAT IV). Epilepsy Res. 34:1–41.

Battino D, Croci D, Granata T, Manoli D, Messina S, Perucca E. (2001). Single-dose pharmacokinetics of lamotrigine in children: influence of age and antiepileptic comedication. Ther Drug Monit . 23:217–222.

Battino D, Croci D, Rossini A, et al. Topiramate pharmacokinetics in children and adults with epilepsy: a case-matched comparison based on therapeutic drug monitoring data. (2005). Clin Pharmacokinet. 44:407– 416.

Berry D, Millington C. (2005). Analysis of pregabalin at therapeutic concentrations in human plasma/serum by reversed-phase HPLC. Ther Drug Monit . 27(4):451-6.

Bialer M. (2006). New antiepileptic drugs that are second generation to existing antiepileptic drugs. Expert Opin Investig Drugs. 15(6):637-47.

Bentué-Ferrer D, Tribut O, Verdier MC. (2010). le groupe Suivi Thérapeutique Pharmacologique de la Société Française de Pharmacologie et de Thérapeutique. Therapeutic drug monitoring of tiagabine. [Article in French] Therapie. 65(1):51-5.

Coppola G, Auricchio G, Federico R, Carotenuto M, Pascotto A. (2004). Lamotrigine versus valproic acid as first-line monotherapy in newly diagnosed typical absence seizures: an open-label, randomized, parallel-group study. Epilepsia . 45:1049–53.

Carmant L. (2011). Vigabatrin therapy for infantile spasms: review of major trials in Europe, Canada, and the United States; and recommendations for dosing. Acta Neurol Scand . 124(192):36–47.

Dworkin RH, Corbin AE, Young Jr JP, Sharma U, LaMareaux L, Bockbrader H, Garofalo EA, Poole RM. (2003). Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial. Neurology . 60:1274–1283.

Dhillon S. & Sander J. (2003). Epilepsy. In: Clinical Pharmacy and Therapeutics. Wolker R., Edward K . Ch. 29, pages 465-479. Third edition. U.K .

Donner E.J. and Snead O.S . (2006). New Generation Anticonvulsants for the Treatment of Epilepsy in Children. The American Society for Experimental NeuroTherapeutics . 3:170–180.

Eke T, Talbot JF, Lawden MC. (1997). Severe persistent visual field constriction associated with vigabatrin. BMJ . 314:180–181.

Emilio Perucca. (2002). Marketed New Antiepileptic Drugs: Are They Better Than Old-Generation Agent. Therapeutic Drug Monitoring . 24:74–80.

Elberry AA, Felemban RK, Hareeri RH, Kurdi SM. (2012). Short communication. Efficacy and safety of levetiracetam in pediatric epilepsy. A Saudi Pharmaceutical Journal , production and hosting by Elsevier B.V. 20: 81–84.

Faught E, Sachdeo RC, Remler MP, Chayasirisobhon S, et al. (1993). Felbamate monotherapy for partial-onset seizures: An active-control trial. Neurology . 43:688–692.

Franz DN, Tudor C, Leonard J, Egelhoff JC, Byars A, Valerius K, Sethuraman G. (2001). Lamotrigine therapy of epilepsy in tuberous sclerosis. Epilepsia. 42(7):935-40.

Fischer JH, Patel TV, Fischer PA. (2003). Fosphenytoin: clinical pharmacokinetics and comparative advantages in the acute treatment of seizures. Clin Pharmacokinet . 42(1):33-58.

French J. A., Kanner A. M., Bautista J., et al. (2004). Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new onset epilepsy: report of the TTA and QSS Subcommittees of the American Academy of Neurology and the American Epilepsy Society. Neurology. 62: 1252-60 .

Fisher R.S., Boas W., Blume W., Elger C., Genton P., Lee P. & Engel J. (2005). Epileptic Seizures and Epilepsy: Definitions Proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia . 46(4): 470-472. Blackwell Publishing.

Faught E. (2007). Topiramate in the treatment of partial and generalized epilepsy. Neuropsychiatr Dis Treat . 3(6): 811– 821.

Grove J, Schechter PJ, Tell G et al. (1981). Increased gammaaminobutyric acid (GABA), homocarnosine and beta-alanine in cerebrospinal fluid of patients treated with gammavinyl-GABA (4-amino-hex-5-enoic acid). Life Sci . 28:2431–9.

Gherpelli J.L.D., Kok F., Fornos, Elkins L.C., Lefevre B.H.W. & Diament A.J. (1992). Discontinuing medication in epileptic children: A stud y of risk factors related to recurrence. Epilepsia. 33: 681-686.

Graves NM. (1993). Felbamate. Ann Pharmacother . 27:1073–81.

Gustavson LE, Mengel HB. (1995). Pharmacokinetics of tiagabine, a γ - aminobutyric acid-uptake inhibitor, in healthy subjects after single and multiple doses. Epilepsia. 36:605–611.

Gilliam FG, Gidal, BE. (2001). Lamotrigine. In: The treatment of epilepsy: principles and practice (Wyllie E, ed.), Vol 63, Ed 3, pp 853–868. Philadelphia: Lippincott Williams & Wilkins.

Glauser TA. (2001). Oxcarbazepine in the Treatment of Epilepsy. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy . 21(8):904-19.

Glauser TA, Pellock JM. (2002). Zonisamide in pediatric epilepsy: review of the Japanese experience. J Child Neurol. 17(2):87-96.

Glauser TA, Pellock JM, Bebin EM, Fountain NB, Ritter FJ, Jensen CM, et al. (2002). Efficacy and safety of levetiracetam in children with partial seizures: an open-label trial. Epilepsia . 43:518–24.

Grosso S, Galimberti D, Farnetani MA, Cioni M, Mostardini R, et al. (2005). Efficacy and safety of topiramate in infants according to epilepsy syndromes. Seizure 14:183–189.

Guerrini R. (2006). Topiramate in the Treatment of Epilepsy – A Review. European Neurological Disease . 2: 40-44.

Greiner HM, Lynch ER, Fordyce S, Agricola K, Tudor C, Franz DN, Krueger DA. (2012). Vigabatrin for childhood partial-onset epilepsies. Pediatr Neurol. 46(2):83-8 .

Howard JR, Dix RK, Shumaker RC, Perhach JL. (1992). Effect of felbamate on carbamazepine pharmacokinetics. Epilepsia .33(3):84-85.

Hussein G, Troupin AS,Montouris G. (1996). Gabapentin interaction with felbamate. Neurology. 47:1106

Hussein Z, Posner J. (1997). Population pharmacokinetics of lamotrigine monotherapy in patients with epilepsy: retrospective analysis of routine monitoring data. Br J Clin Pharmacol. 43:457–464.

Hammoudi DS, Lee SSF, Madison A, et al. (2005). Reduced visual function associated with infantile spasms in children on vigabatrin therapy. Invest Ophthamol Visual Sci. 46:514 –520.

Hamandi K, Sander JW. (2006). Pregabalin: a new antiepileptic drug for refractory epilepsy. Seizure. 15(2):73-8.

Hwang H, Kim K. (2008). Review article, New antiepileptic drugs in pediatric epilepsy. Brain & Development . 30: 549–555.

Jarrar RG, Buchhalter JR. (2003). Therapeutics in pediatric epilepsy, Part 1: the new antiepileptic drugs and the ketogenic diet. Mayo Clin Proc . 78:359–70.

Johannessen SI, Battino D, Berry DJ, Bialer M, Krämer G. ,Tomson T, Patsalos PN . (2003). Therapeutic Drug Monitoring of the Newer Antiepileptic Drugs . Therapeutic Drug Monitoring .25:347-363.

Jan MS, Zuberi SA, Alsaihati BA. (2009). Pregabalin: Preliminary Experience in Intractable Childhood Epilepsy. Neurology . 40(5): 347-350

Kaufman DW, Kelly JP, Anderson T, et al. (1997). Evaluation of case reports of aplastic anemia among patients treated with felbamate. Epilepsia . 38: 1265-1269.

Kelley MT, Walson PD, Cox S, Dusci LJ. (1997). Population pharmacokinetics of felbamate in children. Ther Drug Monit . 19:29–36

Kwan P. & Brodie M.J. (2000). Early identification of refractory epilepsy. New England journal of medicine. 5: 314–319.

Kirmani BF, Crisp ED., Kayani S, Rajab H. (2009). Role of intravenous levetiracetam in acute seizure management of children. Pediatr Neurol . 41:37-39.

Lau AH, Gustavson LE, Sperelakis R, Lam NP, El Shourbagy T, Qian JX, Leyden T. (1997). Pharmacokinetics and safety of tiagabine in

subjects with various degrees of hepatic function. Epilepsia. 38:445–451.

Leppik IE, Rarick JO, Walczak TS, Tran TA, White JR, Gumnit RJ. (2002). Effective levetiracetam doses and serum concentrations: age effects. Epilepsia. 43(7):240.

LaRoche SM., Helmers SL. (2004). The New Antiepileptic Drugs Clinical Applications. JAMA . 291(5):615- 620.

Linda D. Leary, MD, and Martha J. Morrell, MD. (2004). Update on New Antiepileptic Drugs in Children. Primary Psychiatry. 11(4):40-45.

Matsumoto K, Miyazaki H, Fujii T, Hashimoto M. (1989). Binding of sulfonamides to erythrocytes and their components. Chem Pharm Bull (Tokyo). 37:1913–1915.

Mattson R.H. (1995). Antiepileptic drug monitoring: A reappraisal. Epilepsia . 36 (5) : S22-S29.

McLean MJ. (1995). Gabapentin. Epilepsia . 36(2):S57–S86.

Morton LD. (1998). Clinical Experience With Fosphenytoin in Children. J Child Neurol . 13(1):S19-S22 .(

Mimaki T. (1998). Clinical pharmacology and therapeutic drug monitoring of zonisamide. Ther Drug Monit . 20:593–7.

Miura H. (2004). Zonisamide monotherapy with once-daily dosing in children with cryptogenic localization-related epilepsies: clinical effects and pharmacokinetic studies. Seizure: European Journal of Epilepsy . 13(1): S17-S23.

Pellock J.M. & Willmore L.J. (1991). A rational guide to routine blood monitoring in patients receiving antiepileptic drugs. Neurology. 41: 961-964.

Pellock J.M. (1994). Standard approach to antiepileptic drug treatment in the US. Epilepsia . 35 (4): S11-S18.

Pellock JM, BrodieMJ. (1997). Felbamate: update.Epilepsia. 38:1261-1264.

Pellock JM, Glauser TA, Bebin EM, Fountain NB, Ritter FJ, Coupez RM, Shields WD. (2001). Pharmacokinetic study of levetiracetam in children. Epilepsia . 42(12):1574-9.

Pellock JM. (2001). Tiagabine (Gabitril) Experience in Children. Epilepsia. 42(3): 49–51.

Perucca E. (2006). Clinical pharmacokinetics of new generation antiepileptic drugs at the extremes of age. Clin Pharmacokinet . 45:351–363.

Pellock JM, Faught E, Leppik IE, Shinnar S, Zupanc ML. (2006). Felbamate: consensus of current clinical experience. Epilepsy Res .71(2-3):89-101 .

Patsalos, P.N.; Berry, D.J.; Bourgeois, et al. (2008). Antiepileptic drugs—Best practice guidelines for therapeutic drug monitoring: A position paper by the subcommission on therapeutic drug monitoring, ILAE commission on therapeutic strategies. Epilepsia . 49:1239–1276.

Peltzer B, Alonso WD, Porter BE. (2009). Topiramate and Adrenal Corticotropic Hormone as Initial Treatment of Infantile Spasms. J Child Neurol. 24(4): 400–405 .

Rey E, Pons G, Olive G. (1992). Vigabatrin. Clinical pharmacokinetics. Clin Pharmacokinet. 23:267–278.

Rose MA, Kam PCA. (2002). Review article, Gabapentin: pharmacology and its use in pain management. Anaesthesia . 57:451-462.

Randinitis EJ, Posvar EL, Alvey CW, Sedman AJ, Cook JA, Bockbrader HN. (2003). Pharmacokinetics of pregabalin in subjects with various degrees of renal function. J Clin Pharmacol. 43:277–283.

Reimers A, Skogvoll E, Sund KJ and Spigset O. (2007). Lamotrigine in children and adolescents: the impact of age on its serum concentrations and on the extent of drug interactions. European Journal of Clinical Pharmacology. 63(7) 687-692.

Rylance GW et al. (2008). BNF for children , the essential resourse for clinical use of medicines in children. BMJ group , RPS publish in RCPCH publications Ltd.

Singhi P.D & Mitra S. (1997). Approach to the management of a child with epilepsy. Indian Practice. Indian Pediatrics. 34: 27-40.

Serra J., Montenegro M. & Guerreiro M. (2005). Heart Antiepileptic Drug Withdrawal in Childhood: Does the Duration of Tapering Off Mater for Seizure Recurrence ? J Child Neurol. 20(7): 624-626.

Shields WD, Pellock JM. (2011). Vigabatrin 35 years later — from mechanism of action to benefit–risk considerations. Acta Neurol Scand. 124 (192): 1–4.

Taylor C, McLean J, Bockbrader H. (1986). Zonisamide. In Meldrum BS, Porter R. New anticonvulsant drugs. John Libby, London, pp. 277–294.

Takeoka M, Krishnamoorthy KS, Soman TB, Caviness VS Jr. (1998). Fosphenytoin in infants. J Child Neurol. 13(11):537-40.

Thompson CD, Barthen MT, et al. (1999). Quantification in patient urine samples of felbamate and three metabolites: acid carbamate and two mercapturic acids. Epilepsia. 40:769–776.

Tomson T., Dahl M.L. & Kimland E. (2007). Therapeutic monitoring of antiepileptic drugs for epilepsy. Cochrane Database Syst Rev . 24; (1):2216.

Titlic M, et al. (2008). Lamotrigine in the treatment of pain syndromes and neuropathic pain. Bratisl Lek Listy. 109 (9) 421-424.

Tolman JA, Faulkner MA. (2009). Vigabatrin: a comprehensive review of drug properties including clinical updates following recent FDA approval. Expert Opin Pharmacother 10:3077–89.

Uthman BM et al. (1996). Intramuscular use of fosphenytoin. Neurology. 46(1):S24-S28.

Uldall P, Bulteau C, Pederson SA, et al. (2000). Tiagabine adjunctive therapy in children with refractory epilepsy: a single-blind dose escalating study. Epilepsy Res. 42:159–68 .

Vollmer KO, von Hodenberg A, K¨ olle EU. (1988). Pharmacokinetics and metabolism of gabapentin in rat, dog and man. Arzneim Forsch Drug Res. 36:830–839.

Valencia I, Piñol-Ripoll G, Khurana DS, et al. (2009). Efficacy and safety of lamotrigine monotherapy in children and adolescents with epilepsy. Eur J Paediatr Neurol. 13(2):141-5 .

Verrotti A, D'Adamo E, Parisi P, Chiarelli F, Curatolo P . (2010). Review Articles Levetiracetam in Childhood Epilepsy. Pediatric Drugs. 12(3):177-186

Ward DL, Shumaker RC. (1990). Comparative bioavailability of felbamate in healthy men. Epilepsia. 31:642.

Wagner ML, Graves NM, Marineau K, Holmes GB, Remmel RP, Leppik IE. (1991). Discontinuation of phenytoin and carbamazepine in patients receiving felbamate. Epilepsia. 32:398–406.

Ward DL, Wagner ML, Perhach JL, Kramer L, Graves N, Leppik I, Shumaker RC. (1991). Felbamate steady-state pharmacokinetics during co-administration of valproate. Epilepsia. 32(3):8.

Wallace S.J. (1992). Drug management of epilepsy. Dev Med Child Neurol. 34: 1018 - 1021.

Wagner ML . (1994). Felbamate: a new antiepileptic drug. American Journal of Hospital Pharmacy. 51(13):1657-1666.

Wallace S. & Farrell K. (2004). Epilepsy in children. book reviews. Second edition. London, Arnold. ISBN, 0-340-80814-4. PP 737-738.

Willmore LJ, Abelson MB, Ben-Menachem E, Pellock JM, Shields WD. (2009). Vigabatrin: 2008 update. Epilepsia. 50:163–73.