Using antiepileptic drugs in children: recent developments and recommendations

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Educational aims

- To understand the correct use of antiepileptic drugs in different types of epilepsy seizures in children
- To comprehend how an understanding of pharmacokinetics can improve drug therapy in epilepsy
- To recognize how appropriate pharmacological treatment of epilepsy in children can ensure better quality of life and better neurodevelopmental outcomes

Key words
epilepsy, anti-epileptic drugs, paediatrics, pharmacokinetics

Abstract

Epilepsy is one of the most common neurological disorders, with approximately 45 per 100,000 children developing new-onset epilepsy every year. Children are a vulnerable population with unique health needs and a correct diagnosis and thus correct treatment of epilepsy in children, particularly a diagnosis of early onset epilepsy, is important in order to ensure better quality of life, neurodevelopmental outcomes, cognition, education, improved level of function and future employment. Therapy with antiepileptic drugs (AEDs) aims to minimize the frequency of epileptic seizures with minimal side effects. The first generation AEDs (such as phenytoin, carbamazepine and valproic acid) are still widely used, although they are associated with serious side effects and pharmacokinetic problems (narrow therapeutic indices, nonlinear kinetics, and drug-drug interactions due to enzyme inhibition and enzyme induction properties). The novel AEDs (such as lamotrigine, levetiracetam, rufinamide, and zonisamide) have expanded the treatment options of epilepsy, however they are also associated with severe pharmacokinetic shortcomings, especially for paediatric populations.

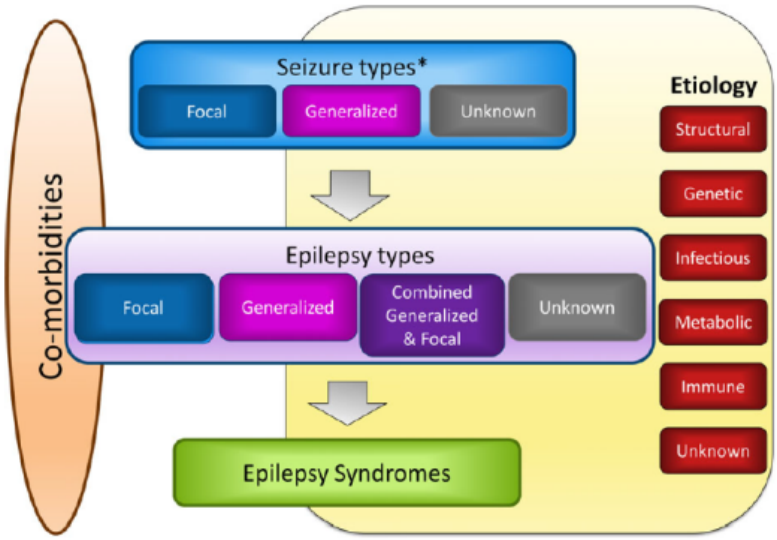
This educational article will discuss how the correct use of these drugs can lead to improved quality of life measures. This paper also provides an overview of ongoing research on the use of population pharmacokinetics in addressing the challenges paediatric populations offer to drug and dose individualisation.

Introduction

Epilepsy is one of the most common neurological disorders, occurring in the range of 0.5-1.0% of the general population.[1] It is a heterogeneous condition and classification of epileptic seizures by the International League Against Epilepsy (ILAE), the most widely adopted scheme, classifies seizures according to seizures symptoms and not underlying aetiology. A revised framework for the Classification of the Epilepsies, designed to work with the classification of seizure types, which considers levels of diagnosis: seizure type, epilepsy type (focal, generalized, combined generalized and focal, unknown) and epilepsy syndrome has just been approved by ILAE[2] (see Figure 1). Most persons with epilepsy first develop the condition in childhood with approximately 45 per 100,000 children per year developing new-onset epilepsy.[3] Between 2% and 4% of all children in Europe develop at least one convulsion associated with a febrile illness before the age of 5 years. The highest incidence of epilepsy is in the first year of life. Neonatal seizures occur in ~1.5% of neonates, febrile seizures in 2-4% of young children, and epilepsy in up to 1% of children and adolescents.[4] The paediatric population poses a challenge to the individualisation of drug therapy and this is even more so in epilepsy.

In Malta, epilepsy is known as a 'Schedule V' condition, meaning that it is one of the medical conditions in which patients can obtain free drug therapy through the Maltese National Health Service (Social Security Act, 2014). At a local level only specifically branded drugs are used in the pharmacological management of epilepsy. In a Maltese study of 220 children with epilepsy by Soler[5] the point prevalence rate of active epilepsy in children up to the age of 15 years in 1999 was 2.22 per 1000 population in females and 2.61 per 1000 in males up to the age of 15 years, with no significant difference between males and females (p=0.25). Similar findings regarding the larger number of boys with epilepsy are found in a number of studies. In Soler's study, 47% of children suffered from generalized seizures which were more common in infants and pre-school children, while 37% had partial seizures. Motor seizures were present in 30% of children while 30% had complex partial seizures with secondary generalization. There was equal prevalence of both generalised and partial seizures in school-aged children. Twenty-three per cent of children (all up to the age of 5 years) also had a history of

Figure 1: New ILAE framework for the classification of the Epilepsies. *Denotes onset of seizure (adapted from Scheffer et al., 2017[2])



febrile seizures (17% simple seizures, 5% complex febrile seizures). In Soler's study, 2% of children had infantile spasms, 30% had major motor seizures, 15% had absence seizures, 37% had partial seizures, 15% had a mixtures of seizure phenotypes, whereas 1% of seizures were unclassified.

Pharmacological therapy with antiepileptic drugs (AEDs)

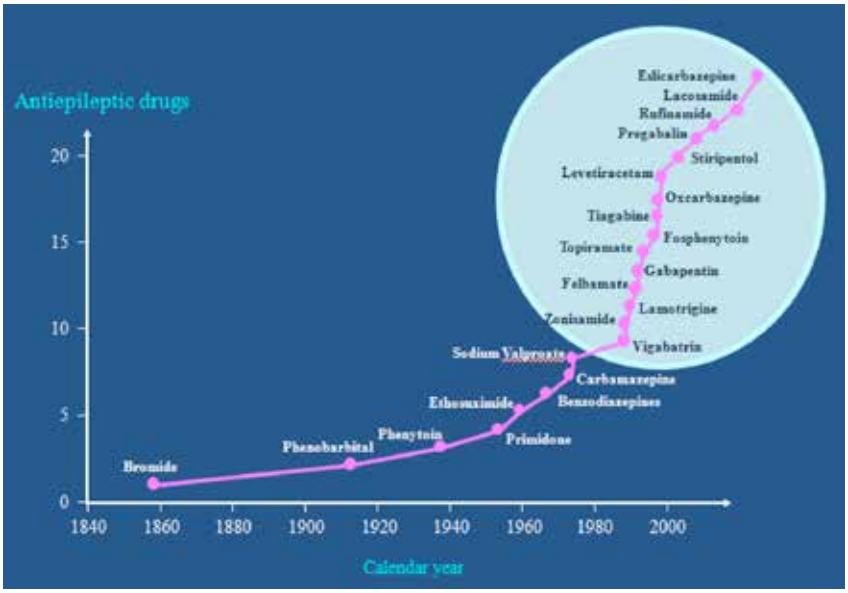
Pharmacological therapy with antiepileptic drugs (AEDs) aims to minimize the frequency of epileptic seizures with minimal side effects.[6] AEDs are used as long term adjunctive therapy or as monotherapy in epilepsy and can result in seizure freedom for around 70% of patients. The target in the treatment of epilepsy is to control seizures with low or no adverse effects. About 20 % of paediatric epilepsy population are not seizure free despite AEDs therapy either as mono or poly therapy.[7] Before 1993, phenobarbital, phenytoin, carbamazepine, valproic acid, ethosuximide, and the benzodiazepines were the only antiepileptic drugs used in the treatment of epilepsy in children. The approval of new generation AEDs expanded the treatment options for epilepsy for children and adults. These new generation AEDs have equal efficacy with better tolerability, pharmacokinetic properties, and side effect profiles compared to the older AEDs.[8]

The first-generation AEDs (phenytoin, phenobarbital, carbamazepine, ethosuximide, primidone, and valproic acid) were mostly developed before the 1960s, and they are still used, although they are associated with serious side effects and problems in the individualisation of drug therapy due to narrow therapeutic indices. They are also associated with numerous drug-drug interactions due to enzyme induction and enzyme inhibition properties and even non-linear kinetics in some case.

In 1990s, second or third generation AEDs were developed (felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, rufinamide, stiripentol, tiagabine, topiramate, vigabatrin, zonisamide, eslicarbazepine acetate, and lacosamide) in attempts to address the shortcomings of the older AEDs and improve the risk-benefit ratio.[9] Consequently, the treatment options of epilepsy have been expanded, however even this novel therapy is still associated with significant shortcomings, especially for paediatric populations.

Felbamate was approved by FDA to be used in United Stated in 1993. It shows efficacy in Lennox-Gastaut syndrome and partial seizures in children.[10] Aplastic anemia and hepatic failure are life-threatening adverse side effects of felbamate. Gabapentin was approved in 1993 as adjunctive therapy in the treatment of partial seizures with or without secondary generalization as adjunctive therapy in patients 3 years and older. It is also effective in some children with refractory partial seizures and in controlling seizures associated with benign childhood epilepsy with centrotemporal spikes.[11] Lamotrigine (LTG) was approved in the USA in 1994 for the treatment of focal seizures, then in 1998 it was approved to be used as adjunctive treatment of Lennox-Gastaut syndrome. LTG is now considered as first line drug for focal seizures and generalized tonic-clonic seizures. Oxcarbazepine was approved in 2000 for the treatment of partial-onset epilepsy as monotherapy or polytherapy in patients aged 4 years or older.

Figure 2: Development of Antiepileptic drugs. Adapted from Brodie, 2010[8]



It shows equal efficacy to phenytoin with better tolerability in a randomized study in children.[12] Levetircetam was approved in 1999 for the treatment of partial-onset seizures in adults as adjunctive therapy. It shows high efficacy and tolerability in refractory mixed seizure in children.[13] Tiagabine was approved in 1997 for the treatment of partial seizures in patients 12 years of age and older as adjunctive therapy. Topiramate was approved 1997 as adjunctive therapy for the treatment of primary generalized tonic-clonic seizures, partial-onset seizures, and seizures associated with Lennox-Gastaut syndrome in patients older than 2 years. Vigabatrin was initially licensed in 1989 however due to its visual toxicity it was eventually with withdrawn.[14] Zonisamide was approved in 2000 for the treatment of partial-onset seizures.

Local practice for the treatment of epilepsy in Malta follows the Guidelines issued by the UK's National Institute of Clinical Excellence (NICE)[15] (see Table 1). NICE guidelines also recommend that patients who do not respond to adjunctive drugs after an adequate trial of first line AED has been unsuccessful are referred to tertiary centres for evaluation in adjunction to consideration of further pharmacotherapy. An adequate trial of AED is one in which an AED (preferably one recommended by the guidelines) has been used at a therapeutic dose (preferably confirmed by means of therapeutic monitoring of serum blood levels), for sufficient duration of time, in a patient who has been adherent to drug therapy. If this trial has not been sufficient to provide seizure control, another drug may be added. If the first drug attempted has not been well-tolerated by the patient, one may change initial monotherapy to another drug which is better tolerated. In some circumstances, one may need to seek the optimum balance between, seizure control, drug efficacy, safety, tolerability and patient quality of life. NICE guidelines recommend that in the case of adults, AED therapy is initiated on the recommendation of a specialist, but in the case of children, NICE guidelines recommend that AED therapy should be initiated by a specialist directly, in the context of communication, discussion and explanation to the patient and their carers/family, as appropriate. The decision with regard to which AED to use as initial therapy depends on the nature of the presenting epilepsy syndrome or type of seizure if the diagnosis of an epilepsy syndrome is unclear. Usually, AED therapy is initiated after a second seizure. It is initiated after the first seizure if there is an associated neurological deficit, there is clear evidence of epileptic activity on electroencephalography, the risk of further seizures is deemed to be unacceptable or there is a structural brain lesion on cerebral radiographic imaging.[15]

Pharmacokinetics of AEDs

Understanding differences in the pharmacokinetics (PK) and /or pharmacodynamics (PD) between children and adults and also between children of different ages is important in the individualisation of drug therapy in epilepsy. Pharmacokinetic processes (absorption, distribution, metabolism, and elimination) and pharmacodynamic effects are affected by developmental changes in childhood.[16] For example, pH of intra-gastric fluid is higher in neonates than in adults and this can cause a decrease in the bioavailability of weak acidic AEDs such as phenytoin and phenobarbital and subsequently higher doses is needed.[17] Additionally, the delayed gastric emptying time in neonates slows the absorption of some drugs. Many studies have shown that the metabolizing enzyme capacity is changed during childhood and maturation of the enzyme systems occur at different rates. Thus, total drug clearance is highest in neonates, and declines with age reaching adult values in adolescence.

This is also the case for AEDs since many studies have indicated that the apparent oral clearance of AEDs is higher in children compared with adults.[18] Moreover, Perucca pointed out that the data available indicates that clearance of novel AEDs in children is increased by 20-170%, depending on the drug and patient's characteristics. Furthermore, the distribution of drugs in children is influenced by the changes in the body composition which is depending also on the age. For instance, the increase in body water:body fat ratio in neonates and infants leads to an increase in the volume of distribution for hydrophilic AEDs such as phenobarbital. [17]

The influence of such developmental changes in childhood on PK of a drug is

Table 1: Drugs used in the management of more common epilepsies (adapted from 2013 NICE guidelines for the management of epilepsy)[15]

TYPE OF SEIZURE	AED RECOMMENDED BY NICE GUIDELINES	TYPE OF THERAPY (INITIAL THERAPY OR ADJUNCTIVE THERAPY)
Focal	Lamotrigine, Carbamazepine	Initial monotherapy
Refractory focal	Carbamazepine, Clobazam, Gabapentin, Lamotrigine, Levetiracetam, Oxcarbazepine, Sodium valproate, Topiramate	Adjunctive
Generalised tonic-clonic	Valproate, Lamotrigine, Carbamazepine, Oxcarbazepine	Initial monotherapy
Refractory generalised tonic-clonic	Lamotrigine, Levetiracetam, Sodium valproate, Topiramate	Adjunctive
Absence	Ethosuximide, Sodium valproate, Lamotrigine	Initial monotherapy
Myoclonic	Sodium valproate, Levetiracetam, Topiramate	Initial monotherapy
Tonic or atonic	Sodium valproate	Initial monotherapy
Refractory tonic or atonic	Lamotrigine	Adjunctive
Infantile spasms	Vigabatrin or (if not due to tuberous sclerosis) add steroid	Initial therapy
Idiopathic generalised epilepsy	Sodium valproate, Lamotrigine, Topiramate	Initial therapy
Refractory idiopathic generalised epilepsy	Sodium valproate, Lamotrigine, Levetiracetam, Topiramate	Adjunctive therapy
Juvenile myoclonic epilepsy	Sodium valproate	Initial monotherapy

investigated using plasma drug concentration time profiles, which require measurements of drug concentrations from biological matrixes. Thus, these age-related PK and PD differences are rarely reported in the literature, since for ethical reasons, children are rarely included in clinical trials. Investigators usually have access only to a small number and volumes of blood samples which makes interpretation and modelling of the pharmacokinetics more difficult.[16]

In addition, it is estimated that between 50 and 90% of medicinal products used in paediatric population have never been specifically evaluated for use in that group. The absence of suitable authorised medicinal products to treat conditions in children is due to the fact that pharmaceutical companies do not perform the necessary research and development to adapt medicinal products to the needs of the paediatric population. The use of off-label and unauthorised products with the associated risks on inefficacy and/or adverse reactions is the only alternative solution for the physician to treat paediatric patients.[18] The current use of many AEDs in children is off-label and is based on the safety and efficacy derived from adult trials and from smaller uncontrolled studies in children that provide early pharmacokinetic data.[19] Most paediatric epileptologists have, to date used, ad hoc reasoning in the design of dosage regimens for AEDs in children. This may cause therapeutic failure and occurrence of severe adverse effects.

Pharmacokinetics of the new antiepileptic drugs

Thus the availability of these new AEDs in the last decades promised an increase in the efficacy of pharmacological treatment for many types of epileptic seizures in children, with reduced adverse effects and less need for therapeutic drug monitoring. Yet various shortfalls were also seen with some of these novel AEDs especially due to some of their pharmacokinetic properties. Pharmacokinetics is the study of the time course of a drug in the body, basically the liberation, absorption, distribution, metabolism and elimination of the drug. The pharmacokinetics of a drug vary from one patient to another due to several factors such as genetic factors, age, concomitant treatment, physiological and pathophysiological conditions such as pregnancy and impaired function of the liver and the kidneys.[20] This pharmacokinetics variability results in altered dosage requirements. Thus an inclusive understanding of pharmacokinetic properties of AEDs and the factors which contribute to their pharmacokinetic variability is essential for the correct use of AEDs in clinical practice.[21]

Felbamate shows linear kinetics in children and adults during mono or polytherapy.[22] The metabolism of felbamate is enhanced by enzyme-inducing AEDs such as phenobarbital, phenytoin, primidone and carbamazepine. Gabapentin's bioavailability decreases with increasing dosage, possibly because of saturation of the transporter system.[23] Lamotrigine (LTG) clearance in infants below the age of 2 months is lower than in older infants. Lamotrigine clearance is influenced by enzyme inducing and enzyme inhibiting AEDs. Enzyme inducing increases LTG clearance in children to 1.8ml/min/kg whereas; enzyme inhibiting decreases LTG clearance to 0.67 ml/min/kg.[24] Levetiracetam is mostly eliminated unchanged in the urine (66%) and 27% as inactive metabolites.[25] Oxcarbazepine is a prodrug and is metabolised to the two equipotent pharmacologically active enantiomers of a monohydroxy derivative (MHD).[26] Enzyme inducing AEDs (phenytoin, Phenobarbital and carbamazepine) enhance the metabolism of MHD and decrease its serum concentrations. Tiagabine is displaced by valproic acid from its serum protein binding sites.[26] Co-administration of enzyme-inducing AEDs decreases topiramate half-life to 12h, increase topiramate clearance and subsequently its serum concentrations decreased to 50%.[27] The half-life of zonisamide is 50-70 h during monotherapy, and it is reduced to 25-35 hrs with co-administration with enzyme inducing AEDs. Clearance of zonisamide is higher in children compared to adults, and children require higher doses to achieve the serum concentrations as that in adults.[18]

Thus, overall, new AEDs are negligibly bound to plasma proteins, except tiagabine which is over 95% bound to plasma proteins. The clearance of the new AEDs has also been found to be higher in children than in adults and thus dosage adjustment is required in paediatric population, which is not only weight-based. Gabapentin and vigabatrin are eliminated primarily through renal excretion and therefore, show low drug-drug interaction potential. On the other hand, the hepatic metabolism of several of the new AEDs such as lamotrigine, topiramate, oxcarbazepine, tiagabine, and felbamate is accelerated by enzyme inducing enzymes, including some of the traditional AEDs. Moreover, the metabolism of lamotrigine is inhibited by valproic acid.

AED use in Malta

In a study carried out by Scerri[28] valproate was found to be the most commonly prescribed conventional AED (65%) in the paediatric population in Malta. This was followed by carbamazepine (24%). Lamotrigine was also the most commonly prescribed of the newer AEDs (16%) in Soler's study and in 19.7% of cases in Scerri's study. It may be that the use of lamotrigine and levetiracetam (both newer AEDs) may have increased in comparison to carbamazepine use, possibly because of the efficacy, safety and tolerability profile of newer AEDs and the relative lack of drug interactions.

In Soler's study[5], the main type of AED therapy was monotherapy (in 70% of cases i.e. 144 children), while 21% were on poly-drug therapy. The findings of predominant AED monotherapy were also described by Dörks *et al* in their 2013 German study[29] and Nicholas *et al* in their 2012 UK study[30] which revealed that more patients were on monotherapy compared to poly-drug therapy in the study populations concerned. It is significant that in the studies in which AED monotherapy was the main type of therapy as well as the studies reporting a dominant use of multiple drugs, a common AED in all the studies in which the main AED used was reported, was valproate. This could be because valproate has been used for a long time and clinicians have good experience with it, but also because it has good efficacy and generic effects on multiple types of seizures. It is important to evaluate the role of drugs and their efficacy in the context of different genetic and environmental risk factors in populations, which may lead to a differential resistance to AEDs between different populations, especially in the context of specific genetic polymorphisms in different populations which alter a drug's pharmacodynamic properties.

However, the use of monotherapy versus poly-drug therapy has a number of implications for patient management. The use of more than one AED could result in reduced quality of life, loss of function and impaired productivity. Poly-drug therapy is also associated with increased adverse drug reactions, worsening of mental function and aggressive behaviour in some patients, which can be a key variable in their adverse health-related quality of life scores. Poly-drug therapy may also be associated with a complex dosing regimen which may also lead to poor adherence to AED therapy. It also increases the risk of drug toxicity.

In Soler's local study[5], mean age at onset of epilepsy was of 5.3 years. In her study,

Soler also confirms that onset of epilepsy had commonly occurred by the time the child was 2 years old. These findings are important because age of onset of epilepsy has implications on prognosis for development. Persons with early onset epilepsy and longer duration of the condition perform poorly in neuropsychological tests carried out in adulthood, showing more generalised, far-reaching and intrusive deficits in comparison to persons diagnosed with epilepsy over the age of 11 years, even when adjusting for confounders such as seizure frequency.[31] These findings emphasise the need for early diagnosis and optimal management of seizure disorders, especially in persons who are diagnosed earlier in life, so as to maximise their functional potential at a neurocognitive level, especially since drug efficacy studies reveal that 30% to 40% of persons with epilepsy remain uncontrolled despite pharmacotherapy.[32]

Epilepsy affects multiple domains in a patient's life, including work and employment, relationships, family and care providers. It is associated with organic, psychiatric and psychological morbidity, stigma, social isolation, cognitive difficulties, dependence on others and difficulties related to employment.[33] Epilepsy is also associated with decreased life expectancy and increased mortality, with increased risk of suicide and accidental injury, and a general decrease in quality of life, especially in patients with active epilepsy who experience frequent seizures. Increased patient self-efficacy is associated with improved quality of life.[34] Support groups and social services may help empower patients with epilepsy, but these services may be under-utilised due to lack of awareness of their existence or due to stigma.[35] In a 2006 survey of 907 patients between the ages of 18 and 65 years, antiepileptic drug (AED) monotherapy was associated with better quality of life than poly-drug therapy for the treatment of epilepsy.[36]

Hermann *et al.*[31] described that cognitive impairment exists at baseline, prior to the initiation of AED therapy and that these impairments can be altered for better or for worse by AEDs. In a study by Meador et al, 2005[36] using the Medical College of Georgia Delayed Paragraph Recall test, lamotrigine and gabapentin were not found to produce deterioration in recall, unlike carbamazepine, phenytoin and topiramate, which produced a 10% to 20% reduction in number of items recalled. A decrease in recall can have a profound impact on the well-being of a child sitting in a classroom, or an office worker, carrying out activities that rely on focus, attention and memory, with a decrease in quality of life as a result of impaired performance and achievement. This also shows us how complex the selection of AEDs can be, since one must consider multiple factors including formulation, concurrent drug therapies and comorbidities, dosage regimen, adherence to therapy, adverse effect profile and frequency, efficacy and likelihood of cognitive effects.

The European task force for drug development in children (TEDDY) was developed as part of the 6th European Framework for Research and Development between 2005 and 2010, with the cooperation of eleven countries seeking to develop new drug therapies to treat a variety of illnesses.[37] TEDDY recommended research on 21 Antiepileptic drugs, including pharmacoepidemiological studies to determine which drugs were to be prioritised in research endeavours. The Scottish Intercollegiate Guideline Development Network (SIGN)[38] (guideline 70) suggests the use of carbamazepine, sodium valproate, lamotrigine and oxcarbazepine as first line AEDs in the management of partial and secondary generalised seizures. Sodium valproate and lamotrigine are used as first-line drugs in the management primary generalised seizures, as well as in the case of doubt about the type of seizure or seizure syndrome. Level 1 evidence suggests that phenytoin, carbamazepine, sodium valproate, lamotrigine and oxcarbazepine have similar efficacy when used in the management of generalised tonic-clonic. The newer AEDs, lamotrigine and oxcarbazepine have a better safety and tolerability profile. Sodium valproate and lamotrigine are also used in the management of absence seizures and myoclonic seizures. Lamotrigine can worsen myoclonic seizures in some cases. Ethosuximide has been used for absence seizures in children for a very long time. Due to improved safety and tolerability profiles – especially with regard to fewer effects on cognition and behaviour, as well as the lack of interactions with other drugs, lamotrigine use may prove to be particularly advantageous in treating adolescents, young women and elderly persons with epilepsy.

Pharmacokinetic modelling and population pharmacokinetics of antiepileptic drugs

Pharmacokinetic modelling is a powerful tool to study how demographic parameters, pathophysiological conditions, genetic factors and other sources of variability influence the dose-concentration relationship in such populations.[16] The population PK approach allows the analysis of data from unbalanced designs and also from studies that are usually excluded from pharmacokinetic analysis, such as concentration data obtained from paediatric and elderly patients. Thus, population pharmacokinetic analysis plays an important role in individualization drug therapy in paediatric epilepsy. In traditional pharmacokinetic studies, the subjects are usually healthy volunteers or highly selected patients and the mean plasma concentration-time profile is the main focus of interest. Pharmacokinetic modelling is thus useful in the determination of pharmacokinetic parameters in a specific patient population. This type of prediction of pharmacokinetic parameters is of great importance in order to individualize dosing regimen in a specific population such as paediatric epileptic population since epilepsy is a chronic neurological condition and developmental changes occur from childhood to adulthood. Many variables influence plasma drug concentrations of AEDs, and thus the pharmacokinetics of these drugs, especially in children. However, satisfactory pharmacokinetic models which allow accurate predictions of drug plasma concentrations still lack especially in paediatric populations and little published research has been found in this area. Most paediatric epileptiologists use ad hoc reasoning in the design of dosage regimens for AEDs in paediatric epilepsy. Pharmacokinetic software packages, such as Adapt® and NONMEM® are useful in the determination of pharmacokinetic parameters and can be very useful in a chronic neurological condition such as epilepsy.[39]

Conclusion

Epilepsy is a common neurological condition and research initiatives are being promoted at an international level, in order to address issues of drug development in epilepsy. This is a move in accordance with the WHO's 2013 report on 'Priority Medicines for Europe and the World', which emphasises the importance of addressing chronic non-communicable diseases which are characterised by high morbidity and mortality.[40] This same document includes children among 'special groups' whose needs need to be addressed and in whom the management of illnesses needs to be prioritised. Children are a vulnerable population with unique health needs – physical, psychological and social. Their physiology is different from that of adults. Hence even the way their body is able to handle drugs differs from that of an adult. Parents play an important role in the healthcare management of young children

who are dependent. As children grow into adolescence they meet unique healthcare challenges, such as possible difficulties in adherence to therapy, especially when they begin to take control themselves over certain aspects of their healthcare such a taking their own medication on their own.

Population pharmacokinetics also play an important role in improving the therapeutic outcomes for paediatric populations with epilepsy, by contributing to the individualization of drug therapy and development of personalised medicine. It will thus lead to improved therapeutic outcomes and reduced adverse events in these patients.

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Key points

- Epilepsy is one of the most common neurological disorders, with approximately 45 per 100,000 children developing new-onset epilepsy every year
- Children are a vulnerable population with unique health needs whose physiology is different from that of adults and thus handle drugs differently from adults
- The novel antiepileptic drugs have expanded the treatment options of epilepsy, however, they are also associated with pharmacokinetic shortcomings, especially for paediatric populations
- The correct use of these drugs can lead to improved quality of life measures
- The use of population pharmacokinetics addresses the challenges paediatric populations offer to drug and dose individualisation