Advances, Challenges and Shortcomings of Epilepsy Drug Treatment

H. Tesfaye

Department of Medical Chemistry and Clinical Biochemistry
Division of Clinical Pharmacology
Faculty Hospital in Motol
2nd Faculty of Medicine
Charles University
Prague, Czech Republic

E-mail: hundie.tesfaye@fnmotol.cz

Abstract: - Epilepsy is the group name for convulsion symptom arising from neural organized function deficits originated within or outside the brain. Since considerable number (around 50 million people) of the World population of all ages is affected, it is one of health care problems worldwide. Many drugs have been used in the past to relieve symptoms by inducing changes in permeability to specific ions thus to stabilize membranes and interfering with release of neurotransmitters or other mechanisms. Nowadays, there are more drugs, but no one is developed for causal therapy as classification of epilepsy itself is very complex despite advanced technology diagnostic strategies. Although there is continuous emergence of new agents, pharmacoresistant symptom and adverse reactions including drug-drug interactions continue to challenge. Hardly preventable adverse effects (gastrointestinal, mental, or behavioral, neurologic or less commonly cutaneous, haematologic hepatic) by some agents may lead to reduction of quality of life, whereas some agents are known teratogens. Despite all developments in the field, no drug is considered as causal therapy for epilepsy to date. Thus aim of antiepileptic drug prescription after management of emergency situation like status epilepticus is prophylactic rather than therapeutic. The purpose of this paper is to emphasize practical challenges and shortcomings associated with old and new antiepileptic drugs (AEDs). The paper also discusses the importance of therapeutic drug monitoring with very qualified interpretation and close interdisciplinary work of clinician and laboratories determining the drug plasma levels. The author purposely included some of own case studies as useful demonstration, how therapeutic drug monitoring in very challenging situations is of vital importance.

Key-Words: - Epilepsy, Antiepileptic Drugs (AEDs), Drug-Drug Interactions, Therapy Failure

1 Introduction

Epilepsy is a chronic neurological condition characterized by recurrent seizures. There are many types of seizures and their symptoms can vary from a momentary disruption of the senses, to short periods of unconsciousness or staring spells, to convulsions. Epilepsy can be described also as a spectrum disorder because of its different causes, different seizure types, its range of co-existing conditions, and because the disorder can vary in severity and impact from person to person. Epilepsy can be caused by many different conditions that affect a person’s brain (e.g., stroke, brain tumor, central nervous system infection, head injury). Often no definite cause can be found. Epilepsy cannot be transmitted from person to person. Epilepsy affects about 2.3 million adults [1] and 467,711 children 0-17 years of age [2]. Data query from
the Child and Adolescent revealed that about 1 in 26 people will be diagnosed with epilepsy at some point in their lives and about 150,000 new cases of epilepsy will be diagnosed in the United States each year [3] resulting in an estimated annual cost of $15.5 billion in medical costs and lost or reduced earnings and production. Epilepsy is a common neurological disorder in the pediatric population, affecting up to one percent of children, and for which the mainstay of treatment is anticonvulsant medication. Despite the frequent use of anticonvulsant drugs, remarkably little is known about the safety and efficacy of most of these medications in the pediatric epilepsy population. Although infants and young children are disproportionately affected by epilepsy, there are currently only few anticonvulsant medications that have been specifically evaluated and approved for use in children younger than 2 years of age. Just one year ago Levetiracetam as an adjunctive treatment for partial onset seizures in infants and children from one month of age has been approved. Cormier and Chu [4] concluded that the current data leading to the approval of levetiracetam for use in infants and children with partial onset seizures is encouraging, although more work needs to be done before definitive conclusions can be drawn about the efficacy of levetiracetam across different pediatric age groups.

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2 SIGNS AND SYMPTOMS

Characteristics of seizures vary and depend on where in the brain the disturbance first starts, and how far it spreads. Temporary symptoms can occur, such as loss of awareness or consciousness, and disturbances of movement, sensation (including vision, hearing and taste), mood or mental function. People with seizures tend to have more physical problems (such as fractures and bruising), as well as higher rates of other diseases or psychosocial issues and conditions like anxiety and depression.

3 CAUSES

The most common type is idiopathic epilepsy and has no identifiable cause, whereas epilepsy with a known cause is defined as secondary epilepsy, or symptomatic epilepsy. In many cases, there is an underlying genetic basis. In general epilepsy may arise when there are disruptions to the normal connections between nerve cells in the brain (much like disruptions in wiring of a complex electrical circuit), when there are imbalances of natural chemicals or neurotransmitters that are important to the signaling among nerve cells, or when there are changes in the membranes of nerve cells, including proteins called ion channels, that alter their normal sensitivity. Some of these disruptions, imbalances, and changes may develop early in life, sometimes related to hereditary factors and sometimes related to early exposures and events. Others may be acquired later. In nearly two-thirds of the cases of epilepsy, a specific underlying cause is not identified. In these instances, the cause may be labeled cryptogenic if the cause is unknown, or idiopathic if the epilepsy is not associated with other neurologic disease but is consistent with certain syndromes that may be inherited.

3.1. THE CAUSES OF SECONDARY (OR SYMPTOMATIC) EPILEPSY COULD BE:

- brain damage from prenatal or perinatal injuries (a loss of oxygen or trauma during birth, low birth weight);
- congenital abnormalities or genetic conditions with associated brain malformations;
• a severe blow to the head leasing to traumatic brain injury
• a stroke that starves the brain of oxygen;
• an infection of the brain such as meningitis, encephalitis, neurocysticercosis;
• certain genetic syndromes;
• a brain tumor.

There are many types of seizures. These can be classified into two broad groups:

• Primary generalized seizures—seizures begin with widespread involvement of both sides of the brain.
• Partial seizures—seizures begin with involvement of a smaller, localized area of the brain. With some partial seizures, the disturbance can still spread within seconds or minutes to involve widespread areas of the brain (secondary generalized seizure).

However, having a seizure not necessarily means to have epilepsy. In general, seizures do not indicate epilepsy if they only occur as a result of a temporary medical condition such as a high fever, low blood sugar, alcohol or drug withdrawal, or immediately following a brain concussion. Among people who experience a seizure under such circumstances, without a history of seizures at other times, there is usually no need for ongoing treatment for epilepsy, only a need to treat the underlying medical condition. Some people have seizures that are hardly noticeable to others. Sometimes, the only clue that a person is having an absence seizure—a type of primary generalized seizure sometimes called petit mal—is rapid blinking or a few seconds of staring into space. In contrast, a person having a complex partial seizure may appear confused or dazed and will not be able to respond to questions or direction for up to a few minutes. Finally, a person having a generalized tonic-clonic seizure, sometimes called grand mal, may cry out, lose consciousness, fall to the ground, and have rigidity and muscle jerks lasting up to a few minutes, with an extended period of confusion and fatigue afterward.

4. SOCIAL AND ECONOMIC IMPACTS

Epilepsy accounts for 0.5% of the global burden of disease, a time-based measure that combines years of life lost due to premature mortality and time lived in states of less than full health. Epilepsy has significant economic implications in terms of health-care needs, premature death and lost work productivity. An Indian study calculated that the total cost per epilepsy case was US$ 344 per year (or 88% of the average income per capita). The total cost for an estimated five million cases in India was equivalent to 0.5% of gross national product. As an economic burden of epilepsy the United States estimates that about 2.0 million people in the United States have epilepsy and nearly 140,000 Americans develop the condition each year, while new cases of epilepsy are most common among children and older adults bearing the total indirect and direct cost of epilepsy in the United States is estimated to be $15.5 billion in the year 2004. [5] It is clear that, all over the world, the social consequences of epilepsy are usually more difficult to overcome than the seizures themselves. [6] Although the social effects vary from country to country, the discrimination and social stigma that surround epilepsy worldwide are often more difficult to overcome than the seizures themselves. People with epilepsy can be targets of prejudice. The stigma of the disorder can discourage people from seeking treatment for symptoms and becoming identified with the disorder.

5. LIFE EXPECTANCY AND FATALITY OF EPILEPSY

Most people with epilepsy live a full life span. Nevertheless, the risk of premature death is increased for some, depending on several factors:

Sometimes epilepsy is a symptom of a more serious underlying condition such as a stroke or a tumor that carries an increased risk of death. People with some types of epilepsy who continue to have major seizures can experience injuries during a seizure from falling or hurting their head that may occasionally be life-threatening. Very prolonged seizures or seizures
in rapid succession, a condition called status epilepticus, can also be life-threatening. Status epilepticus can sometimes occur when seizure medication use is stopped suddenly. Rarely, people with epilepsy can experience sudden death. These events are not well understood, although they are suspected sometimes to be due to heart rhythm disturbances during a seizure. The risk of sudden death is not increased for all types of epilepsy, but occurs more among people with major seizures, especially generalized tonic-clonic seizures that are not well controlled. To a great extent, it appears that optimal seizure control and some safety measures can reduce the risk of epilepsy-related mortality. WHO and its partners recognize that epilepsy is a major public health concern. WHO, the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) are carrying out a global campaign, ‘Out of the Shadows’ to provide better information and raise awareness about epilepsy, and strengthen public and private efforts to improve care and reduce the disorder’s impact. Projects to reduce the treatment gap and morbidity of people with epilepsy, train and educate health professionals, dispel stigma, identify potential for prevention and develop models integrating epilepsy control into local health systems are ongoing in many countries. For instance, in a project carried out in China, the treatment gap was reduced by 13% and there was improved access to care for people with epilepsy. [7]

6. TREATMENT

In certain types of partial epilepsy, especially when it can be determined that seizures consistently arise from a single area of the brain (the “seizure focus”), surgery to remove that focus may be effective in stopping future seizures or making them much easier to control with medication. Epilepsy surgery is most commonly performed when a seizure focus is located within the temporal lobe of the brain. Other supplemental treatments are sometimes beneficial when medications alone are inadequate and surgery is not possible. These include vagus nerve stimulation, where an electrical device is implanted to intermittently stimulate a large nerve in the neck, and the ketogenic diet, a high fat, low carbohydrate diet with restricted calories. Whatever are the options, before beginning with treatment, the first step is to ensure that the diagnosis of epilepsy is correct and to determine, if possible, the type of epilepsy and whether there are any underlying conditions that also need treatment. The medical decision about how best to treat the epilepsy is based on this evaluation. Antiepileptic drugs are the mainstay of treatment for most people. There are now many drugs available, and a doctor may recommend one or more of these based on several individual patient factors such as the type of epilepsy, the frequency and severity of the seizures, age, and related health conditions. After starting a medication, close monitoring is required for awhile to assess the effectiveness of the drug as well as possible side effects. Early in treatment, adjustments in dosage are often required. Sometimes, because of continued seizures or significant side effects, it is necessary to change to a different drug. For about two-thirds of people with epilepsy receiving optimum treatment, drugs are successful in fully controlling seizures. For the remainder, although drugs may have a partial benefit, some seizures continue to occur. Novel agents also appear in the trials, however, given the minimal improvement in prognosis and disappointing efficacy outcomes, it seems unlikely that these novel agents will have a major impact on outcomes for people with epilepsy.[8] The role of the new agents in the treatment algorithm will be increasingly defined as clinical experience accumulates. At present, their use is largely restricted to the adjunctive treatment of focal seizures, with or without secondary generalization, in adults with epilepsy who failed to achieve seizure freedom after having tried two or more first-line agents. [9] The search for new, more effective antiepileptic drugs (AEDs) continues. The three most recently approved drugs, the so-called third-generation AEDs, include lacosamide, retigabine and eslicarbazepine acetate and are licensed as adjunctive treatment of partial epilepsy in adults. However, the precise role
that these new AEDs will have in the treatment of epilepsy and whether they will make a significant impact on the prognosis of intractable epilepsy is not yet known and will have to await further clinical experience. [10] In a review discussing the efficacy and safety of the newer adjuvant antiepileptic therapies that may improve outcomes in patients unresponsive to monotherapy, including clobazam, vigabatrin, lamotrigine, gabapentin, topiramate, tiagabine, levetiracetam, oxcarbazepine, pregabalin, zonisamide and eslicarbazepine, with focus on lacosamide, Becerra et al. [11] published that lacosamide has been shown to exert its anticonvulsant effects predominantly by enhancement of the slow inactivation of voltage-gated sodium channels. [11] A priori- defined and post hoc pooled data analyses from phase II/III trials demonstrate that lacosamide effectively reduces seizures in patients at all three dosages evaluated with an early onset of efficacy, regardless of patient surgical history and concomitant AED regimen. [12] Beyond methodological interferences concentration effect relationship of AED is also a matter of concern [13], [14], [15] In a study to evaluate the efficacy and tolerability of levetiracetam (LEV) as add-on therapy in children with refractory epilepsies and to determine the value of LEV blood level monitoring in this population, Giroux et al [16] published that the most frequently observed adverse effects were drowsiness, behavioral difficulties, increase in seizure frequency and headaches, while no clear correlation between drug plasma concentration and efficacy has been found. [16] According to the study to evaluate the efficacy and tolerability of Levetiracetam in a large pediatric cohort with drug-resistant epilepsy from a prospective multicenter observational study it has been reported that Levetiracetam is a well-tolerated new AED that may effectively improve seizure control as an add-on drug in resistant epilepsy in childhood with good tolerability, however, neurologically handicapped children appear at increased risk for reversible neurocognitive side effects and have a poorer treatment response. [17]

<table>
<thead>
<tr>
<th>Drugs / Group</th>
<th>Possible mechanism of antiepileptic effects</th>
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<tbody>
<tr>
<td>Phenobarbital and Benzodiazepines</td>
<td>promote Cl- infix and hyperpolarization through GABAa/Cl-channel complex, both at different sites. (Phenobarbital at – picrotoxinin site</td>
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<tr>
<td>Valproic acid (VPA)</td>
<td>GABA mediated inhibition and Sodium channel blockade</td>
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<tr>
<td>Ethosuximide and trimethadione</td>
<td>Block specific type (T) Calcium channel</td>
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<tr>
<td>Vigabatrin and Progabalbin</td>
<td>Mainly interact with GABA complex</td>
</tr>
<tr>
<td>Phenitoin and Carbamazepine</td>
<td>Block the Sodium channel and stabilize it at inactive state.</td>
</tr>
</tbody>
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Table 1. Some AEDs and known mechanisms of actions against epilepsy

7. ANTIEPILEPTIC DRUG INTERACTIONS AS A CHALLENGE

Because antiepileptic drugs are frequently used together in polytherapy, knowledge of the major interactions between these drugs is of interest. Carbamazepine causes decreased concentrations of phenytoin and valproic acid. Phenobarbital stimulates P450 enzymes, leading to enhanced metabolism and thus lower concentrations of primidone, phenytoin, carbamazepine, and valproic acid. Valproic acid leads to increased phenobarbital concentrations. The acidification of urine by valproate enhances reabsorption of phenobarbital, which is also acidic. The resulting increase in the
1/2 of phenobarbital leads to a 10–20% (up to 40%) increase in its concentration after 24–26 days [18]. Phenytoin enhances the conversion of primidone to phenobarbital [19] the burden of drug-drug interactions is very challenging even in a patient, who initially adopted to several combinations.[20] (Fig. 1.).

Fig. 1. Typical pharmakokinetic interaction for three AEDs in a female child. The phenobarbital level was extremely high after addition of Valproic acid.

Many drug interactions have been also identified between various antiepileptic drugs and drugs from other classes. [21] Salicylate, phenylbutazone, and sulfonyleureas can increase the free fraction of phenytoin. Salicylate can increase the free fraction of valproic acid. Erythromycin interacts with valproic acid, leading to increased blood concentrations of valproic acid. Chloramphenicol, dicoumarol, disulfiram, isoniazid, cimetidine, and some sulfonamides cause increased phenytoin concentrations through enzyme inhibition.[22]

8. IMPORTANCE OF THERAPEUTIC DRUG MONITORING (TDM) OF AEDS

In 1994 it was reported that the cost of uncontrolled epilepsy in the UK was £4167 per patient per year. That of controlled epilepsy was found to be £1630. [23] If complete seizure control could reduce the costs of managing patients with epilepsy in a significant number of patients, the gains would be appreciable. TDM can help to improve seizure control in numerous ways including:

• identification of therapeutic failure due to under-dosage.

• identification of therapeutic failure in the presence of 'optimal' dosage suggesting that a different AED should be tried.

• detection of non-compliance with prescribed therapy, which may be responsible for unnecessary and avoidable therapeutic failure.

• identification of the uncommon situation in which over-dosage causes increased seizures.

• detection of pharmacokinetic interactions which may compromise the adequacy of the therapy.

Among the AEDs, principal feature of phenobarbitone TDM is related to its very low clearance. It has a long half-life (80-100 h) and takes 3 weeks to reach steady-state; therefore optimisation of therapy is slow. However, because of its long elimination half-life, sampling time in relation to dose is not critical, therefore sampling at trough is not an absolute requirement. Marked inter-individual variability in the blood level associated with good seizure control limits the value of TDM. Although routine TDM of phenobarbitone is of limited value, monitoring can be useful for improving compliance, confirming the clinical diagnosis of toxicity, and minimising the effects of drug interactions. The blood level at which toxicity with phenobarbitone appears is not well defined, but adverse neurological effects - nystagmus, ataxia and lethargy - are usually only seen with blood levels above 100 mmol/L. Many other side effects, including behavioural problems, are unrelated to blood levels. [24], [25] The target range for phenobarbitone is up to 170 µmol/L. Phenytoin is a highly protein bound drug that undergoes saturable hepatic metabolism. It is very loosely bound to and is readily displaced from the hepatic cytochrome P450 isoenzymes that are responsible for its metabolism. Therefore, small changes in dose or the introduction of a drug that displaces phenytoin from its protein binding sites or inhibits its metabolism can result in a disproportionate and unpredictable increase in phenytoin levels. This in turn may cause neurological toxicity. In addition, the phenytoin dosage at which saturation of hepatic enzymes
occurs varies from one patient to another, and this complicates phenytoin therapy further. As a result, accurate titration and use of phenytoin is very difficult without TDM. Sampling time in relation to dose is not critical but it should be noted that due to its half-life of up to 100 hours at high concentrations, phenytoin may take up to 4 weeks to achieve steady-state. The target range for phenytoin is up to 80 µmol/L. Ethosuximide is exclusively used in the treatment of absence seizures, which are frequent and easy to quantify by use of EEG telemetry. Consequently, it has been very easy to define a target range for ethosuximide.[26], [27], [28] In most patients ethosuximide blood levels correlate well with dose and the dosage can be adjusted empirically on the basis of response. Although routine TDM of ethosuximide is generally unnecessary, it is therefore useful in identifying those patients who do not respond to treatment despite an apparently adequate dose. This helps to distinguish between patients who are non-compliant, those who are rapid metabolisers and those who are refractory to the drug. The target range for ethosuximide is up to 700 µmol/L. The dose of carbamazepine is a poor guide to serum levels, and so TDM can be helpful when complete seizure control is not readily obtained (ref. 10). The target range for carbamazepine is up to 50 µmol/L. Carbamazepine exhibits auto-induction, therefore after initiation of therapy, steady-state blood levels are only achieved after 20 days. Due to substantial variation in blood levels, sampling should ideally be undertaken just prior to the next scheduled dose. A further confounding problem with carbamazepine is the presence of the pharmacologically active metabolite carbamazepine-epoxide. This contributes to toxic effects and has been implicated in numerous drug interactions. [29], [30], [31] Carbamazepine-epoxide can now be routinely monitored; its target range is up to 9 µmol/L. Levetiracetam is a new antiepileptic drug prescribed for the treatment of patients with refractory partial seizures with or without secondary generalization as well as for the treatment of juvenile myoclonic epilepsy. A wide variability in concentration-response relationships was observed in patients. Nevertheless, the levetiracetam plasma concentration could be used to help clinicians detect severe intoxication or to verify compliance by repeating the measurement in patients.[32] A new generation of antiepileptic drugs (AEDs) has reached the market in recent years with ten new compounds: felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, vigabatrin and zonisamide. The newer AEDs in general have more predictable pharmacokinetics than older AEDs such as phenytoin, carbamazepine and valproic acid (valproate sodium), which have a pronounced inter-individual variability in their pharmacokinetics and a narrow therapeutic range. For these older drugs it has been common practice to adjust the dosage to achieve a serum drug concentration within a predefined ‘therapeutic range’, representing an interval where most patients are expected to show an optimal response. However, such ranges must be interpreted with caution, since many patients are optimally treated when they have serum concentrations below or above the suggested range. It is often said that there is less need for therapeutic drug monitoring (TDM) with the newer AEDs, although this is partially based on the lack of documented correlation between serum concentration and drug effects. Nevertheless, TDM may be useful despite the shortcomings of existing therapeutic ranges, by utilisation of the concept of ‘individual reference concentrations’ based on intra-individual comparisons of drug serum concentrations. With this concept, TDM may be indicated regardless of the existence or lack of a well-defined therapeutic range. Furthermore, TDM is likely to be useful in many clinical settings for the newer AEDs due to pharmacokinetic variability.[33]

CONCLUSION

Epilepsy is one of the most common serious neurological conditions worldwide, with an age-adjusted incidence of approximately 50 per 100,000 persons per year in developed countries. Antiepileptic therapy can result in long-term remission in 60-70% of patients, but
many patients will require combination treatment to achieve optimal seizure control, as monotherapy is ineffective at controlling seizures in 30-53% of patients. Despite the increase in available treatment options, patient outcomes have not improved significantly and there is still a need for more effective therapies. Drugs used in the treatment of focal-onset seizures are a diverse range of compounds, and in most cases their mechanism of action is unknown or poorly defined. Advances in diagnostic prosuders, understanding of epilepsy as a disease is are obvious. Drugs for epilepsy treatment are also developing based on neuropathophysiology and electrophysiology. However, existing challenges such as clear diagnosis or classification failure as well as drug choice including unclear drug concentrations effect relation ship or multi-drug interaction in many cases warrant much further studies in the field to intensively continue yet.

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