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General Aspects of Therapeutics in the Patient with Epilepsy

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ABSTRACT

After the diagnosis of epilepsy, before defining the behaviour to follow, the doctor must take into account a series of general principles, which, if not fulfilled, will result in the control or not of the epileptic seizures, which is why it is significant importance that they are listed and known, with the aim of improving the quality of life of patients. These aspects include the objectives of drug treatment, patient recommendations, errors in antiepileptic treatment, which patients to treat, when to start treatment with Antiseizure Medications (ASMs), aspects to manage after a single seizure, indication of studies after treatment, stopping treatment, predictors of relapse and common precipitating factors for seizures, and serum dosing of ASMs. Satisfactory results are not obtained in the control of epileptic seizures and the quality of life of the patient, if these principles or guidelines are not taken into account.

INTRODUCTION

Epilepsy is one of the most common and disabling chronic neurological disorders. It is, in turn, a complex, multifaceted disease and so is its treatment [1]. There is currently no cure, so symptomatic drug treatment continues to be the mainstay of therapy for people with epilepsy [2]. Therefore, its comprehensive management acquires a special significance, aimed at controlling the quality of life of patients who suffer from it. Obviously, the diagnosis of the disease is essential and essential. In turn, after making the correct diagnosis of a patient, but before prescribing Antiseizure Medications (ASMs), previously referred to as anticonvulsant or antiepileptic drugs [1], the doctor must take into account a series of additional questions. A full understanding of these issues should allow the best outcome for the patient, regardless of the drug or other therapy chosen [3-7].

However, before getting into the complexities of treatment strategies, we need to make a brief reminder about the accuracy of the patient's diagnosis. The correct diagnosis is, after all, the foundation on which therapy is based. An improper diagnosis is likely to lead to insufficient and potentially harmful treatment [4,8]. This is a difficult subject, since epilepsy is a heterogeneous set of syndromes with innumerable causes and a wide variety of clinical expressions, one of which ultimately leads to an epileptic seizure itself [8]. So, how are we going to make a correct diagnosis of the patient with the disease? We can only do this by recognizing that

multiple levels of diagnosis are present, and these must be identified in each patient: [9]

• Positive and differential diagnosis

• Etiological diagnosis

• Diagnosis of seizures / epilepsy.

• Diagnosis of epileptic syndrome (if possible)

Once the Patient's Diagnosis is Certain, What are the Treatment-Related Issues that must be Considered to Optimize the Outcome for the Individual?

For this, we must consider that the treatment of epilepsies can be summarized in four topics: [4]

• Prophylactic / preventive

• Pharmacological

• Non-pharmacological: surgery and alternative treatments

• Psychological / Psychiatric

Some authors also include, as part of the treatment, the regulation of physical and mental activity [10]. Therefore, therapeutics should not be limited to the indication of Antiseizure Medications (ASMs), but rather the management that is needed should be analyzed casuistically. However, the objective of this review is to describe some general aspects, which, if not taken into account, may negatively influence the evolution of the patient due to inefficiency of the established therapy.

For its preparation, the Google Academic search engine and the descriptors epilepsy, positive and differential diagnosis, treatment of epilepsies / epileptic seizures and general principles of treatment were used. The Medline, Scielo, Scopus and Medscape databases were used.

General considerations [4,9,11,12]

Suffering from epilepsy commonly presents several consequences that must be anticipated by the doctor:

• Restrictions on driving and other unsafe activities, the persistence of stigma, and the small but real possibility of sudden death.

• Chronic unwanted effects of Antiseizure Medications (ASMs) on cognitive ability, mood, weight (gain and loss), Child bearing and sexual function.

• Cultural and financial stress, and some ASM regimens can be inconvenient and may not be performed correctly.

These issues are just as important, and can be just as complex, in patients with controlled epilepsy (or even a first seizure), as in those with intractable seizures.

Objectives of pharmacological treatment: [1,4,9,10,13,14]

➢ The objective of selecting a therapeutic regimen is to find a drug that is fully effective and without side effects.

➢ Allow patients to live as normally as possible, without seizures and with an adequate quality of life.

➢ For patients with epilepsy the important thing is: "not to have epileptic seizures, or side effects of drugs", having to provide the necessary information for them to manage their condition.

➢ The availability of a number of new Antiseizure Medications (ASMs) has helped us achieve this goal, particularly in terms of "side effects".

➢ Unfortunately, there has been no comparable benefit in the number of patients who become seizure-free.

The Physician must Never Forget: [1,9]

➢ Inform the person with epilepsy about the nature of their disease and the desirable life rules for adequate social integration.

➢ The diagnosis of epilepsy is eminently clinical, therefore pharmacological management should begin when the diagnosis of epilepsy is made, even when the etiology is undetermined.

➢ Successful treatment requires that therapeutic management plans be individualized for each patient, depending on the epilepsy syndrome and the type of seizure, the profile of adverse effects, the pharmacokinetic profile, the possible interactions with other drugs, the comorbidities that may affect ASMs, patient age, and reproductive considerations [15].

➢ Provide each patient with adequate management of psychiatric comorbidity, especially depression, which profoundly affects quality of life.

➢ Take into account the psychosocial difficulties of patients and the stigma it represents for society.

➢ For a patient with epilepsy, independence, driving, employment and safety are very real and serious concerns.

➢ The pharmacokinetic principles of treatment with antiseizure medications (absorption, apparent volume of

distribution, protein binding, elimination, control of serum levels) [16].

➢ The older Antiseizure Medications (ASMs) produce alteration of liver metabolism, through alteration of the cytochrome P450 system. Strong hepatic enzyme inducers are: Phenytoin, Carbamazepine, Phenobarbital and Primidone.

➢ The new ASMs do not have hepatic inducing properties or induce it only minimally.

➢ Despite the availability of numerous drugs with different mechanisms of action, 30% of all patients with epilepsy may be resistant to treatment [4,10,17-19].

Recommendations to the Patient: [4,20]

• No ingestion of alcoholic beverages.

• Do not drive vehicles (except 3 years or more crisis free).

• Maintain proper sleep habits. Sleep at night no less than 8 hours.

• Avoid stressful situations and additional responsibilities.

• Do not work unprotected at heights, or in places that offer danger in case of epileptic seizures.

• Avoid great physical effort.

• Encourage school and work insertion, and the fulfillment of family and social responsibilities. Conduct systematic, non-exhausting study.

• Avoid spearfishing and swimming (unless supervised).

• Remind the patient that the efficacy of the treatment is the suppression of the seizures and not the disappearance of the intercritical electroencephalogram (EEG) abnormalities.

• Control infectious diseases and avoid elevated body temperature.

• Guide the registry with the number, duration, schedule and severity of the seizures.

Errors in Antiseizure Treatment: [4,9,10]

• Incorrect positive diagnosis.

• Do not start therapy when the diagnosis is made (wait for the EEG or imaging studies to impose it).

• Establish medication at a total entry dose and not progressive.

• Initial use of combination therapy.

• No choice of drug according to type of seizure, syndrome or special group.

• Treatment of a single seizure.

• Interrupt him: during puberty, without a crisis-free period or suddenly (abrupt replacement) [21].

• Do not take into account the half-life of Antiseizure Medications (ASMs) and their plasma levels.

• Ignore drug interactions. Combination of drugs with similar effects.

• Use of drugs that lower the epileptogenic threshold or proconvulsants.

• Not taking into account the collateral (adverse) effects of antiseizure medications (ASMs).

• Consider the efficacy of the treatment: disappearance of intercritical EEG abnormalities and not the suppression of seizures (with normal functionality).

Should We Treat all Patients with Epilepsy? [4,9]

A single seizure in adults or children usually does not require treatment unless:

• There is evidence of brain injury or EEG abnormalities (particularly generalized spike-wave discharges).

• A first non-febrile seizure between 2 and 5 years may be the first manifestation of epilepsy (astatic-myoclonic type) that will require vigorous treatment to prevent the development of an epileptic status or encephalopathy.

• Benign childhood epilepsy with centrotemporal spikes with infrequent seizures and juvenile myoclonic epilepsy with myoclonic seizures only do not indicate the need for drug treatment, unless the seizures are frequent and disturbing to the family [22].

• A provoked crisis, related to metabolic disorders, exposure to toxins or other insults, does not imply the need to establish treatment with ASMs.

• If a second attack would be dangerous for an adult, for reasons related to employment or driving, treatment can be guaranteed after a first isolated crisis [23].

The risk of recurrence followed by a first unprovoked attack in children and adults ranges from 27% to 71%. Most recurrences occur early, with approximately 50% of recurrences within 6 months of the initial seizure and more than 80% in the first 2 years of the initial seizure. Late recurrences are unusual, but can occur as early as 10 years after the initial event [24].

According to current concepts, the diagnosis of epilepsy after a single unprovoked seizure, associated with a high risk of

recurrence, may lead to the decision to start treatment or not [4,9].

It must be taken into account that a therapeutic decision is not the same as a diagnosis and must be personalized according to the wishes of the patient, the risk-benefit ratio in each specific case and the available options.

The physician must weigh the possibility of avoiding a second attack and the risks that it entails, against the risk of adverse pharmacological effects.

When to Start Treatment with Antiseizure Medications (ASMs) after a Simple Crisis?:

Drug treatment should be started only if the diagnosis of epilepsy is confirmed. However, the appropriate approach and management of the first seizure is relevant, which will depend on the correct identification of the risk of recurrence [4,20,25-27].

However, in clinical practice, we can specify situations that require the use of antiseizure therapy, such as the following:

Definitely:

-With Structural Injury

• Brain tumors

• Arteriovenous malformation

• Infection, such as abscess, herpetic encephalitis.

-No Structural Injury

• History of epilepsy in siblings (but not parents)

• Electroencephalogram (EEG) with defined epilepsy pattern

• History of previous symptomatic seizure (seizure in the context of illness or childhood)

• Febrile crisis, which is a very controversial topic

• History of previous brain injury, brain hemorrhage, Central Nervous System infection, head trauma

• Initial status epilepticus Possible.

• Unprovoked seizure with any of the risk factors listed above

Probably not **(although short-term therapy can be used)**

• Alcohol withdrawal

• Drugs abuse

• Seizures in the setting of an acute illness (ie high fever that can trigger simple febrile seizures, dehydration, hypoglycemia)

• A crisis immediately after an acute head injury.

• Specific benign epilepsy syndromes, such as benign epilepsy with centro temporal spikes.

• Crisis caused by excessive sleep deprivation (for example, college student at exam time)

Aspects to consider after a single seizure (which creates real uncertainty in the attending physician): [4,9,26]

• Was it really a seizure? Or was it a paroxysmal non-epileptic disorder?

• What type of seizure?

• Caused crisis or not? Acute symptomatic crisis? Remote symptomatic crisis? Epileptic seizures associated with epileptic syndromes? Crisis without identified cause?

• Was it the first crisis for sure?

• Are there risk factors for a second attack?

• Is the neurological exam abnormal?

• Is the Electroencephalogram (EEG) pathological?

• Is the structural study abnormal?

• Is the history of siblings and parents known? Do they have seizures too?

• Can this person be allowed to drive?

• Should there be limitations in your work?

• To treat or not to treat the patient?

• What are the risks of not treating him?

• What are the risks of treating him?

Of the total number of patients who are evaluated for a first seizure, a significant number will be diagnosed with epilepsy immediately or in the short term and the remaining will be explained the low, but existing risk of developing a second seizure in the following years [28].

Indication of Studies after an Epileptic Seizure: [4,9]

The indication for a brain imaging study should be considered, depending on the clinical context (history and physical examination).

The Electroencephalogram (EEG) should generally be obtained as soon as possible after the seizure.

When it is not certain that the paroxysmal episode that led the patient to the emergency room was an epileptic seizure, even after obtaining auxiliary tests such as neuroimaging and EEG, the patient should be followed up. It must be remembered that the EEG can be normal in patients with epilepsy, which is why the clinical method is of extraordinary value in this disease [26].

The use of techniques such as sleep deprivation before performing an EEG increases the chances of being able to record some interictal activity or even a seizure during the investigation.

Pseudoseizures can sometimes be difficult to diagnose and require prolonged video-EEG monitoring. This is an extremely important alternative, but reserved for patients with recurrence of episodes that are difficult to characterize and that generate diagnostic doubt [29].

Initiation of Treatment:

Drug selection and dose depend on many factors including gender, age, other drugs used by the patient, as well as kidney or liver dysfunction or other clinical and psychiatric conditions that could be positively influenced by a particular agent [27].

The most important risks of recurrent epileptic seizures are death, physical injury to the patient or others, brain injury, driving restrictions, and adverse psychosocial consequences [4,20,27,30].

The Decision to Start Treatment Involves:

• Having established the diagnosis that it was an epileptic seizure and not a pseudo-seizure, such as a syncopal episode or an event of psychogenic origin [31-33].

• Correctly identify the type of epilepsy.

• Be certain that the risk of recurrence for the patient is high.

• The selection of therapy with ASMs must be made carefully in relation to the type of seizure, severity, type of epilepsy or epileptic syndrome, the etiology and the triggering factor.

• Therapy should be started (preferably monotherapy) at a low dose and its dose gradually increased, until sustained therapeutic concentrations are achieved to avoid side effects. ("start low, go slow") [10,21,34].

• If there is toxicity with low doses that may be ineffective, gradually replace the first ASM with a second drug.

• If the attacks continue (without toxicity), increase the dose according to tolerance.

• If the epileptic seizures still persist, the transition to another first-line drug (in a second monotherapy) can be considered.

• If monotherapy with ASMs is unsuccessful, adjuvant treatment with a second-line drug should be considered (dual therapy).

• Rational combination therapy (selecting the most appropriate association to the characteristics of the patient and their epilepsy, taking into account the pharmacokinetic and pharmacodynamic characteristics of each ASM) has been advocated, but remains speculative regarding the best efficacy based on use of ASM with different modes of action.

• For the association of ASMs to increase efficacy without increasing toxicity, the theoretical bases of rational combination therapy propose considering the mechanism of action of each drug, its spectrum, tolerability, and pharmacodynamic and pharmacokinetic interactions. It is sensible not to use combinations with supposedly similar mechanisms because their adverse reactions can be additive.

• Faced with continuous epileptic seizures, a reassessment of the differential diagnosis should be made and surgery and other alternative methods should be considered.

Stopping Treatment: [4,9,10,35]

When patients go into long-term remission, discontinuation of ASMs may be considered in some people. However, it is not possible to determine whether the remission will persist after withdrawal of the medication. While there are indicators that help predict the successful removal of ASMs, there is no way to be absolutely sure that seizures will not reoccur. When deciding to withdraw medications, both the consequences of recurrence of seizures and the benefit of eliminating side effects must be considered.

Children have a lower risk of seizure recurrence than adults, in general, although it depends on the type of seizure and the etiology. This means that an ASM withdrawal test may be considered earlier in children (1 to 2 years of absence of seizures) than in adults (4 to 5 years of absence of seizures).

It should be noted that abrupt discontinuation of antiseizure medications (ASMs) is never a good idea. Serious seizures can occur during withdrawal of some ASMs, particularly benzodiazepines, carbamazepine, and oxcarbazepine. It is generally better to withdraw medications slowly [22].

There are no clear rules regarding the best moment or even the best way to proceed when deciding to suspend treatment, considering that at 12 months 60% -70% of treated patients will be seizure free.

According to recent considerations by a group of ILAE experts, it is estimated that epilepsy is resolved in subjects with an age-dependent epileptic syndrome who have exceeded the corresponding age or in those who have remained seizure-free

for the last 10 years and who have not taken antiepileptic medication for at least the last 5 years [24].

The presence of paroxysmal graphoelements in the electroencephalogram should not be taken into account for the decision to interrupt treatment with ASMs [10].

Predictive Factors for Recurrence of Epileptic Seizures: [4,24]

• Epileptic syndrome, eg Juvenile myoclonic epilepsy (JME)

• Underlying structural pathology, mental retardation, pathological neurological examination

• Continuous epileptiform abnormality on EEG

• Severe prolonged epilepsy before remission

• Increase in age

• Use of previous combination therapy.

Although there are no specific guidelines to suggest how ASM discontinuation should be managed in patients with these characteristics, the patient should understand that there is a substantial risk of recurrence if they are in these high-risk groups.

The ideal rate at which Antiseizure Medications (ASMs) should be withdrawn is unknown. In general, most epilepsy specialists prefer to gradually reduce ASMs as a precautionary measure. Epilepsy is a chronic disease and sudden or rapid changes in ASM treatment are rarely justified in the outpatient treatment of epilepsy [27].

In children, it is possible to try to stop the medication after they have been seizure-free for 2 years, while for adults the interval of absence of seizures before reducing and stopping an ASM is 3 to 5 years. In general, it takes 2 to 5 years without seizures. And the gradual reduction in ASMs should spread slowly over 6 to 12 months [36].

The risk of recurrence of seizures after having suffered unprovoked seizures decreases over time, although it never reaches the level of people who have never had a seizure. Most relapses are early. Late recurrences are rare after 5 years. After 10 years without antiepileptic medication, the annual risk of seizures is likely to be very low.

Common precipitating factors for seizures: [4,9]

• Stress, depression, anxiety, and sleep deprivation [27]

• Fatigue and exercise (intense physical effort)

• Strobe lighting (photosensitive / reflex epilepsy)

• Alcohol consumption

• Skip antiseizure medication

• Use of medications that can lower the seizure threshold or proconvulsant.

• Metabolic factors, Menstruation (catamenial epilepsy), fever (infection) and hyperventilation [37].

Serum Dosage of Antiseizure Medications (ASMs):

The choice of the initial dose of an antiseizure medication, the monitoring of plasma levels, or the substitution of another bioequivalent by the physician for a third party, are concepts to bear in mind when caring for the person with epilepsy.

Approximately half of the patients with epilepsy who start treatment with Antiseizure Medications (ASMs) are controlled in monotherapy and in low doses. A low initial dosage allows re-evaluation and avoidance of "over treatment", facilitating better treatment tolerability. The initiation of doses in monotherapy, seeking a low-medium range of doses, is the most appropriate approach [4,38,39]

The evidence from non-randomized studies and especially from clinical experience, indicates that the measurement of serum concentrations of old and new generation Antiseizure Medications (ASMs) can play an important role in guiding patient management, provided that the concentrations are measured with a clear indication and interpreted critically, taking into account the entire clinical context, which in our opinion is essential [4,21]

Some General Indications for the Measurement of Serum Concentrations of Antiseizure Medications [39]:

1. After initiation of treatment or after dose adjustment, when the physician decides to aim for a pre-selected concentration for that patient.

2. Once the desired clinical response has been achieved, to establish the "individual therapeutic range."

3. to assist the clinician in determining the magnitude of a dose increase, especially with ASMs that show dose-dependent pharmacokinetics (most notably, Phenytoin).

4. When there are uncertainties in the differential diagnosis of signs or symptoms suggestive of concentration-related ASM toxicity, or when toxicity is difficult to assess clinically (eg, in young children or in patients with mental disabilities).

5. When epileptic seizures persist despite apparently adequate dosage.

6. When an alteration in pharmacokinetics is suspected, due to factors related to age, pregnancy, associated diseases or drug-drug interactions.

7. To evaluate the possible changes in the concentration of ASMs in steady state, when a change is made in the formulation of drugs, including switches that have generic formulations.

8. Anytime there is an unexpected change in clinical response.

9. When poor treatment compliance is suspected [38].

Therapeutic monitoring of the antiseizure medication has been used as a tool to optimize the treatment of epilepsy for almost 50 years. Although there is little solid evidence for its usefulness in improving clinical outcomes, it continues to play a role in the management of this disease [4,40].

However, the practitioner should be aware that due to individual variation, many patients may require concentrations outside of the reference ranges.

In many situations, patient management is best guided by determining the "individual therapeutic concentration" defined as the concentration with which an individual is seizure-free, with good tolerability, or the best compromise between improvement in control. of seizures and concentration-related adverse effects.

With this concept, serum monitoring of ASMs can provide important information for decisions about dose adjustments of most antiepileptic medication in patients with unexpected treatment results or in situations associated with pharmacokinetic alterations, for example, during pregnancy, in different disease states, in conjunction with drug interactions, and in certain age groups (children and the elderly), where clinical evaluation of the effects of treatment can be particularly difficult [4,9].

CONCLUSION

There are general principles that must be taken into account by the modern practitioner, in the proper use of antiepileptic medications to achieve scientific management of the disease, with judgment and individuality.

CONFLICT OF INTEREST

There are no conflicts of interest between the authors

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