Epilepsy

Table of Contents

Epilepsy *2*

Disease Description: *2*

Etiology *2*

Seizure Types: *3*

Partial (focal, local) seizures 3

Generalised seizures 3

Unclassified epileptic seizures 4

Agency Guidelines *5*

FDA 5

EMA 5

Japan (Ministry of Health and Welfare) 6

Clinical Trial Endpoints *6*

Safety Assessment *6*

Clinical Trial Design *6*

References *7*

Epilepsy

Epilepsy is a common neurological disorder in which the normal activity of brain cells is sometimes disturbed. This can result in strange sensations, emotions and behaviour. Epilepsy can also cause convulsions, muscle spasms and a loss of consciousness.Around 50 million people have epilepsy worldwide; it is especially prevalent in childhood, adolescence and old age. Epilepsy is the most common serious brain disorder worldwide.

Disease Description:

Normally within our brain, millions of tiny electrical charges are passing between nerve cells and to all parts of the body. Epilepsy interrupts this normal pattern of charges with excessive electric discharges of nerve cells. This can affect a person's consciousness, movements or sensations for a brief period of time. Epilepsy is a nervous system disorder that causes seizures. Seizures can be caused by head injury, stroke, genital defect, meningitis, aneurysm, withdrawal of alcohol, prescription medicine.Having a single seizure does not necessarily mean that a person has epilepsy. Only when a person has had two or more unprovoked seizures separated by at least 24 hours he or she is considered to have epilepsy.

In order to ease medical communication for treatment purposes but also for clinical trials, it is good to use common international terminology and classification for epilepsy. The International League Against Epilepsy (ILAE) serves the medical community by suggesting formal classifications for epilepsies and seizures.

Etiology:

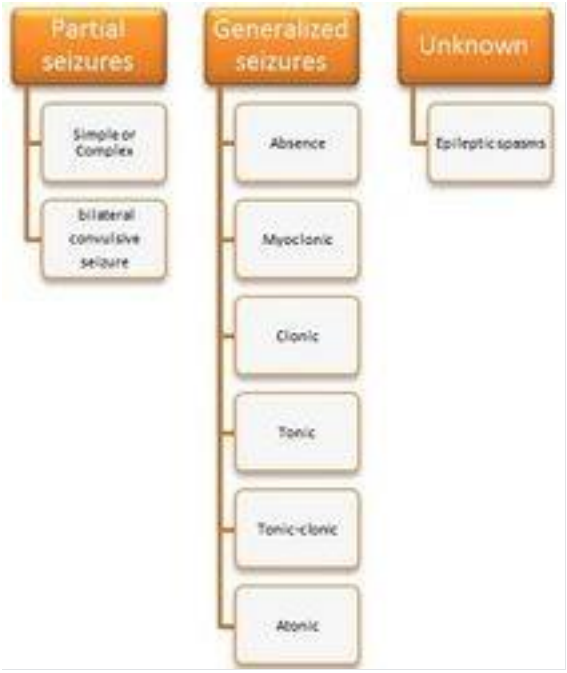
Epilepsy is classified into three main types (Etiology):

- Idiopathic: where there is no apparent cause, but it is possible that there may be a genetic link
- Symptomatic: where a cause has been found. Causes can include: head injury, brain damage at birth, stroke, brain infection and occasionally brain tumour
- Cryptogenic: where doctors believe there is likely to be a cause but they are unable to find it.

60% of people with epilepsy have idiopathic epilepsy.New terminology and concepts update the classification of 1989 to be consistent with current understanding of the epilepsies in clinical practice. Although the recommended terminology since 2010 for etiology is Genetic, Structural, Metabolic, Immune, Infectious and Unknown, the classification terminology of 1989 is still used in a lot of clinical trials.

Seizure Types:

Following epileptic seizures classification is based on ILAE proposal of 2010:



Partial (focal, local) seizures

Partial (focal) seizures occur when this electrical activity remains in a limited area of the brain. The person retains awareness or has an altered awareness. The differentiation between simplex and complex partial seizures is not anymore recommended.Partial seizures evolving to secondarily generalised seizures: The seizure starts in one part of the brain but then spreads to both parts. This seizure type was formerly known as secondarily generalised seizure.

Generalised seizures

Generalised seizures (convulsive or non-convulsive) affect both sides of the brainAbsence seizures: They start suddenly and are characterised by staring, loss of expression, unresponsiveness and, stopping any activity they are doing.Myoclonic seizures: A myoclonic seizure is a single or series of jerks (brief muscle contractions). Each jerk is typically milliseconds in duration. Although Myoclonic seizures are classifies ad generalised seizures, for this seizure type the person does not loose consciousness. This seizure type still belongs to generalised seizures as the person is likely to have other seizures (such as tonic clonic seizures) as well as myoclonic seizures.[5]Clonic seizures: A clonic seizure is a seizure involving bilaterally rhythmic jerking. The jerking in a clonic seizure is more sustained and rhythmic than seen in a myoclonic seizureTonic seizures: In a tonic seizure the person's muscles suddenly become stiff. If they are standing they often fall.Tonic-clonic seizures: An older term for this seizure type is "grand mal." As implied by the name, they combine the characteristics of tonic seizures and clonic seizures.The tonic phase comes first: All the muscles stiffen. Air being forced past the vocal cords causes a cry or groan. The person loses

consciousness and falls to the floor. The tongue or cheek may be bitten, so bloody saliva may come from the mouth. After the tonic phase comes the clonic phase: The arms and usually the legs begin to jerk rapidly and rhythmically, bending and relaxing at the elbows, hips, and knees. After a few minutes, the jerking slows and stops. Bladder or bowel control sometimes is lost as the body relaxes. Consciousness returns slowly, and the person may be drowsy, confused, agitated, or depressed.Atonic seizures: In an atonic seizure the person's muscles suddenly relax and they become floppy

Unclassified epileptic seizures

This is a grouping of seizures that cannot Underline be diagnosed as either a focal or generalised seizure and are thus grouped as unknown.Epileptic spasms: Epileptic spasm consist of a sudden forward flexion of the upper body followed by stiffening.

Further details regarding classification and commonly used diagnostic procedures for epilepsy can be found in the guidance of National Institute for Health and Care Excellence (NICE).

Agency Guidelines

The design of clinical trials often depends on what needs to be fulfilled for registration of a drug. Agency guidelines normally provide a lot of information on target populations and endpoints of studies. For those new to Epilepsy, agency guidelines can be an excellent point to start learning about the setup of trials in this therapeutic area. However, in Epilepsy, guidelines are not as detailed as in other therapeutic areas. Although they describe what is needed to register a new drug or indication, more detail on how to assess endpoints can be found in guidelines from scientific medical organisations like the International League Against Epilepsy (ILAE).

FDA

The FDA guideline has remained the same for more than 30 (!) years. The last changes were made in 1981. The guideline discusses clinical trial setups for phase I-III studies in both adults and children. It is a relatively small document (10 pages of main text) and mainly addresses long-term therapy of seizure disorders. However, clinical endpoints are mentioned in the guideline although no further advice, e.g. about non-inferiority/superiority margins is given. Measurements of efficacy include reduced seizure frequency and increased seizure-free intervals. Apart from seizure diaries, patient reported outcomes (PRO) are not discussed which may also be due to the relative age of the guideline. All in all the FDA guideline leaves much room for interpretation on how a trial should be designed to be sufficient for submission to the FDA.

EMA

The EMA Guideline is currently available as second revision and was issued in 2010. This relatively new guideline gives a general overview on prevalence and aetiology of the disease as well as current (as of 2010) success of therapy with Anti-epileptic Dugs (AED). The main text gives detailed instructions on selection of the study population under investigation. Populations are selected according to epileptic syndrome, seizure type and age of study subjects. The development of drugs in children and in the elderly is discussed in two separate sections to address special considerations in these patient cohorts. The assessment of efficacy is discussed in detail for a variety of study designs with explicit statements on duration of studies, (primary) efficacy parameters and PRO instruments. General considerations on the statistical analysis of efficacy are also provided. As opposed to the FDA guideline the primary efficacy endpoint is defined as analysis of responders/non-responders, where responders are patients who obtained at least a certain pre-defined percentage reduction of seizure frequency. Therefore in studies submitted to both FDA and EMA both endpoints are defined, where reduction in seizure frequency is used in the US and percentage of seizure reduction is used in Europe (see Clinical Trial endpoints for details). There are clear statements on the methodology of studies in the development of a new anti-epileptic drug for both Add-on and Monotherapy.

Japan (Ministry of Health and Welfare)

There is no PMDA (Pharmaceuticals and Medical Devices Agency) specific guideline for conducting epilepsy studies available. PMDA seems to follow international guidelines. Regarding submission of electronic data, PMDA might mandate this in CDISC format for NDA from 2016 onwards.

Clinical Trial Endpoints

- Efficacy Assessment
- Change in seizure frequency
- Seizure-free intervals
- Responder analysis (i.e. subjects achieving XX% reduction in seizure frequency)
- Decreased total seizure time
- Improved functional capacity
- Decreased incidence of adverse reactions
- Decreased generalisation of focal seizures
- Quality of Life (e.g. QOLIE-31-P)

The assessment of efficacy is primarily based upon seizure frequency and occurrence. This is due to the primary goal of treatment in epilepsy: seizure freedom of subjects.

Safety Assessment

- Extend of exposure
- Evaluation of treatment-emergent adverse events (TEAE)
- Evaluation of TEAE of interest

The overall safety assessment does not differ much from evaluations done in other therapeutic areas. However, there is a special focus on TEAE of interest

Clinical Trial Design

Study designs usually start with a baseline period during which the subject does not receive any study drug. This period is mainly to assess baseline seizure counts. The baseline period needs to have a certain length to be able to detect a reasonable amount of seizures as well as changes in seizure frequencies. This phase is also needed to finally confirm that subjects are eligible, e.g. number of seizures fits the study design, concomitant AED(s) are stable etc.

After the baseline period the study medication is introduced. This often happens in a separate titration period to increase the investigational drug up to the pre-defined dose regimen and/or to adjust concomitant AED doses. At the end of the titration phase the

subject should be on a stable pre-defined dose of the study drug. Following next is the treatment phase. Depending on whether the subject receives add-on or monotherapy this phase can last weeks to several years. Monotherapy studies usually take longer since study subjects are new on a AED and long term efficacy as well as safety need to be assessed. Add-on therapy needs shorter time windows to assess primary efficacy, however, also add-on trials can run several months to years. Trials in epilepsy are often split in two parts. The first part (core or double-blind part) lasts until primary efficacy and safety can be assessed. The second part is for long-term follow-up to further assess safety and long-term efficacy. During long-term follow-up subjects receive usually receive open-label study drug.

References

Epilepsy Information Page