Anti-epileptic Drugs

We will continue talking about epilepsy which is a chronic disease that has to be managed, so the treatment will be a management treatment , not a single day or week treatment we will deal with drugs that will be used for years or lifelong.

You know that in the CNS when we have an over excitement, we will have a seizure and this seizure results from opening of **Na^+ and Ca^{+2}** channels, mostly Na^+ channels and **activation of K+** channels(this will lead to increase in the repolarization)

So the strategies that we use to treat seizures are :

1) Inhibit the depolarization by inactivation of **Na^+ and Ca^{+2}** channels or inhibit repolarization by **activation of K^+** channels.
2) Work on neurotransmitter by increasing the gamma amino benzoic acid(GABA) or inhibit the glutamate by working on NMDA receptors .

Partial seizures:

❖ *Hydantoins - Phenytoin*

In the previous lecture we talked about **Hydantoins - Phenytoin** and we said that it is a very complex drug that is still in use although it is not the drug of choice for any type of the seizures , but sometimes we need to use it because some patients can't tolerate other drugs . Phenytoin is a good drug for **partial seizures**, but it is not the best. It may have an activity on Tonic-Clonic seizures.

Phenytoin mechanism :

it antagonises (block) the Ca^{+2} channels to reduce its activity and increase the duration of inactivation.

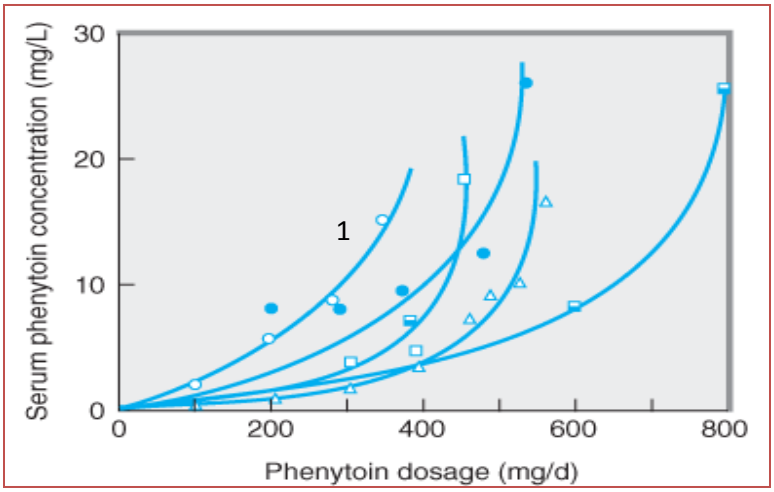
Phenytoin problems:

1) it is one of the most complicated drugs that we will use.
2) High drug-drug interaction
3) Highly bound to plasma protein.
4) It has a saturation issue within the excretion, it is not a first order kinetic, that means we can't reach something called rate of administration = rate of elimination. It is a Zero order reaction where build up of drug in the body occurs, so we have to monitor our patient who takes phenytoin . sometimes a little increase in the dose will leads to a high increase in the drug blood level within the patient and because of that ,the way we deal with phenytoin is not increasing by large increments (we **will not jump** from 300 mg/dl to 400 mg/dl),it is by small increment titration (we increase by 20s, usually we use a dose around 300 mg/dl dose)

** TO summarize : if the level of the drug with in the blood is not high enough for the recommended effect we have to increase the dose how??

We don't jump from 300 mg/dl to 400 mg/dl, we increase from 300 mg/dl mostly to 320 mg/dl . And because of its Excretion saturation issue (Excretion saturation issue of these drugs means that when you increase the dose by a certain amount, the concentration in the blood increases

severely) any small increment may produce high increase in the drug blood level and the patient may enter the zero order stage .



These are 5 different patients, every single patient responds to phenytoin in a different way, but they are close to each other. Patient number 1 from the beginning he has a buildup of the dose and enters the zero order at early stages because the saturation, excretion, metabolism and the buildup of the drug in his body is different from the other patients.

This problem is not in phenytoin alone, it is a problem in all the drugs that we use. This problem is " The Inter-individual variation " and it is the reason why we give different patient different doses .

Keep this in your mind that phenytoin is a really complex drug so don't increase and jump in the concentration of the drug , give the patient small increments (20s) and titrate the concentration for your patient well.

Phenytoin has a narrow therapeutic index so it has many adverse effects as :

1) Nausea and Vomiting.
2) Impairs brainstem & cerebellar function (dizziness, tremor, nervousness, blurred vision, **nystagmus** which is the first side effect that you will see even with the normal dose)
3) Folic acid (especially with long-term treatment with phenytoin) and Vit. D deficiency.

   The folic acid comes in the food as folate and it needs to be broken down by an enzyme then the body can use it . This enzyme will be inhibited by phenytoin. (This is the mechanism that we think is responsible for the reduction of the folic acid) .Every single lady who wants to be pregnant we start the administration of the folic acid 3 months before the pregnancy to reduce the neuronal defects, so its Important for safe pregnancy. .
   if your patient is a pregnant lady, she has to keep taking folic acid, it is not a choice now, it is a must.

4) Interaction: increases metabolism of the contraceptive pill (so it will reduce its activity), anti-coagulants (reducing its activity is very bad), and pethidine may be affected as well.

Drugs	Grand mal	Status epilepticus	Petit mal (absence seizure)	Partial seizure
Carbamazepine (p.o.)	++		contraindicated	+++
Clonazepam (p.o./i.v.)	+	+	++	
Diazepam (p.o./i.v.)		+		
Ethosuximide (p.o.)			+++	+
Lamotrigine (p.o.)	+++		+++	++
Lorazepam (i.v.)		+		
Midazolam (i.v.)		++		
Oxacarbazepine (p.o.)	++			+++
Phenobarbital (p.o./i.m.)	+	+++	contraindicated	
Phenytoin (p.o./i.v.)	+	+++	contraindicated	++
Topiramate (p/o.)	+			++
Valproic acid (p.o.)	+++		+++	++

In this sheet, Whenever you see this sign , TABLE

return back to this table

As you can see, we deal with 4 types of seizures : Grand mal ,Status epilepticus , Petit mal (absence seizure) , and Partial seizure .

Now look at the Phenytoin , it has a weak activity on Grand mal (+), a good activity on Status epliepticus, it is contraindicated in Petit mal , it has a nice activity on Partial seizure so we will use it **here** but not as a first line therapy, the first line therapy is Carbamazepine which is as you see the only drug that has (+++) effect on Partial seizure.

(Oxacarbazepine is a derivative of Carbamazepine with different side effects)

So the first line therapy for Partial seizure is Carbamazepine and the second one is Phenytoin . we use it because some patients don't respond well with Carbamazepine (as those 20% patients that are refractory after using several drugs) we will treat them with Phenytoin.We can treat them with Oxacarbazepine but we usually go to Phenytoin.

In the Petit mal (absence seizure) the Carbamazepine, Phenytoin and Phenobarbital are contraindicated . (explained later)

❖ *Carbamazepine*

mechanim of action :

Antagonism action on Na+ channels to inhibit repetitive neuronal firing, and there is an additional mechanism of action which is decreasing the production (or release) of glutamate (excitatory chemical).

Carbamazepine uses:

1) Because of that additional mechanism , the Carbamazepine has a preferable profile of efficacy against the Partial seizure
2) It can also be used in the treatment of neuropathic pain, because it inhibits the glutamate. Another drug that can be used is Gabapentin we will talk about it later.
3) Carbamazepine is the drug of choice in the treatment of the Trigeminal neuralgia

Trigeminal neuralgia is a very important disease that leads to a very severe pain, it can lead to suicide in ladies of the west but not in the Middle East (we return back to the idea of reference)

Carbamazepine Adverse effects:

1) Nausea & vomiting (especially in early treatment), constipation, diarrhea and anorexia
2) Skin irritation
3) The most important one is **CNS toxicity, it leads to Sedation, dizziness, drowsiness, confusion**
4) Bone marrow suppression (rarely, only 10% of the patients) and they may have leukopenia
5) it is inducer for **CYP1A2** and **CYP3A4** so there is high drug- drug interaction (as you remember the **Rifampicin** that is used in treatment of **Tuberculosis** has also a high drug- drug interaction)

At the end of the day we should remember that we deal with a narrow therapeutic index drug , the patient will have many side effects but he should take it to not suffer from seizure

Some patients can't tolerate it especially if they get bone marrow suppression or sever dizziness and drowsiness, so we move to the other choice which is Phenytoin

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Absence seizures

In this type there is no jerking, no tonic-clonic, the patient loses the alertness of what is surrounding him. Absence seizures are caused by oscillations between thalamus and cortex that are generated in thalamus by T-type (transient) Ca^{+2} currents .in other words, There is Ca^{+2} current that causes a type of confusion, and makes the patient out of surrounding

so, in order to treat it, we need a type of drug to inhibit those t-type Ca^{+2} channels which is **Succinimides – Ethosuximide**

❖ *Succinimides – Ethosuximide*

** Is the first choice, use for patients with absence seizures, it inhibits T-type Ca^{+2} channels.

Adverse effects: Slightly wider therapeutic index

- Nausea, vomiting and anorexia
- Cerebellar disturbance (drowsiness, dizziness, photophobia, headache, depression)
- Skin irritation
- Not to be used when pregnant (teratogenicity)

NOTE: The same side effects which are present in the usage of carbamazepine, phenytoin, but they are weaker here, so the profile for this drug is better than the previous mentioned drugs

TABLE

On the Petit mal (absence seizure) you will find that the ethosuximide is a great drug (+++), if the patient is a pregnant woman we use other drugs because this drug is teratogenic, we can give in this case **valproic acid or lamotrigine**, up to now the drug of choice for a non-pregnant lady with absence seizure is ethusuximide.

DO NOT USE THESE DRUGS IN ABSENCE SEIZURES:

carbamazepine , phenytoin, and phenobarbital (it is not used now at all) these drugs are **contraindicated** because they increase the incidence of absence seizures , because when you inhibit Na^+ channels the Ca^{+2} channels can work more , this causes more absence seizures .

To sum up:

Partial seizure → carbamezapine and phenytoin

Absence seizure → ethosuximide

GRAND MAL epilepsy

Here we need a drug with a different type of mechanism to cover the **generalized problems** that happens in the brain of the patient in the generalized epilepsy, and this drug is valproate (valproic acid), it is used in all forms of epilepsy, as it suppresses the initial seizure discharge and its spread.

❖ *Valproic acid (valproate)*

First-line for generalized seizures, also used for **partial seizures**, but the carbamezapine has a better activity as a partial seizure drug and as evidence for this that carbamezapine has been used for a long time approximately 50 years .

The mechanism of action

- Depends on K^+ channels stimulation to increase the repolarization.
- K^+ channels have important inhibitory control over neuronal firing in CNS — repolarizes membrane to end action potentials
- K^+ channel agonists would decrease hyper excitability in brain
- So far, the only Antiepileptic drug with known actions on K^+ channels is valproate
- Also blocks Na^+ channels and enhances GABAergic transmission (highly pleiotropic*: has multiple mechanisms of action).

TABLE look at the valproic acid drug (+++)so it is better than all other choices in the grand mal

Adverse effects :(narrow therapeutic index)

- GI upset (Nausea, vomiting, anorexia, abdominal pain and diarrhea)
- **Weight gain (appetite stimulation)**
- Transient hair loss
- Tremor
- Coma (rare)
- Thrombocytopenia (platelets)
- Edema
- **Severe hepatotoxicity (liver damage)**

• Contraindications: People with liver damage or a history hepatic dysfunction

All of what we have talked about of drugs until now (phenytoin, carbamazapine, ethosuximide, valporic acid) are old drugs, they have been used for 30-40 years. These days we have new generations of these drugs, which are probably better, but the question is why we don't use them?!

The answer simply due to something called ***clinical experience***; it's difficult to convince a doctor- who, for example, for 40 years has prescribed the valproic acid for generalized seizures -to prescribe a new drug like the lamotrigine. Especially that we are dealing with the central nervous system which is a complicated issue, so they see that using something we know better than something new.

NEW DRUGS

we will talk about three new drugs

1. **Lamotrigine**
2. **Gabapentin (neurontin)**
3. **Topiramate**

Lamotrigine:(much wider therapeutic index)

- this drug has a nice activity on the ***grand mal*** and ***absence seizures*** ,it is a new drug with a new identity and new mechanism of action with less side effects
- Act Primarily on Na^+ Channels ,it also inhibits excitatory neurotransmitter glutamate (its mechanism very similar to the carbamezapine)
- Lamotrigine is effective for the treatment of partial and secondarily generalized tonic-clonic seizure.
- It is generally well tolerated but may cause serious side effects on the skin, Including Stevens–Johnson syndrome (severe rash) in 1%-2% of patients especially in children, it may be fatal

TABLE look at the lamotrigine action on the grand mal (+++) and on the partial seizure (++) but because of its wider therapeutic index the new generation of doctors prescribe it in most of the cases for partial seizures even through its only (++).
Also in the absence seizure it has a nice activity. lamotrigine is the most prescribed drug these days although there some doctors still stick on the old drugs.

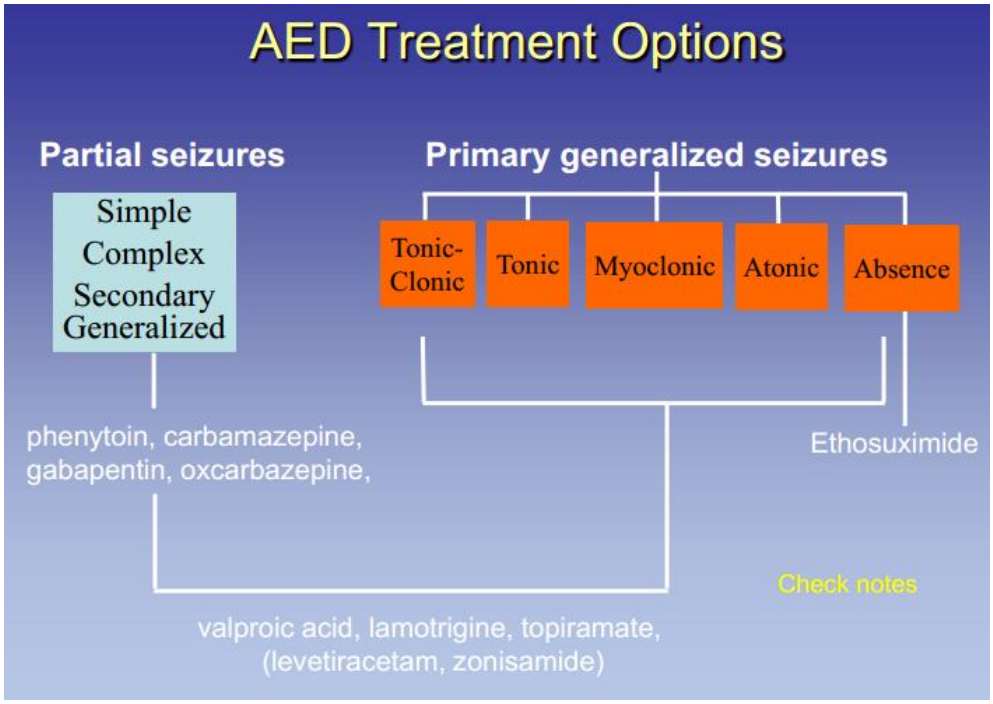
Topiramate

- Acts on AMPA receptors, blocking the glutamate binding site, but also blocks kainate receptors and Na+ channels, and enhances GABA currents **(highly pleiotropic)** .
- Used for ***partial seizures***, as an adjunct for absence and tonic-clonic seizures (add-on or alternative to phenytoin) .
- Very long half-life (20h). note

Gabapentin (Neurontin)

- NOT an anti-epiliptic drug , but it always mentioned there because it has an **adjuvant activity**.
- It is an add-on drug (i.e. not suitable as a single agent)… and as it is used for ***partial seizures*** in adults, we will add it to carbamezapine and phenytoin
  It can be added to lamotrigine & Topiramate, too.
- Do I use multiple treatments in seizures?
  Usually no, but sometimes we have to.
- Designed to be a structural analogue of GABA but unfortunately, it does not mimic GABA in the brain.
- Acts via:
  - Increased synthesis and release of GABA
  - Decrease degradation of GABA
  - Inhibition of Ca++ channels
    So, it is not a real anti-epiliptic drug . However, it is found –by chance- that it has a nice analgesic activity (inhibits neuronal pain) in Migraine
- **Remember** that the **carbamezapine** is the drug of choice for **trigeminal neuralgia**. If the patient can't tolerate it , we give him Gabapentin.
- It is used to treat idiosyncratic neurological pain that happens more in ladies (symptoms are pain in the arms , back ..). one of the drugs used in this case is Gabapentin .

To sum up the whole story :



NOTES :

- Up to 80% of pts can expect partial or complete control of seizures with appropriate treatment.
- **Antiepileptic drugs *suppress* but do NOT CURE seizures.**
- Antiepileptics are indicated when two or more seizures occurred in a short interval (6m -1 y), because here the patient is epileptic.

- An initial therapeutic aim is to use **only one drug** (*monotherapy*), and most patients respond to this. Addition of a second drug is likely to result in significant improvement in only approx. 10 % of patients.
  (i.e. changing the drug when it is not suitable is better than adding another drug to it).
- The sudden withdrawal of drugs should be avoided (there must be tapering).
  Not because of physical dependence, tolerance or addiction, but the reason is to avoid the inducing new seizures, which might happen upon abrupt withdrawal.
  "its NEVER been reported that these drugs have tolerance effect"
- Withdrawal may be considered after seizure- free period of 2-3 or more years (the doctor said 2-5 years or longer).
- Relapse rate when antiepileptics are withdrawn is 20 - 40 % (it's a high percentage).
  because we don't cure the seizure, we just suppress it even if there was 5 years seizure-free period.
- Do anti-epileptic drugs affect the cognition or the ability of decision in the patient?
  yes, why ?
  They are CNS suppressors, so some patients will have confusion or dizziness.
  "Old type drugs have drowsiness effect. Although the new drugs also do, but it is not as much as the old drugs"
- The effect of these drugs on the cognition and development is not very clear –it's not reported- (NOT as benzodiazepen which will cause mental retardation in case of long term use)
- How to deal with a pregnant woman having epilepsy ?
  Suppose that she has grand mal epilepsy –she may have abortion or her foetus may be affected with several defects.
  - What is the percentage of pregnant women with epilepsy that their foetus will be affected??
    10%
  - This makes the using of the anti-epeliptic drugs a MUST for pregnant ladies with epilepsy
  - It is not a choice ,if the patient is epileptic and pregnant, to stop taking the drugs
  - What are the drugs with teratogenic effect?
    Ethosuximide, DO NOT EVER USE IT WITH A PREGNANT WOMAN
  - We can use instead :
    1. valporic acid
    2. phenytoin
    3. carbamazapine
    4. or one of the new drugs (Lamotrigine, Gabapentin ,Topiramate)
    - do these drugs have effects on the baby ?
      yes indeed
      In a normal pregnant lady, the teratogenic effect reaches 1-2%. If she was using these drugs , the percentage will increase to reach 5-6%
    - what to do ?
      you advise the lady to stick with the drug , remembering that the baby may be affected in 10% of cases if she didn't use the drug, which is a higher percentage.
      also, it is important to monitor vit.D and folic acid levels especially with phenytoin
  - note : phyntoin may, but rarely, cause arrhythmia.
  - Anti-epileptic and anti-arrhythmic drugs are somehow similar in their actions, like blocking Na channels. And as we know anti-arrhythmic drugs are pro-arrhythmic.

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