CENTRAL NERVOUS SYSTEM

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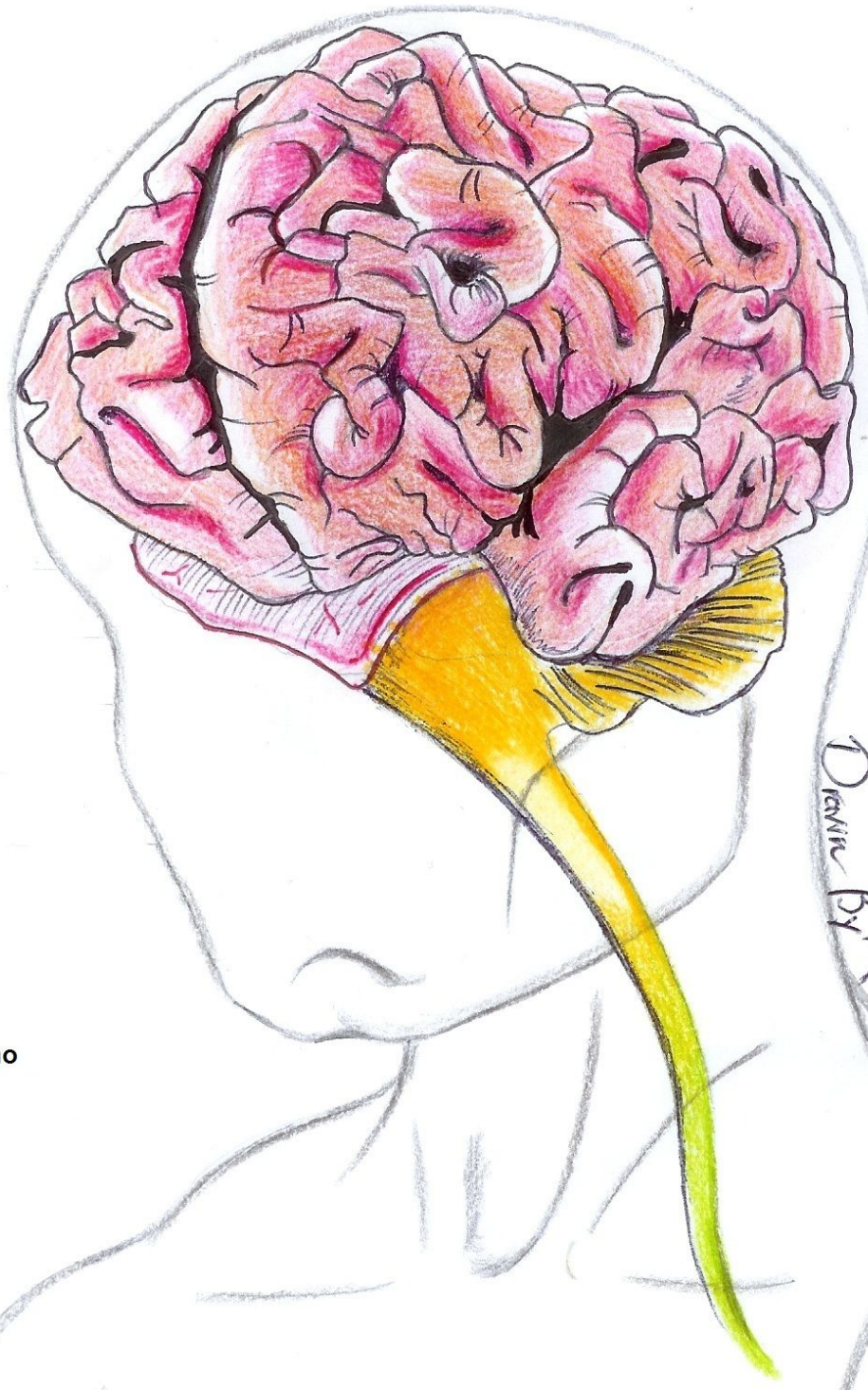

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Lec # : **9**

Antiepileptic drugs

Note: This sheet is written based on the records of both sections, I tried my best to rearrange details and make them as understandable as possible. Your feedback would be appreciated (not really :p).

Epilepsy overall is caused by the overexcitement of the neurons in the CNS resulting in unusual movement or activity (a sudden complex electrochemical activity).

1 person in 20 will have an epileptic seizure at some point in his life but that doesn't mean he has epilepsy since it is diagnosed on the basis of having two or more seizures, it is more common in the younger age groups.

Epilepsy affects around 450,000 people in the UK (40 million people worldwide) and many drugs used in the hospital cause seizures so that's why it's important to know how to deal with it.

There are many types of seizures, each has a specific treatment. Seizures are generally similar to cardiac arrhythmia in having an abnormal electrical discharge but these are due to the complex connectivity of the neurons.

Mainly epilepsy is caused by loss of control (Imbalance) between excitatory and inhibitory pathways; either too much down regulation (little activation) in the inhibitory pathway (mainly through GABA receptors) or over excitation in the excitatory pathway (glutamate receptors/NMDA).

Etiology:

Can be congenital or **acquired** …. Most common causes:

-Head injury -Hypoxia -Hypoglycemia

-Trauma -CNS depressants -Antidepressants

-Infections (meningitis, encephalitis…) - Fever in children (febrile convulsion)

Classification: We have 2 types of seizures:

1-Partial (focal): in a specific part of the brain (isolated), further divided into:

-Simple: only small part affected, abnormal involuntary movement (shaking) in the part controlled by the affected region in the brain (upper limb, lower limb, or trunk), patient is conscious and completely aware of his surroundings.

-Complex: shaking + loss of awareness/contact with the surroundings.

These partial seizures require one type of treatment.

2-Generalized (primary): in the entire brain (more common), several types:

Absence (Petit mal seizure): loss of both: contact and movement (except maybe blinking), common in children affecting 1% between ages of 4 and 12, lasts for 5-30 seconds. This needs intervention as it affects the child while doing normal activities like riding a bicycle or swimming.

Myoclonic: the patient is usually awake and suffering from muscle jerks, it lasts from 1-2 minutes.

Tonic-clonic (Grand mal seizure): can be of two phases or only one where the body becomes stiff then losses contact and falls down while jerking.

Treatment

Most of the antiepileptic agents affect ion channels, they work either by blocking further depolarization (through closing sodium and calcium channels or opening potassium channels to cause hyperpolarization and prevent extra firing), or by enhancing GABA effect (through barbiturates and benzodiazepines).

Currect Pharmacotherapy:

- Just under 60% of all people with epilepsy can become seizure free with drug therapy.
- In another 20% the seizures can be drastically reduced.
- ~ 20% epileptic patients don't response and eizures are refractory to currently available drugs.

Phenytoin (hydantoid drug):

It is the drug of choice in **partial seizures**, it works through blocking Na channels (in their inactive state) in order to reduce excitability in brain and increase duration of inactivation.

Characteristics:

1-**Zero** order reaction drug: Increase in dose leads to severe increase in blood concentration since elimination is not equal to administration (saturable elimination at a constant rate).

Its levels in the blood must be monitored as different patients have different kinetic profiles according to interindividual variations.

2- Common inducer for cyp450 enzymes specifically cyp3a4 so it will affect other drugs metabolism like oral contraceptives. (drug drug interaction).

3-wide inter-individual variation: different individuals respond differently to the effects of this drug (different kinetics).

4-narrow therapeutic index: so it needs to be carefully monitored.

5- 90% of it is bound to plasma protein.

Side effects:

-Nausea, vomiting, confusion, sedation

-Impaired brain stem and cerebellar functions; dizziness, drowsiness, nystagmus, blurred vision, tremor and ataxia (almost found in all anti-seizure drugs).

-Allergic Reaction: skin rash (in 10% of people getting treated with phenytoin or carbazepine); so we start with low doses and increase them gradually (usually in increments of 20) to reduce its incidence (dose related side effect).

-Non dose related side effects: gingival hyperplasia (also occurs when using Ca channel blockers).

-May cause cardiac arrhythmia.

Carbamazepine:

Everything that applies to phenytoin is applied here (narrow therapeutic index, induces cyp450, for partial seizure, interindividual variations etc.) except that this drug has additional side effects like constipation, sedation, nausea and bone marrow suppression (very rarely) as well as it causing rash that's why it needs to be administered gradually starting from low concentrations. This drug is also a **first** order drug (so it is easier to prescribe carbamazepine although it should be monitored as well).

Carbamazepine is also the DOC for: **Trigeminal neuralgia**

NOTE:

- Both phenythoin and carbamenzepine and Phenobarbital are **contraindicated in absence seizure** as in this type of seizures there is no movement so blocking Na channels will lead to exacerbation of the situation and increase in their frequency.

-They are both very strong sedative drugs like Phenobarbital. (from barbiturates).

Ethosuximide:

DOC in **absence seizures**, it is a Ca channel blocker (t- type Ca channels in the thalamus).

Absence seizures are caused by oscillations between thalamus and cortex that are generated in thalamus by T-type (transient) Ca2+ currents, the T-type Ca channels

are found in the brain. When there's too much Ca, it causes the seizures so we look for a drug to block that.

It has a wider therapeutic index .However, it also causes nausea, vomiting, sedation and skin rash.

Valproic acid (sodium valproate):

This is the only anti-epileptic drug that works on K channels.

It's used in all types of epilepsy as it suppresses initial seizure discharge and its spread, it is also used in partial seizures but mainly it's the DOC in **generalized seizures**: works by causing hyperpolarization through opening K channels, blocking Na channels, and enhancing GABA to decrease hyperexcitability (poly-mechanism of action).

K+ channels have important inhibitory control over neuronal firing in CNS, they repolarize the membrane to end action potentials. This is why K+ channel agonists decrease hyperexcitability in brain.

Side effects: Sedation, nausea, vomiting, weight gain (increases appetite), tremor, thrombocytopenia, edema, hepatotoxicity

It has a narrow therapeutic index, teratogenic and contraindicated in hepatic diseases.

Lamotrigine:

Part of the new generation anti-epileptic drugs, it has a wide therapeutic index. It is also DOC in **generalized seizure:** blocks Na channels, inhibits glutamate on NMDA.

Side effects: strong skin rash (worst with this drug) although it's the least one causing sedation.

Both valproic acid and lamotrigine can be used in grand mal as well in petit mal (absence) seizure/not contraindicated.

NOTE: **All** of the previous drugs are **teratogenic** or cause problems for the fetus with some being more dangerous than others (phenytoin is considered to have the least effect on pregnancy while the others are completely teratogenic/given according to risk-benefit ratio).

Gabapentin (GABA like drug):

It mimics the structure of GABA and it acts by:

-Increased synthesis and release of GABA

-Decrease degradation of GABA

-Inhibition of Ca++ channels

Used in partial seizures as an add-on drug but not effective on its own. However it's used as an analgesic in cases of **migraine** (neuronal pain)**.**

Also causes sedation and dizziness.

NOTES:

-We manage migranes prophylactically using inderal (propranolol) which is a B-blocker to decrease stress, yet these patients will still have headaches.

-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 there is two or more seizures occurred in short interval (6m -1 y)

- An initial therapeutic aim is to use only one drug (monotherapy). Addition of a second drug is likely to result in significant improvement in only approx. 10 % of patients

- The sudden withdrawal of drugs should be avoided. Withdrawal may be considered after seizure- free period of 2-3 or more years

- Relapse rate when antiepileptics are withdrawn is 20 - 40 %

-When to Withdraw Antiepileptic Drugs? Normal neurological examination Seizure- free for 2-5 yrs or longer

Good Luck!

This sheet is dedicated to: Aseel, Om shagra, Yanal, 7jaz, Lara, Nadia, Maswadeh, Dina, Bana, Qarqash, Sophia and Munjed.