Antiepileptic Drugs

<u>Epilepsy</u>: is a brief disorder of cerebral function, occurs due to sudden excessive electrical discharge of cerebral neurons

<u>Types of epilepsy</u>:

1. Generalized epilepsy: characterize by loss of consciousness types:

a. tonic-clonic seizures characterized by muscle contraction in tonic and clonic phases associated with loss of consciousness.

b. absence seizures: brief loss of consciousness With out muscle activity, more common in children.

2. Partial epilepsy: occur due to focal neuronal discharge ,

a. partial simple; no loss of consciousness

b. partial complex: with spread of neuronal discharge to all areas of the brain lead to loss of consciousness

Antiepiletic drugs classification

1. **Drugs act by inhibiting sodium ion channels (membrane stabilizing); Pheyntoin, carbamazepine, lamotrigene, topiramate**
2. **drugs act by enhancing GABA effect and blocking sodium ion channels; Sodium valproate, benzodiazepines, phenobarbitone**
3. **Drugs blocking calcium ion channels only; ethosuximide**
4. **Drugs enhance GABA only; as vigabatrin**
5. **Inhibitors of excitatory neurotransmitters like glutamate, as lamotrigine**

Phenytoin

- **Acts by preventing the spread of epileptic neuronal discharge. It inhibits the movements of sodium ions across the cell membrane.**

<u>Clinical uses</u>

- **generalize tonic-clonic seizures and partial seizures**
- **ventricular dysrrhythmias; act probably as membrane stabilizer (sodium ion channels blocker)**

Phenytoin pharmacokinetics

- **absorption following oral administration is slow but complete**
- **variations in the serum concentrations(20 folds)**
- **metabolized in the liver and follows zero-order kinetics(saturation kinetics)**
- **highly protein bound (> 90%) to albumin and alpha globulin**
- **half life 6-24 hours**
- **narrow therapeutic index (10-20ųg/ml)**
- **enzyme inducer, ,increase the metabolism of drugs as warfarin**
- **Require serum level measurement (TDM)**

Phenytoin adverse effects

- **CNS causes ;cerebellar syndrome (ataxia, nystagmus, intention tremor and dysarthria)**
- **Collagen changes; gum hyperplasia, coarse facial features and hirsutism**
- **hematological; megaloblastic anemia due to folic acid deficiency; also causes deficiency of Vit.D lead to osteomalacia, agranulocytosis**
- **Fetus; when taken during pregnancy increase the incidence of congenital anomalies as cleft lip and cleft palate, congenital heart diseases**
- **Endocrine effects: inhibition of antidiurertic hormone.**
- **allergic skin reactions and hepatitis and lymphadenopathy**

Phenytoin drug interactions

- **Drugs can induce the metabolism of phenytoin and decrease its serum levels as phenobarbitone and carbamazepine**
- **Drugs can inhibits phenytoin metabolism and increase its Serum levels and toxicity; as cimetidine isoniazid and chloramphenicol**
- **Autoinduction; it induce its own metabolism**

Carbamazepine

- **Acts by blocking sodium ion channels in similar way to phenytoin**

<u>Clinical uses</u>

- **generalized tonic-clonic seizures, temporal lobe epilepsy and partial seizures**
- **Trigeminal neuralgia**
- **co-analgesic (in combination with analgesic drugs to enhance their effects)**
- **prophylaxis of manic depressive psychosis**

Carbamazepine

Pharmacokinetic features

- **absorbed well but slowly from the GIT**
- **metabolized in the liver by first-order kinetics**
- **half-life is 10-20hrs. (active metabolites prolonged)**
- **its highly protein bound**
- **is an enzyme inducer**

Adverse effects

- **on the CNS causes ataxia, tremor and nystagmus**
- **causes water intoxication and hyponatremia due to antidiuretic effect**
- **megaloblastic anemia and agranulocytosis.**
- **allergic skin reactions**

Sodium valproate (valproic acid)

- **Acts by inhibiting GABA-transaminase enzyme, increase the GABA in the brain (inhibitory neurotransmitter), in addition it inhibits sodium and calcium dependent ions channels.**

Clinical uses

- **Generalized tonic-clonic and partial seizures**
- **absence seizures**

- **Pharmacokinetic features**
- **absorbed well following oral administration**
- **is highly protein bound (more than 95%)**
- **the plasma half-life is 7-10 hours**
- **enzyme inhibitor and can potentiate the effect of phenytoin and phenobarbitone**

Sodium valproate Adverse effects

- **GIT, including nausea, vomiting and abdominal pain**
- **sedation and CNS depression**
- **can cause hepatitis and severe liver damage, which may be fatal**
- **Alopecia (hair loss), which reversible**

Other antiepiletic drugs

Ethosuximide

- **Acts mainly by inhibiting calcium ion channels**
- **It is useful in the treatment of absence seizures. Not effective in generalized seizures.**
- **Has little adverse effects as GI disturbances, skin rash and enzymes inducer and sedation**

Phenobarbitone

Is a barbiturate useful in generalized seizures, It is a potent causes excessive sedation which limit its clinical uses

Clonazepam

- **Is a benzodiazepine useful in absence seizures and myoclonic epilepsy.**
- **Prolonged use lead to tolerance.**

Newer atntiepileptic drugs

Vigabatrin

- **acts by inhibiting GABA-transaminase enzyme increase GABA levels useful in partial and secondary generalized**
- **It worsen the absence and myoclonic seizures**
- **Causes visual field defect**

Lamotrigene

- **inhibits sodium ion channels, stabilizes cell membrane and reduce the release of excitatory transmitters as glutamate and aspartate, useful in partial and generalize, can be used alone or in combination with other drugs**
- **Causes cutaneous toxicity**

Newer antiepiletic drugs cont…

- **Gabapentin**
- **analogue of GABA useful in partial seizures, it is also useful in bipolar depression, neuropathic pain and migraine**
- **Causes sedation, myopia and increase intraocular pressure**

Topiramate

- **block sodium ion channels and enhance GABA effect useful in partial seizures**
- **Causes sedation, tremor and weight loss**

Livetiracetam

useful in partial seizures

Status epileptics

- Status epilepticus, is continous seizures that can be fatal unless seizures terminated
- It is a medical emergency
- Useful drugs

  diazepam i.v

  lorazepam i.v

  phenytoin i.v

  Thiopentone, propofol and midazolam

Narcotic analgesic

- **Narcotic analgesics** are used to relieve pain. Some of these medicines are also used just before or during an operation to help the anesthetic work better. Codeine and hydrocodone are also used to relieve coughing. Methadone is also used to help some people control their dependence on heroin or other **narcotics.**
- **Opioids**: a term applies to natural or synthetic substance which produce morphine-like effect that are blocked by naloxone.
- **Opiate**: is a term restricted to drugs such as morphine and codeine obtained from the opium poppy.
- **Opium:** is an extract of the juice of the ***poppy papaver somniferum***. This juice was used from thousands of years.

The main groups of opioid analgesic

STRONG AGONISTS	MODERATE AGONISTS	MIXED AGONIST-ANTAGONIST	ANTAGONIST	Other analgesic
Fentanyl Heroin Meperidine Methadone Morphine Sufentanil	Codeine Propoxyphene	Buprenorphine Pentazocine	Naloxone	Tramadol

1. Morphine and morphine analogues: structurally related to morphine.

a. Agonist: morphine, diamorphine (heroin), codeine.

b. partial agonist: nalorphine, pentazocine

c. Antagonist : naloxone

2. Synthetic derivatives: structurally unrelated to morphine.

a. pethidine (meperidine)

b. methadone and dextropropoxyphene

3. Others:

Thibaine derivatives: etrophine is a highly potent morphine-like drug used mainly in veterinary practice.

Mechanism of action of opioid:

Effect of opioid on various receptors results in:

Inhibition of adenylate cyclase which results in reducing intracellular cAMP.

And Opening of K^+ (potassium) channels

Inhibition of opening of voltage-gated calcium channels.

And theses action will lead to the following:

a. neuronal excitability (because of increased K^+ conductance causes hyper polarization of membrane)

b. Transmitter release (because of inhibition of calcium entry)

Pharmacological actions:

1. Effects on the central nervous system:

a. analgesic

b. euphoria: is mediated through μ (Mu) receptors and is balanced by dysphoria produced by the effect on (Kappa)-receptors

c. respiratory depression: caused by reduction of the sensitivity of respiratory center to carbon dioxide. However, respiratory depression is the commonest cause of death in opioid poisoning.

d. **depression of cough reflexes**: suppression of cough seems not correlated with analgesic effect; for example, codeine suppress cough at sub-analgesic doses.

e. **nausea and vomiting**: this occur in up to 40% of patients to whom morphine is given.

f. **papillary constriction**: Pinpoint pupils are an important diagnostic feature of morphine overdose.

2. Effects on gastro-intestinal tract.

Morphine increases tone and reduces motility in many parts of the GIT resulting in constipation. Morphine also results in contraction of the gall bladder and results also in constriction of the biliary sphincter.

This effect is harmful in patients suffering from biliary colic due to gall stones.

3. Other actions of opioid:

Morphine releases histamine from mast cells by an action not related to opioid receptors. Release of histamine may cause urticaria and itching at the site of injection.

Bronchoconstriction is also recognized with morphine treatment

which is due to histamine release? Morphine is dangerous in asthmatic patients.

Hypotension is also noticed in morphine treated patients**.** Hypotension

and bradycardia occur as a result of an action on the medulla.

Histamine, which causes vasodilatation may also contributes to hypotension.

Pharmacokinetic of morphine and morphine analogues:

Morphine is slowly absorbed and is commonly given by IV or IM. Codeine is well absorbed from the GIT. The half life of morphine is 3-6 hours, and the liver is the main site of metabolism usually by conjugation with glucouronides. Morphine is being reabsorbed (entero-hepatic circulation). **Diamorphine** and **codeine** are metabolized in the body to morphine.

- **Side effects of opioid:**
- Nausea and vomiting
- Constipation
- Drowsiness
- Respiratory depression and hypotension.

- **Choice of drugs:**

1. Morphine: is the most commonly used analgesic for severe pain. It is frequently causes nausea and vomiting.

2. Codeine: it is effective for the relief of mild to moderate pain. Unlike Morphine it causes little or no euphoria and is rarely addictive. Codeine produces respiratory depression similar to morphine,

however, this is rarely a problem in clinical use. The main use of codeine is in treatment of cough.

3. Diphenoxylate: This is a widely used drug for treatment of diarrhea. It is present in combination with a small dose of atropine. Atropine toxicity in this combination is used to limit abuse of the drug.

4. Dexterpropoxyphen: has little analgesic effect (similar to codeine). It is usually given in combination with paracetamol.

5. Diamorphine (heroin): it is a powerful analgesic. It may cause less nausea and hypotension.

6. Pethidine: The pharmacologic effect of pethidine is very similar to morphine but there are substantial differences:

it causes restlessness rather than sedation. Pethidine has Antimuscarnic effect which may cause dry mouth. It causes euphoria and is liable for dependence.

Pethidine is preferable to morphine for analgesia during labor because it is short acting.

A significant drug interaction is reported with monoamine oxidase

inhibitors. This is manifested as excitement, hyperthermia, and convulsion. The possible source of this interaction is the increased formation of norpethidine metabolites

7. Fentanyl and Alfentanil: these drugs are used for intra-operative analgesia.

8. Methadone: it is less sedating than morphine and the duration of action is longer than morphine. Withdrawal syndrome is less acute than with morphine. For this reason, methadone is widely used in the treatment of morphine and diamorphine addiction.

9. Pentazocine: is a mixed agonist-antagonist. It has agonist activity on Kappa-receptors and antagonist activity on Mu- receptorsIts potency is similar to morphine but less respiratory depressant than morphine. It causes **dysphoria** rather than euphoria. It tends to **raise blood pressure** rather than to decrease it. Because it has antagonistic activity it antagonizes various effects of morphine such as analgesic effect when given in the same time.

10. Tramadol is an opioid with additional actions; the basis of its analgesic effects is due to a combination of, **first**, (relatively weak) agonist action on μ -receptors, **second** inhibition of neuronal noradrenaline uptake and **third** enhanced serotonin release. It is rapidly absorbed from the gastrointestinal tract, 20% of an oral dose undergoes first-pass metabolism and less than 30% of the dose is excreted unchanged in the urine (t1/2 6 h). Tramadol is approximately as effective as pethidine for postoperative pain and as morphine for moderate chronic pain. Tramadol is claimed to be less likely to cause constipation, depression of respiration and less addicting liability. Confusion, convulsions, hallucinations and anaphylaxis have been reported with its use.

11. Naloxone: it is pure opioid antagonist for the three opioid receptors (μ -, Delta, and kappa-receptors). It antagonizes morphine effects, Naloxone has no effect on pain threshold. The main clinical use of naloxone is to treat respiratory depression caused by opioid overdose. Naloxone has no important unwanted effects but precipitate withdrawal symptoms in addicts. It can be used to detect opioid addicts.

12. Etorphine: is a morphine analogue of remarkably high potency,(more than 1000 times that of morphine), but otherwise very similar in its actions. Its high potency confers or provide no particular clinical advantage, but it is used to immobilize wild animals for trapping and research purposes, since the required dose, even for an elephant, is small enough to be incorporated into a dart or pellet.