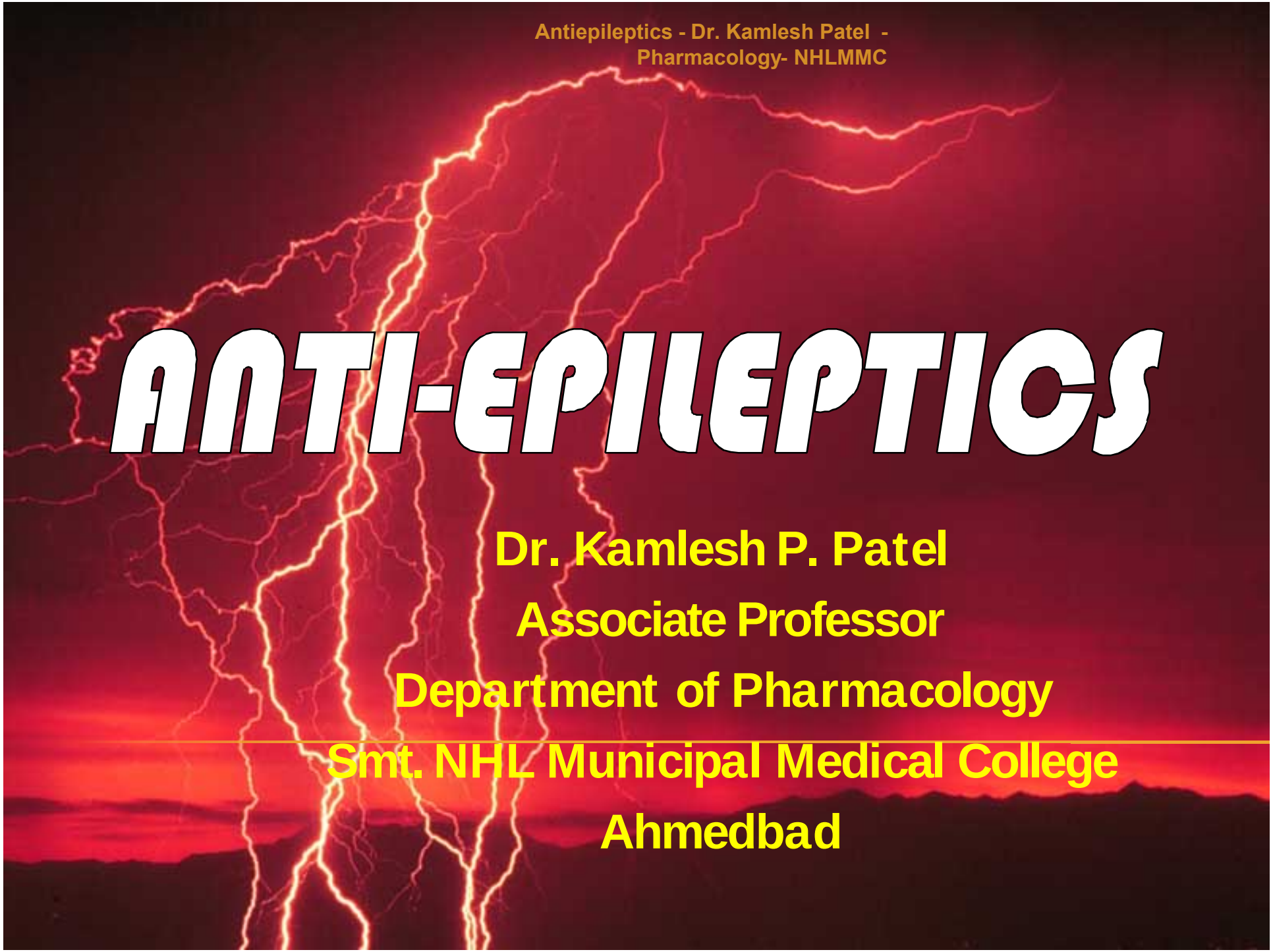

ANTI-EPILEPTICS

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EPILEPSY

- John Hughlings jackson : Disease of Lightening
- Abnormal firing of neurons **simultaneously**
- **Clinically** characterized by :-
- ** Sudden, excessive, rapid, local discharges from grey matter... followed by.....
- ** Loss of consciousness
- ** With/without characteristic body movements (Tonic / Clonic Convulsions)
- ** With autonomic hyperactivity
- ** Associated with abnormal electrical discharges (seizures)
- ** EEG changes shows — Diffuse, Bilateral, synchronous, 3/secs waves + spike discharges

EPILEPSY(NEUROPHYSIOLOGY)

- **Neurophysiology-:**

** **Imbalance** between **Excitatory** (Glutamate & Aspartate) and **Inhibitory** (GABA(Gamma Amino Butyric Acid& Glycine)**Neurotransmitters in brain**

** **Involvement of Na+,K+,Ca++ & Cl- channels**

** **Precipitates seizures / convulsions**

EPILEPSY(PATHOPHYSIOLOGY)

- 2 events…
- **i) Hyperexcitability:-**
- * * Abnormal response à Multiple discharges
- **ii) Hypersynchrony-**
- * * Recruitment of neurones à abnormal firing mode
- * * Asynchronous (at different time)
- * * Synchronous (simultaneously)
- Paroxysmal Depolarization Shift (PDS)
- Post Tetanic Potential (PTP)

EPILEPSY (ETIOLOGY)

- **Etiology of seizures:**
- **Trauma during birth process,**
- **Childhood fever**
- **Head injury,**
- **Brain Tumor,**
- **Genetic inheretance**
- **Meningitis,**
- **Neurocysticercosis**

STRATEGIES IN TREATMENT

Stabilize membrane & prevent depolarization by action on ion channels

Increase GABA – mediated inhibition

Decrease EAA transmission

TYPES OF EPILEPSY

- **(I) GENERALIZED SEIZURES :-**
- **(1) Tonic – Clonic seizures (Grand Mal Epilepsy)**
- **(2) Tonic – seizures**
- **(3) Clonic seizures**
- **(4) Absence seizures (Petit Mal /Minor Epilepsy)**
- **(5) Atonic / Akinetic seizures (Drop attack)**
- **(6) Myclonic seizures**
- **(7) Febrile seizures**
- **(8) Infantile spasm / West's syndrome / Hypsarrhythmia**
- **(9) Lennox Gastaut Syndrome**
- **(10) Status Epilepticus**

- **(II) PARTIAL SEIZURES :-**
- **(1) Simple Partial seizures**
- **(2) Complex Partial seizures (Temporal Lobe / Psychomotor epilepsy)**

ANTI – EPILEPTIC DRUGS (CLASSIFICATION)

- **1) Hydantoins:** Phenytoin sodium
- **2) Barbiturates :** Phenobarbitone, Primidone
- **3) Iminostilbone:** Carbamazepine
- **4) Succinimide :** Ethosuximide
- **5) Aliphatic Carboxylic Acid:** Sodium valproate
- **6) Benzodiazepines :** Diazepam, Clonazepam
- **7) Newer Antiepileptic Drugs-:** Lamotrigine, Vigabatrin,Gabapentin and Topiramate

MECHANISM OF ACTIONS OF ANTI-EPILEPTIC DRUGS

- **(1) Enhancement of Sodium Channel Inactivation / Blockade (Membrane Stabilizing Effect) ; Maintenance or Prolongation of Inactivated state of Na – channel and Delay in recovery of Na- channel from inactvation**

  Eg. Phenytoin, Carbamazepine, Sodium Valproate, Lamotrigine

- **(2) Enhancement (Facilitation) of GABA– mediated Synaptic Transmission**

  Eg. Phenobarbitone, Benzodiazepine

- **(3) Prevention of Degradation of Inhibitory neurotransmitter (GABA) by Blocking Transaminase enzyme.**

  Eg. Sodium valproate, Vagabatrin

MECHANISM OF ACTIONS OF ANTI-EPILEPTIC DRUGS

- **(4) Enhancement (Facilitation) of synthesis of Inhibitory GABA neurotransmitters by Direct stimulation of GABA–Synthetase enzyme (GABA – mimetic effect)**

  Eg. Progabide

- **(5) Blockade of Calcium Channel (T- Type) Current / Function**

  Eg. Ethosuximide, Phenytoin, Sodium valproate

(6) Blockade of Excitatory Neurotransmitter Glutamate (NMDA) receptors

Eg. Lamotrigine

PHENYTOIN

- Diphenylhydantoin derivative
- 2 – Phenyl rings – Toxicity
- No alkyl group – No sedation
- **(I) CNS Effects :**
- * Anti – seizure activity
- * Suppresses Tonic – Clonic seizures
- * No CNS depression – No drowsiness
- * Abolishes Tonic phase of Maximum Electroconvulsive seizures

PHENYTOIN

- **(II) CVS Effects :**
- * Depresses ventricular automaticity
- * Decreases duration of action potential
- **Useful in Treatment of ;**
- * Ectopic beat suppression
- * Recurrent Paroxysmal Tachycardia (Prophylactic)
- * Rapid Supraventricular Tachycardia

PHENYTOIN (MECHANISM OF ACTION)

- **(A) At Therapeutic Concentration**

Phenytoin

- * Enhances inactivation of sodium channels
- * Reduces neuronal Na– concentration
- * Decreases Paroxysmal Depolarisation Shift (PDS)
- * Inhibits Generation of Repetitive Firing of Neurones
- * Blocks Post– Tetanic Potentiation (PTP)
- * Prevents spread of seizure activity

PHENYTOIN (MECHANISM OF ACTION)

- * Shortens duration of after discharge
- * Governs refractory period of neurones
- * Selectively inhibit high frequency discharge without affecting low frequency discharge

  (Trigeminal neuralgia, cardiac arryhthmia)

* Produces stabilizing effect
  * All neurone membrane
  * Excitable/ non-excitable
* Generalized abnormalities in EEG disappears

PHENYTOIN (MECHANISM OF ACTION)

- **(B) AT HIGH CONCENTRATION :**
- (1) Inhibits Ca2+ influx
- (2) Inhibits Excitatory Glutamate enzyme
- (3) Inhibits release of NE, 5-HT
- (4) Inhibits release of secretary– Hormones, NTs
- (5) Inhibits MAO activity
- (6) Interacts with membrane lipids– promotes membrane stability

PHENYTOIN (MECHANISM OF ACTION)

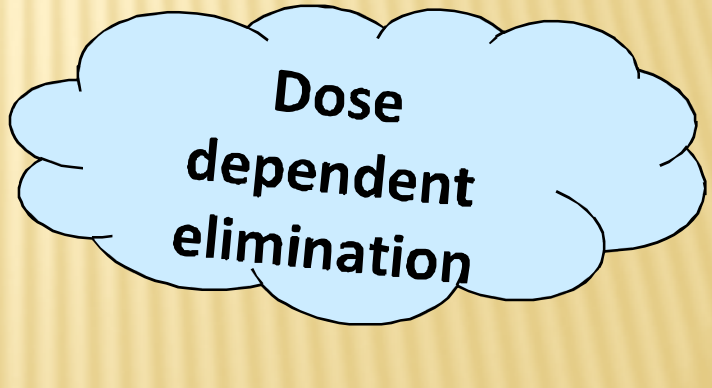
- (7) Enhances GABA- mediated Cl- channel opening
- (8) Restores balance between :
- Excitatory Glutamate + Inhibitory GABA pathway -à Anti – Epileptic activity

PHENYTOIN : PHARMACOKINETICS

- **(1) DIFFERENT/VARIABLE BIOAVAILABILITY**
- Poor aqueous solubility , Diverse problem for I.V. use à Lead to production of **Fosphenytoin.**
- Fosphenytoin - **(water soluble prodrug)à** Phosphatase **(liver,RBC)** à Phenytoin. T1/2 = 8-15 min
- **Uses : P**artial Generalised Seizures (parenterally)
- **Administer :** Rate < 150mg/min (I.V.) à **otherwise,** Cardiac arrhythmias, Hypotension, CVS collapse & CNS depression

PHENYTOIN : PHARMACOKINETICS

- Nearly complete absorption – **GIT**
- Unpredictable absorption – **I/M , painful**
- Plasma protein – **High**
- $t_{1/2}$ ----**increase with higher doses**
- Metabolized – **inactive metabolites**



Low dose first order kinetics
High dose zero order kinetics

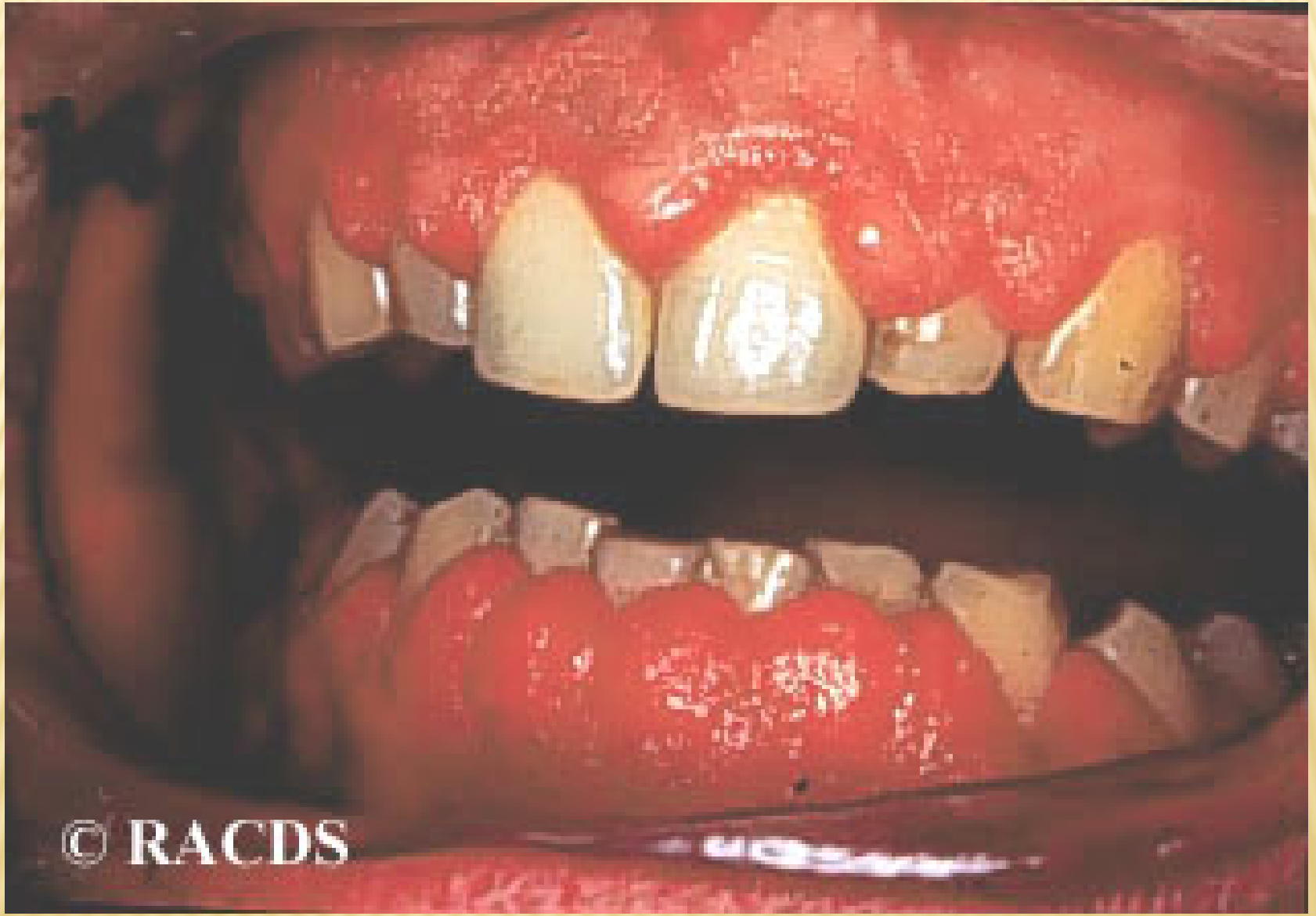
PHENYTOIN : PHARMACOKINETICS

- **(2) Saturation Kinetics (Non– Linear Kinetics)**
- **(i) Low conc : First – Order kinetics (Exponential)**
- **(ii) High conc : Zero – order kinetics**
- **(a) At Low Conc (Pl. Conc < 10 mcg/ml)à t1/ 2= 12-24 hrs.**
- **(b) At High Conc (Pl. Conc. > 10 mcg/ml)à t1/ 2= 60 hrs**
- **Consequences :**
- *** * Slight increase in dose-à Disproportionate rise in plasma levelà Prolongs plasma t1/2 -à Marked Toxicity**

(3) Enterohepatic circulationà Parahydroxylationà ↑ Phenytoin Toxicity

PHENYTOIN : ADVERSE EFFECTS

- Gingival hyperplasia – Gum Hypertrophy
- Phenytoin facies
- Hirsuitism,Hypertrichosis,Acne
- Megaloblastic anemia
- Vestibulo-cerebelar syndrome
- Hyperglycemia
- Osteomalacia
- Lupus Erythemus, Lymphoadenopathy
- Intolerance-S J syndrome
- Fetal hydantoin syndrome – Aneroxide syndrome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PHENYTOIN : USES

- 1) Grand Mal Epilepsy
- 2) Simple & Complex Partial Epilepsy
- 3) Trigeminal Neuralgia
- 4) Cardiac arrythmias – Digitalis – induced
- 5) Status Epilepticus
- **DOSE :**
- **(1) 100 mg B.D. orally– Max. 400 mg/ day**
- **(2) Children : 10 mg/ kg/ day ; Susp : 100 mg/ 4 ml**

PHENYTOIN : DRUG - INTERACTIONS

- **1) Inhibits Phenytoin Metabolism :**
- ↑ Pl. Phenytoin Levels, ↑ Phenytoin toxicity
- Eg. Phenobarbitone, Warfarin, INH, Chloramphenicol
- **2) Phenytoin induces Hepatic Microsomal Enzymes :-**
- ↑ Metabolism of other drugs, ↑ Excretion of other drug, reduce s therapeutic efficacy of other drugs
- Eg. * Oral contraceptives, carbamazepine, Digitalis,
- Vitamin-D, Theophyline, oral anticoagulants, Phenobar.

PHENYTOIN : DRUG - INTERACTIONS

- **3) Phenytoin Displaces Drugsà**
- ↑Concentration & Toxicity of displaced drugs
- * sulfonamide, Salicylates, Vit B12
- **4) Phenytoin inhibits Tolbutamide Metabolism**
- à Hypoglycemic coma

CARBAMAZEPINE

- Iminostilbene = TCA = Imipramine
- M/ A : Blocks sodium channels
- Pharmacokinetics ;-
- Slow absorption, Poor water solubility
- Enzyme induction à Oral contraceptives, Vit D
- Erythromycin, INH à inhibit Carbamazepine metabolism à t1/ 2 à 20-40 hrs à reduces t1/ 2 à 10-20 hrs (induces its own metabolism)
- Pl. levels à ↑ linearly with ↑ dose (Phenytoin à disproportionate ↑)

CARBAMAZEPINE

- Block – Na+ channels – ¯ high frequency repetitive firing
- Postsynaptic action -
- Uptake & release – ¯ noradrenaline

Peak: 6-8 hrs, **t½:** 36 hrs initially
Plasma protein binding: 70%, **Active metabolite**

Enzyme induction

Oxcarbazepine :

t½ : 8-12 hrs

More potency & less enzyme induction

CARBAMAZEPINE :

Therapeutic uses

- Partial seizures
- Generalized tonic clonic seizures
- Diabetes Insipidus
- Alcohol withdrawal
- Trigeminal neuralgia
- Bipolar disorder

CARBAMAZEPINE : USES

- 1) Trigeminal neuralgia / Deafferentiation pain
- **Advantages ;**
- * Improvesà concentration, personality, irritability, nervousness, restlessness, psychomotorperformance.
  * makes person more attentive
- 2) Grand mal epilepsy
- 3) Simple/ complex partial seizures
- 4) Diabetic insipidus of pituitary origin (antidiuretic action à enhances ADH action
- 5) Manic Depressive illnessà alternative to Lithium
- (400-600mg/ day)

CARBAMAZEPINE : SIDE EFFECTS

- 1) Foetal malformation (↑with Sod. Valproate)
- 2) Mental Motor disturbances
- 3) Bone marrow depression
- 4) CVS S/Es

PHENOBARBITONE

- **Action :**
- 1) ↑Threshold for neuronal firing
- 2) Enhances GABA synaptic transmission à open Cl- channel à ↑ Cl- conductance
- 3) GABA – mimetic
- 4) Inhibits excitatory Glutamate
- 5) Anti-convulsant with sedation
-

PHENOBARBITONE : PHARMACOKINETICS

- * Slow absorption
- Long t1/2: 80-120 hrs
- Steady state : 2-3 weeks
- Enzyme Inhibitor (at low dose)
- --- Inhibit Phenytoin Metabolism
- Enzyme Inducer (Chronic administration)
- --- Enhance metabolism of Phenytoin & itself & vit. K

PHENOBARBITONE : ADVERSE EFFECTS

- Sedation, lethargy, nystagmus, ataxia
- Osteomalacia, Vitamin K depletion
- Memory loss, Frozen shoulder
- Teratogenicity :
- * Diminution of intelligency
- * Impaired learning & memory
- Hyperactive child, Confusion in elderly

PHENOBARBITONE : USES

- 1) Grand mal epilepsy
- 2) Simple partial seizures
- 3) Status Epilepticus (i.V.)
- N.B.
- Abrupt withdrawal à ↑ frequency of convulsions à Not treated with Phenytoin

SODIUM VALPROATE

- M/ A :
- 1) Blocks Na+ channels
- 2) Inhibit GABA– Aminotransferase (GABA-T) + Semialdehyde Dehydrogenase→
- ↑ Cl conductance
- ↑ GABA conductance → Terminates seizure activity
- ↓Aspartate levels
- ↑ K+ concentration → Hyperpolarization (at high conc)

SODIUM VALPROATE : ADVERSE EFFECTS

- 1) Hepatotoxicity :↑ hepatic transaminases
- Fulminant Hepatitis (< 2 yrs children)
- 2) Acute Pancreatitis
- 3) Hyperammonemia
- 4) Teratogenicity :
- ** Neural Tube Defect (NTD)
- ** Spina Bifida
- ** CV, oral,digital congenital abnormalities
- 5) Alopecia, Thinning + Curling of hairs
- 6) N,V, ataxia, tremors

SODIUM VALPROATE : USES

- **1) FIRST LINE THERAPY :**
- ** Absence seizures (Petit Mal Epilepsy)
- **2) SECOND LINE THERAPY:**
  - i) GTCS,
  - ii) SPS,
  - iii) CPS,
  - iv) Myoclonic seizures
  - V) Atonic seizures

SODIUM VALPROATE : D/I

- 1) Phenobarbitone Pl. levels increases
- (by inhibiting its metabolism)
- 2) Displaces Phenytoin - ↓its metabolism à
- ↑ phenytoin Toxicity
- 3) Induces metabolism of Carbamazepine
- 4) Increases Foetal toxicity with carbamazepine
- **DOSE :** Adult & children : 10mg/Kg in 2 d.d.
- **Max :** 60 mg/kg/d

SODIUM VALPROATE

- **ADVANTAGES :**
- **1) Improves**
- * Cognitive functions
- * Learning ability
- * Pt. Behaviour
- * Alertness
- * Performance

NEWER ANTI-EPILEPTIC (A-E) DRUGS

- **(1) Lamotrigine (2) Gabapantin (3) Vigabatrin (4) Felbamate (5) Topiramate (6) Clobazam (7) Clonazepam**

UNIQUE FEATURES OF NEWER-EA DRUGS

1) **Fast acting , orally effective , potent anti-convulsantaction**
2) **Multiple mechanism of actions**
3) **Prolong plasma Half– Life (10-20 hrs)**
4) **Prolong duration of actionà Once or twice daily dosage**
5) **Has supplemental (additive) effect when given along with conventional anti-epileptic drugs**
6) **Reduces frequency of seizures– completely control seizures**
7) **Raises seizure threshold**

NEWER ANTI-EPILEPTIC (A-E) DRUGS

UNIQUE FEATURES (Contd….)

1) Used as an "Add–on" or "Adjuvant" therapy in Generalized or Partial seizures, Neuropathy etc..
2) Used as First– Line Therapy only in refractory cases
3) Sometime, used as monotherapy as first – line therapy
4) No teratogenic adverse effects à No congenital abnormalities such as spina bifida, cleft palate or hare lips
5) No gum hypertrophy, hirsuitism, osteomalacia , hepatotoxicity on long term use
6) No alteration in metabolism (enzyme induction or inhibition) of other drugs à less chances of Drug– Drug Interactions

NEWER ANTI-EPILEPTIC (A-E) DRUGS

- **UNIQUE FEATURES (CONTD) …..**
- **ADVERSE EFFECT PROFILE :**
- **1) Well tolerated**
- **2) Mild to moderate side effects:- sedation, dizziness, tiredness, diplopia and rashes**
- **3) In children :-**
- **Does not alter cognitive functions / concentration**
- **Does not impair memory or make them attention deficit**
- **But, Improves performance & personality in children**

LAMOTRIGINE

- Newer anti-epileptic drug
- Has Phenyl Triazine ring
- Needs to be converted into Triazine
- Effects similar to Carbamazepine
- **Action ;-**
- 1) Blocks Na-influx (channel) & NMDA receptors
- 2) Inhibits EAA- Glutamate release
- 3) Reduces Glutamate levels
- 4) Stabilizes neuronal membrane
- 5) Half – life – 24 hrs

LAMOTRIGINE – USES , ADVERSE EFFECTS

- **Uses :-**
- **1) As an "Add on' Therapy with conventional antiepileptic drugs**
- **2) In refractory cases of Partial / Generalized seizures**
- **3) Atonic + Absence seizures**
- **Adverse Effects :-**
- **1) Diplopia 2) Ataxia 3) Aggressiveness 4) Dizziness**
- **5) Headache**
- **Doses of Lamotrigine ;**
- **1) 50 mg / day ; Increase upto 300 mg/ day**
- **2) Tab : 25 mg**

GABAPENTIN

- GABA– analogue (Agonist)– centrally acting
- High lipid solubilityà crosses BBB
- Releases GABAà GABA–mimetic
- No action on GABAA receptors
- Absorbed by active transport mechanism (Amino acid Carrier)à Process more saturable à Makes drug saferà Free from S/Es
- Half-life = 8 hrs

GABAPENTIN

- No drug– interactions
- **USES :**
- 1) Add– on therapy
- Partial seizures– refractory cases
- **Adverse Effects :**
- 1) Somnolence, 2) Tiredness (Fatigability)
- 3) Ataxia 4) Unsteadiness
- **Dose ;-** 300 mg. OD then 900-1800 mg /d
  - Cap ; 300, 400 mg.

VIGABATRIN

- Irreversible inhibitor of GABA-Aminotransferase
- ↓
- Increase GABA concentration at synaptic site
- ↓
- Produces inhibitory effect
- ↓
- Reduces hyperexcitability
- ↓
- Terminates seizures discharge

VIGABATRIN

- **Uses :-**
- 1) "Add-on' Therapy ; 2) Partial seizures

- **Adverse Effects :-**
- 1) Behavioral changes 2) Depression
- 3) Psychosis 4) Amnesia
- 5) Agitation in children 6) Weight gain, 7) Diplopia

- **Precautions :-**
- 1) Elderly 2) Poor renal function
- **Dose :-** 2-4 G/ d ; 40 – 100 mg/ kg/ d in children

FELBAMATE

- Weak NMDA (N-Methyl D-Aspartate receptor antagonist
- Effective in -- Partial Generalized Seizures
- -- Intractable seizures in Children
- S/ Es :- Aplastic Anaemia
- (Withdrawn from Market)
- Now, reintroduced in market for the treatment of -à Lennox Gestaut Syndrome

TREATMENT OF STATUS- EPILEPTICUS

- 1) Prolong, repetitive seizures (>15 mins)
- 2) Without recovery between attacks
- 3) Life threatening -- Medical Emergency

- **DIAGNOSIS:**
- 1) Age of onset 2) Genetic factor
- 3) EEG findings 4) Associated neurological defects
- 5) MRI 6) Response to Treatmentà Prognosis

TREATMENT OF STATUS- EPILEPTICUS

1) **Diazepam :-** 10 mg I.V. Bolus Inj. (2mg/min over 5 min).
   Repeated twice at 15 mins.
   (Watch à Hypotension, Respiratory Depression)
   (or) Clonazepam – 1-3 mg I.V.
2) **Phenytoin :-** 18-25 mg/kg (50 mg/min)
   (or) Phenobarbitone à 100 – 200 mg im/iv
3) **Paraldehyde :-** 5-10 ml deep i.m. or 16 ml per rectum
   (if resucscitative facilities unavailable)
4) **Pentobarbitone I.V.** + Curarization with +ve pressure
5) **Gen. measures à** Fluid, air, elec. Balance, Infections

PREGNANCY WITH EPILEPSY

- 1) 90 % healthy baby ; 2% incidence of congenital abnormalities :- **Spina Bifida & Neural Tube Defects (Sodium Valproate); Cleft palate, Hare lips & Microcephaly (Phenytoin sodium) ; Hemorrhagic diathesis in neonates.**
- 2) No need to terminate pregnancy …….otherwise, lead to à **Complications :-** Toxemia, Intra – partum hemorrhage, Premature labor
- 3) Sudden withdrawal à Precipitates Status Epilepticus à Reduce dose to minimum à
- Supplement 5mg/d Folic acid (conception à Pregnancy)

PREGNANCY WITH EPILEPSY

- 5) Examine new born baby for à congenital abnormalities à give Vit-K inj. (to prevent bleeding due to deficiency of Vit.- K dependent clotting factor)
- 6) Give Phytonodione (20 mg/d) to mother in last month of pregnancy
- 7) vit. K + Phenobarbitone à in Neonatal kernicterus

GENERAL PRINCIPLES OF MANAGEMENT OF EPILEPSY

- 1) Disease not a social stigma (Don't Neglect)
- 2) Give opportunity to work
- 3) Avoid driving a vehicle, working with heavy machinery or indulge in swimming
- 4) Accurate evaluation of disease
- 5) Find underlying cause :
- (Rule out à Syncope, Hypoglycemia, Hypocalcemia, Hypo-parathyroidism, Brain Tumor or Hypoxia).

GENERAL PRINCIPLES OF MANAGEMENT OF EPILEPSY

- 6) No Drug cure 7) Aim to achieve:- Control of seizures, Minimum Drugs, Minimum S/Es.
- 8) Treat under proper supervision
- 9) Start antiepileptic drugs after 1st seizures in adults onset; postpone till 2nd seizure in childhood onset
- 10) Start treatment :-
- * With most establish & least toxic drug
- * Start with low dose & with monotherapy
- * Repeat EEG, Pl. Levels of Phenytoin, Carbamazepine

GENERAL PRINCIPLES OF MANAGEMENT OF EPILEPSY

- 11) Increase dose of drug & then change to other brand after tapering the dose of previous drug
- 12) continue treatment for 2-3 months
- 13) Taper previous drug dose & then replace new drug
- 14) Most patient require life time treatment
- 15) In idiopathic GTC seizures ,discontinue drug treatment after 4-5 yrs seizure - free interval
- 16) Avoid drugs precipitating seizures :-
- * Penicillin, INH, Imipenem Ciprofloxacin
- * Lignocaine, Cocaine, Alcohol, Ether, TCA, Ketamine
- * Methotrexate, Cyclosporine

GENERAL PRINCIPLES OF MANAGEMENT OF EPILEPSY

- **17) In Children :-**
- ** Educate their parents
- ** Observe proper precautions
- ** Follow proper instructions
- ** Keep seizure record
- ** Attend follow-up clinics regularly
- ** Give regular drug to the children