Anti-epileptic

- drugs ↑ GABAergic activity
- drugs ↑ Glutamatergic activity.
- Calcium channel blockers.
- Sodium channel blockers.
- New drugs.
- Epilepsy in pregnancy.

✓ Epilepsy ⇒ tendency to have seizures.

✓ Seizures → episodes of abnormal electrical activity discharge in brain.

- convulsion → motor movements seen in seizures.

- seizure can occur with/ without convulsions

(- Fit = layman term)

---

seizure → abnormal electrical discharge in brain

↓

overactivity in brain

↓

we have to depress.

---

to depress brain →

Increase inhibitory A.A

ie, ↑ GABA activity.

stimulatory A.A in brain.

→ glutamate.

so ↓ glutamate.

Ca^{2+}

Na^{+}

Ca^{2+}, Na^{+} are depolarizers... so we block them.

So drugs in epilepsy act by 4 mech

1. ↑ GABA
2. ↓ glutamate
3. Ca^{2+} channel blocker
4. Na^{+} channel blocker

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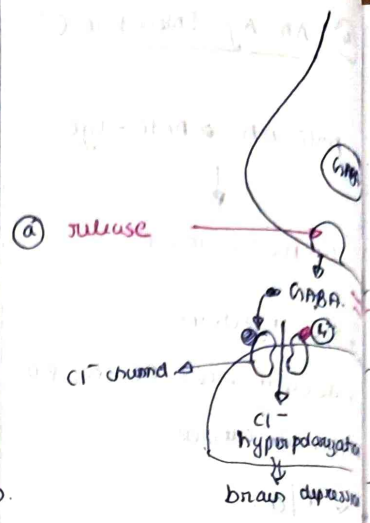
(1) GABA ↑ drugs



drugs can:

(a) ↑ GABA release

(b) ⊖ metabolism

(c) ⊖ reuptake.

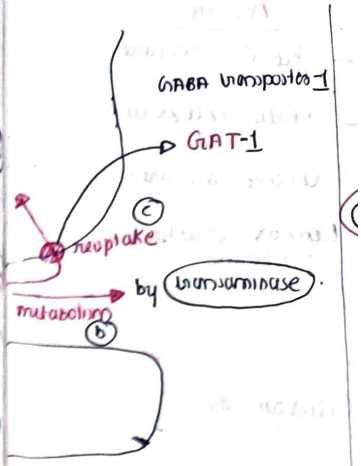
(d) directly bind & open Cl^- channels.

(a) Drugs ↑ release of GABA

⇒ GABAPENTIN

PREGABALIN.

- they are used in epilepsy but, DOC in → Neuropathic pain (nerve associated pain)
  - diabetic Neuropathy.
  - post herpetic neuralgia.



Gabapentin

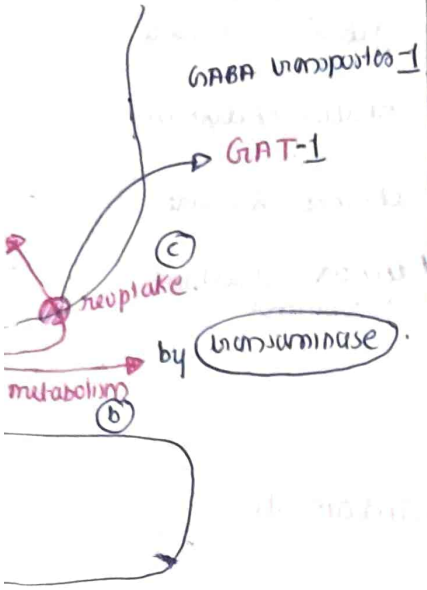
↓

DOC → restless leg Sx.

---

they (G & P) are (DOC) in many nerve associated pains eg. pain due to nerve pressing... etc...

Earlier it was thought. their MOA was ↑ release. but now discovered. that their main MOA is by Ca^{2+} channel # in epilepsy



(b) Inhibit metabolism

VIGABATRIN

↓

(−) transaminase.

Other use → infantile spasm

muscle spasms in new born baby.

→ Ca²⁺ channel blocking - calcium regulates.

→ EEG → hypsarrhythmia.

↓

Bizzare arrhythmia.

(c) Inhibits reuptake.

GAT-1 (−)

↓

TIAGABINE

(d) Drugs acting on Cl⁻ channels

Barbiturates

↓

phenobarbitones

(not used nowaday)

Barbiturates in children causes which S/E?

Hypokinesia (freq MCQ)

Gabapentin

↓

DOC → restless leg syndrome.

They (G & P) are (DOC) in many nerve associated pains — eg: pain due to nerve pressing ... etc ...

Earlier it was thought that MOA was ↑ release.

but now discovered that their main MOA is by Ca^{2+} channel # in epilepsy

Infantile spasm seen in

↓

(west syndrome)

DOC → ACTH

S/E of (VIGABATRIN)

visual field contraction

V I — visual field contraction (S/E)

G A B A — GABA

T R — transaminase

I N — inhibitor

Benzodiazepines

DOC used in (febrile seizures)

D - diazepam

L - lorazepam

C - clonazepam

Clobazam

↓

They are used in Treatment of episodes

not prophylaxis.

How to prevent? prevent fever

→ paracetamol. if temp rises in sick children, cold sponging - with normal room temp water

febrile seizure — occurs when there is fever, in children.

DOC → diazepam

- What is febrile seizures?
- In children ... during fever seizure occurs.
- In that DOC → diazepam.

- How to prevent this?
- In children with H/o febrile seizure educate parents to prevent child from having ↑ Body temperature.

ie, use paracetamol – even after that if temp doesn't ↓

do - cold sponging.

→ Common misconception →

① don't do cold sponging with ice water ✗
- for a feverish child, even RT water is cold.

Cold from ice cold water can ⊕ brain & trigger seizures. ★

Cold sponging → use Room temp water.

② In movies we see just on forehead we put cloth ∇ 0 It's B.S

- we are trying to heat exchange ...

→ wipe entire body with water ✓

→ not just forehead

In status epilepticus → DOC ↓ lorazepam.

↓

seizure one after another continuously.

{like brain pollution status}.

DOC in

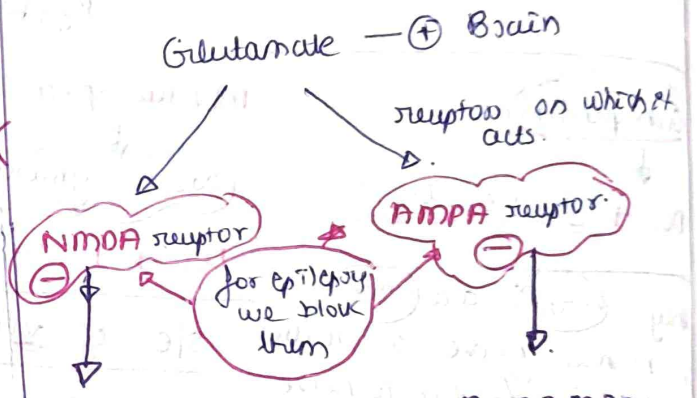
Diazepam – febrile seizure.

Lorazepam – status epilepticus

Clonazepam – absence seizures.

Clobazam – Lennox Gastaut syndrome.

Drugs ↓ Glutamate



Not used ✗

why ?

BM supression ★

MCQ

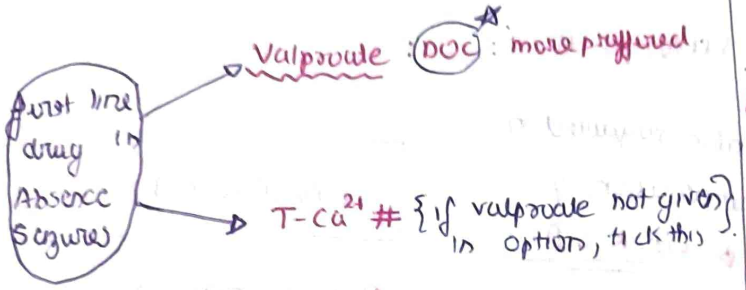
---

③ Ca2+ channel blocker.

In brain we have ↓ T-type Ca2+ channel.

T-Ca^{2+}

- Ethosuximide.
  - useful in (only) Absence seizures.
    {not even focal seizures}



① Na^+

- ✓ phenytoin.
- ✓ Carbamazepine (CBZ)
- ✓ Oxcarbazepine (OXC)
- ✓ Topiramate, Zonisamide → cause Kidney stones due to CA ⊖ action.
- Lacosamide, Rufinamide → New drugs for focal seizures.

Topiramate.

uses: epilepsy, focal, GTCS. / LGS.

other uses: C - ↓ craving of food.
O - Obesity : FDA approved.
M - migraine prophylaxis
B. - Bipolar disorder.

Topi vekkumbo (comes) venda. | most epi drugs causes weight gain but Topi → ↓ weight

CBZ/OXC

uses.: focal seizures, GTCS.

C/I → Absence & myoclonic seizures.

CBZ

DOC → focal seizure, trigeminal Neuralgia.

can be used in

- Bipolar disorder, diabetes Insipidus.

S/E

A - autoinduction of metabolism.
A - aplastic anemia.
A - ADH ↑ - dilutional hyponatremia. in elderly.
A - ataxia, Nystagmus, vertigo (cerebellum S/E)

autoinduction of metabolism ⇒ ↑ metabolism of itself. so we have to ↑ dose. but is why OXC is preffered over CBZ but OXC has higher chance of hyponatremia.

CBZ

C/I in Elderly. - due to dilutional hyponatremia.

all antiepileptic drugs if toxicity.

ataxia, Nystagmus vertigo → affects cerebellum.

phenytoin.

a) Non-bioequivalence.
b) Induer (+)
c) Zero order.
d) Anti-arrhythmic
↳ class Ib

C/I – absence seizures
myoclonal seizures.

use – focal, GCTS.

SIE ✱ MCQ.

H8 – hirsutism., Gum hypertrophy.
O – osteomalacia {not osteoporosis} → phenytoin ↑ vit D metabolism.
{osteoporosis is due to Ca^{2+} deficiency}
T – teratogenic – fetal hydantoin syndrome.
m – megaloblastic anemia. → phenytoin ↓ Folic acid by ↑ metabolism.
A – arrhythmia @ overdose.
L – lymphadenopathy → lymph node ↑ in size "pseudolymphoma"
I – hyperglycemia., so C/I in diabetic patients.
K – ↓ vitamin K. → Hemorrhagic disease of new born.
A – Ataxia, Nystagmus, Vertigo. → in all epileptic drugs toxicity.

(Why at overdose)

Hirsutism causing drugs.

P – phenytoin
C – cyclosporin
M. – minoxidil.

If MCQ is asked,

a patient taking phenytoin has bone problems...
what will you give?

Ans:
- Ca^{2+}
- vitamin D.
- vitamin K.

vit K is also required in bone mineralization & phenytoin ↓ vit K & D.

phenytoin ↓ LVI ↓.
following vitamins {By ↑ metabolism}

- vitamin K
- vitamin D
- folic acid.

But the stars are

→ Valproate → all 4 MOA

→ Lamotrigene. – 3 MOA (except Ca^{2+} #).

VALPROATE

DOC in many seizures

- GTCS generalized tonic clonic.
- Absence
- myoclonic
- Atonic
- LGS.

SIE

S/E

V – Vomiting.

A – Alopecia / curling of hair

L – Liver toxicity ★ high in children. → how to prevent valproate hep Tox
Carnitine.

P – pancreatitis, PCOD → Gender specific s/e of valproate. (MCQ)

R – Rash

O – obesity

A – Ataxia, Nyst, vertigo → Symptom of cerebellum damage
↓
only at toxic doses.

T, E – Teratogenic. most among anti-epileptic (D)

New drugs

① K+ channel openers

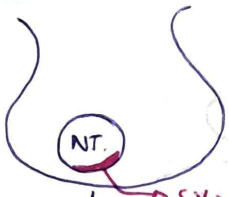
K+ goes out → hyperpolarization
↓
neurons can't work.

RETIGABINE.

MCQ
- all works through GABA except ?

S/E
→ Retinitis
→ metabolized by microsomal enzyme (D/I)

② SV2A



Levetiracetam
Brivaracetam.
↓
bind to SV_2A
↓
↑ release of GABA
↓ release of Glu

– a protein
↓
synaptic vesicular protein.
↓
in vesicles, near side of synapse.

* they are least Teratogenic
* can cause psychiatric S/E.

③ Cannabidiol

(+) CB_1 – cannabinoid R
used in Dravet syndrome.

④ Stiripentol.

GABA A ↑.
used in

DOC in different epilepsy

	DOC	alternatives
(1) Generalized Tonic clonic seizures (Generalized) – Tone ↑, Clonic – jerk movements. → Grand mal epilepsy.	Valproate	phenytoin, CBZ, L
(2) Absence seizures (Generalized) → momentarily stares at one point, for some time only. → petit mal epilepsy. EEG → 3 spike wave pattern	Valproate / CBZ	Ethosuximide. Elderly → Leve/Lamo
(3) focal seizures (focal) – temporal lobe epilepsy, parietal lobe epilepsy etc...		
(4) myoclonic, (5) Atonic, (6) LGS	Valproate (DOC)	
(7) febrile s →	diazepam (DOC)	
(8) status epi →	Lorazepam.	
(9) Infantile spasms →	ACTH	

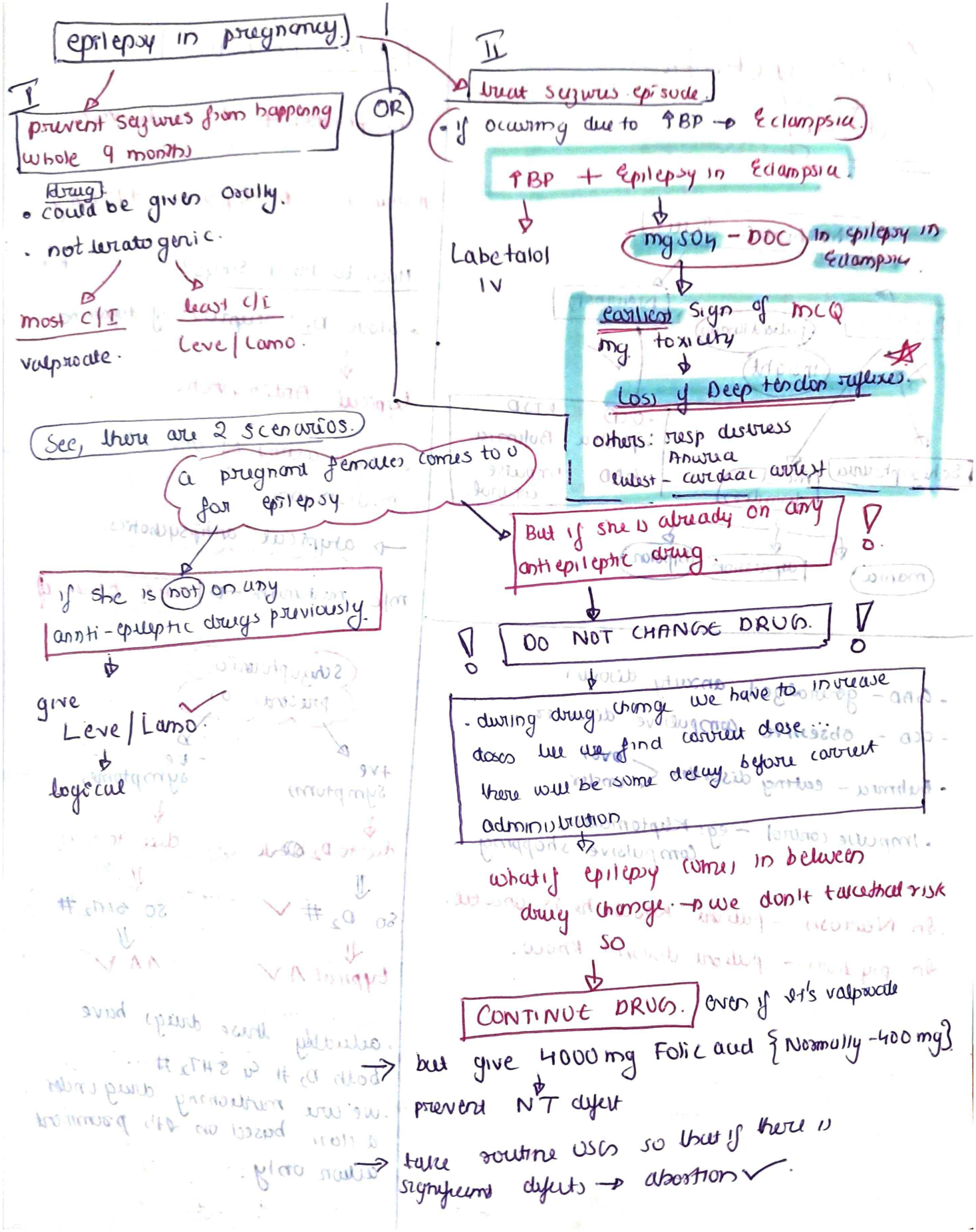
Impt MCQ

NOTE Lamotrigene

- impt s/e of lamotrigene. Steven Johnson Sx.
- at high doses – Toxic epidermal necrolysis
- to prevent this we give lamotrigine in incremental doses one by one.

MCQ why is Lam given in ↑ dose ↓ to prevent skin rash ↓ SJS

Seizures
- Generalized – Entire brain affected
- focal – on certain part.


epilepsy in pregnancy
I
prevent seizures from happening whole 9 months
OR
II
treat seizures episode
- if occurring due to ↑BP → Eclampsia
↑BP + Epilepsy in Eclampsia
Labetalol IV
mgSO4 - DOC
in epilepsy in Eclampsia
Earliest sign of MgSO4 toxicity
Loss of Deep tendon reflexes
others: resp distress
Anuria
Latest - cardiac arrest
Drug
- could be given orally.
- not teratogenic.
most C/I
valproate.
least C/I
Leve/Lamo.
See, there are 2 scenarios.
a pregnant females comes to OPD for epilepsy
if she is not on any anti-epileptic drugs previously.
give Leve/Lamo
logical
But if she is already on any antiepileptic drug.
DO NOT CHANGE DRUGS.
- during drug change we have to increase doses till we find correct dose....
there will be some delay before correct administration
what if epilepsy comes in between drug change → we don't take ethical risk
so
CONTINUE DRUGS.
even if it's valproate
but give 4000 mg Folic acid {Normally - 400 mg}
prevent NT defect
take routine USGs so that if there is significant defects → abortion

Q) classify - antiepileptic drugs ✓

Q) management of status epilepticus ++

Q) enumerate newer drugs used in epilepsy. MOA of any two agents?

Q) MOA, ADR of phenytoin

Q) drugs in absence seizures.

Q) uses of CBZ.

Q) DOC in tonic-clonic seizures? (Valproate CBZ.)
↓
Pkinetics & ADR of any one such drug

Q) valproic acid ++.

Q) Lamotrigere

Q) CBZ

Q) drugs used in each type of epilepsy - table - text
s.c/photo

Status epilepticus

Status epilepticus is defined as a seizure lasting for ≥ 5 minutes, or two or more seizures occurring without full recovery of consciousness in between.

- medical emergency

Treatment

first priority is to maintain the airway patent

↓

→ left lateral position.

→ check, airway, breathing, circulation.

→ prevent aspiration, physical injury.

→ 20-50 ml 50% IV dextrose
↓
to correct hypoglycemia.

→ $NaHCO_3$ - if metabolic acidosis

✓ flow chart S.C

Anticonvulsant therapy

① LORAZEPAM - 4 mg

- (0.1 mg/kg - children)

@ rate - 2 mg/min, repeated after 10 min if required.

* first choice drug
- repeated after 10 min if required.
- effective in 75-90% of cases
- lasts 6-12 hours > diazepam.
- thrombophlebitis less likely.

② DIAZEPAM

10 mg (0.2-0.3 mg/kg)

IV at 2 mg/min,

repeated once after 10 min if required.

↓

has been std therapy, but its anticonvulsant effect fades after 20 minutes.

⇒ more doses may be required.

⇒ more damaging to injected veins.

③ Fosphenytoin

100-150 mg/min IV.

to max 1000 mg

- slower acting drug, which should be given subsequently, irrespective of response to lorazepam.
- should be given earlier if seizures recur or dont respond to lora/dia within 30 minute of onset.

④ phenytoin sodium

only used when Fosphenytoin is not available.

⑤ Phenobarbitone Sodium

- alternative to Fosphenytoin
- 50-100 mg per minute IV to max of 10 mg/kg
- slow acting.

* refractory cases - that fails to respond to Lora / fos. within 40 min of onset may be treated with

↓

IV MIDAZOLAM / propofol / thiopentone anaesthesia.

General Measures → in beginning ✓

- airway maintenance ✓
- fluid & electrolyte balance ✓
- BP. ✓
- ~~normal cardiac rhythm~~
- ~~care of unconsciousness~~
- euglycemia should be taken care of ✓

NEWER DRUGS

phenytoin

CI - absence & myoclonic seizures.

* CNS depressant.
* abolishes tonic phase of seizures.

MOA

pdf ✓

- phenytoin prevents repitative detonation of normal brain cell by:

at therapeutic conc ✓

→ prolongation of voltage sensitive sodium channel inactivation.

Needs higher concentration.

→ depresses presynaptic release of glutamate

→ ↑ GABA release

→ reduces Ca^{2+} influx. - Inhibition of 'T' typ Ca^{2+} current.

→ high frequency discharges are ⊖

→ little effect on normal low frequency discharges.

PK

absorption: oral route, slow.

metabolism: CYP 2C9, 2C19.
↓ in liver.

Kinetics of metabolism is capacity limited : i) 1st order to. ↓ zero order {over therapeutic range}.

T1/2 - 12-24 hours).

ADR

USES - (APTs.)

* Generalized - tonic-clonic seizures
* Partial seizures.
* Trigeminal neuralgia {2nd choice}
* Status epilepticus.

ADR

@ Therapeutic plasma concentration. (on prolonged use)

* Gum hypertrophy
* Hirsuitism
* Hypersensitivity
* megaloblastic anemia. {folate absorption ⊖}
* osteomalacia. {⊖ vit D activation}.
* fetal hydantoin syn. hydantoin.

@ overdose toxicity due to high plasma con

, Cerebellar & vestibular manifestation
→ Ataxia, Vertigo, diplopia, nystagmus

. Drowsiness, hallucination

. Nausea, vomiting.

. IV → fall in BP. {only during IV, so monitoring reduced}

local tissue injury → damage & thrombosis given
↓
edema & discolouration of injected limb {tissue necrosis}

D/I

Metabolised by: P450 enzyme.

Inducer of: CYP 3A4.

#with #

- **phenobarbitone** → by enzyme induction, both enhances each other's degradation. ↓ Unpredictable overall interaction
- **Carbamazepine** → Induce each other's metabolism.
- **Valproate** → displace protein bound Phen. ↓ ↑ plasma Lvl of unbound phenytoin.
- **warfarin** → phenytoin competitively ⊖ warfarin metabolism.
- **OCP** → induce microsomal enzymes. ↓ failure of oral contraception.

Carbamazepine.

* first line drug for focal seizures. alternative in GTCS.
  - C/I – absence seizure, myoclonic.

MOA

prolong the inactivated state of Na+ channels.
→ high freq neuronal discharges are selectively ⊖
⊖ kindling

PK

- slow absorption.
- 75% plasma protein bound.
- metabolism - Liver.
- autoinduction of metabolism ✓

ADR SADES HAI.

Type A

- ✓ Neurotoxicity – ataxia, Vertigo, diplopia, Stupor, drowsiness.
- ✓ Sensitize ADH – hyponatremia water retention. SIADH.
- ✓ Hepatotoxicity.

Type B

Idiosyncratic reactions.

- ✓ Skin rashes – SJS, TEN
- Hepatic dysfunction.
- ✓ aplastic anemia
- teratogenicity – neural fetal abnormalities.

Uses:

* GTCS, focal seizures. ✓ * bipolar ds.
* Neuralgic pain – ✓ Diabetes Insipidus.
  - trigeminal Neuralgia DOC
  - herpetic pain.
  - diabetic Neuralgia.

D/I

CB2 ↑

Enzyme ⊖ → valproate.
Erythromycin.

CB2 ↓

- Enzyme inducers - phenytoin
phenobarbitone.

CB2 induces metabolism of.

- OCP
- Haloperidol.
- Lamotrigene.
- Tiagabine

NEWER DRUGS

* drugs developed after 1990.
* Better tolerated, less ADR.
* less drug interactions.
* Broad spectrum of action.

TOPIRAMATE
ZONISAMIDE
LEVETIRACETAM
VIGABATRIN
TIAGABINE.
LACOSAMIDE

① Topiramate

Multiple mechanisms (Q)

1. prolongation of Na+ channel inactivation.
2. AMPA - glutamate receptor blocker
3. open voltage gated K+ channel. {hyperpolarization}
4. GABA potentiation by postsynaptic effect.

Broad spectrum of activity (Q)

- partial seizures.
- focal to BTCS, refractory focal seizures
- GTCS.
- myoclonic epilepsy.
- LGS.
- migraine prophylaxis

ADR (Q).

- CNS toxicity - ataxia, word finding
Renal stones

② LEVETIRACETAM

MOA

⊖ SV2A protein.
- modify synaptic release of Glu & GABA

USES

- GTCS, CPS, myoclonic seizures.

③ VIGABATRINE ✓

- ⊖ GABA transaminase.
- ↑ GABA conc.

S/E
visual field abnormalities

---

② drugs in absence seizures

- Valproate {Na^+ ⊖}
- Ethosuximide {Ca^{2+} ⊖}

Valproate

- Carboxylic acid derivative.
- Broad spectrum antiepileptic drug.

MOA Figures.

* multiple mechanisms

① phenytoin like – prolongation of inactivation of Na^+ channels. ✓

② Suppress (T) Ca^{2+} - current ✓

③ ↑ GABA → ↑ synthesis
✓ ↓ metabolism - GABA-T ⊖

④ ⊖ NMDA glutamate receptor ✓
Figures ④

PK UG

- oral – good.
- liver metabolism – CYP 2C9, 2C19.
- urine excretion

ADR

dose related

- GI upset
- CNS; sedation, ataxia, tremor.

prolonged use

- weight gain
- hair loss
- curling of hair.
- → PCOD.

Idiosyncratic

Rash
Hepatotoxicity.
Thrombocytopenia.

Teratogenic ★

Spina bifida.
Neural tube defect

Uses

- absence seizures – DOC
- myoclonic & atonic.
- T-C.
- focal.

→ Bipolar ds.
→ Migraine prophylaxis

D/E

Enzyme Inhibitors

phenobarbitone

Lamotrigine

Lorazepam

Phenytoin - displaces phenytoin from plasma protein site.

LAMOTRIGINE

UQ

Diazepam MOA, uses

Thiopentone sodium

Uses, ADR

Define Analeptics & their uses

Febrile seizures - usually children.

DOC - Diazepam.

route - rectally diazepam - 0.5 mg/kg.

↓

{Suppository}

Rationale :

① In seizing child IV access is difficult & time consuming

② Rapid absorption via rectal route ✓ {lipid soluble drug}

③ Quick onset ✓.

④ Non invasive - easy administration. can be given even outside of hospital by parents etc.