SNS COLLEGE OF PHARMACY AND HEALTH SCIENCES
Sathy Main Road, SNS Kalvi Nagar,
Saravanampatti Post, Coimbatore - 641 035,
Tamil Nadu.

ANTI-CONVULSANTS

Antiepileptic drugs: a) block initiation of electrical discharge b) prevent spread of electrical discharge (most current AED)

1. **Na+ channel blockers** - stabilize inactive state of Na+ channels (prevent return of Na+ channels to active state) in frequency-dependent manner → prevented rapid, repetitive, sustained firing of axons (normal action potentials are not inhibited!). Most common and most well-characterized mechanism of currently available AEDs! each sodium channel dynamically exists in 3 states: a) resting state - allows Na+ passage into cell b) active state (during action potential) - allows increased Na+ influx into cell c) inactive state (during refractory period) - does not allow Na+ passage. Na+ channels – action potential CARBAMAZEPINE OXCARBAZEPINE ESLICARBAZEPINE PHENYTOIN – the only AED metabolized through nonlinear, zero-order kinetics. FOSPHENYTOIN, LAMOTRIGINE, ZONISAMIDE, LACOSAMIDE, RUFINAMIDE.
2. **Ca2+ channel inhibitors** Ca2+ channels in CNS exist in 3 forms - L, N, T. these channels are small and are inactivated quickly. influx of Ca2+ currents in resting state produces partial depolarization of membrane (Ca2+ channels function as “pacemakers” of normal rhythmic brain activity), e.g. T-calcium channels in thalamus. Ca2+ channels - “pacemakers”, voltage-dependent neurotransmission ETHOSUXIMIDE METHSUXIMIDE PHENYTOIN also has some Ca2+ channel blocking activity.
3. GABA enhancers GABA binds to GABAA receptor → Cl- influx → hyperpolarization (repolarization). GABA is produced by glutamate decarboxylation (glutamic acid decarboxylase, GAD). GABA is catabolized by GABA transaminase (GABA-T). GABA (inhibitory neurotransmitter) - hyperpolarization
4. **GABAA RECEPTOR AGONISTS** Benzodiazepines - CLONAZEPAM, DIAZEPAM, CLOBAZAM Barbiturates - PHENOBARBITAL, PRIMIDONE
5. GABA REUPTAKE INHIBITORS TIAGABINE
6. GABA TRANSAMINASE INHIBITORS VIGABATRIN
7. POTENTIAL GABA MECHANISM OF ACTION GABAPENTIN VALPROATE

Na+ channel blockers

N.B. Na-channel blockers (esp. carbamazepine) increase sudden cardiac death risk!

CARBAMAZEPINE (CBZ) (Tegretol®, Carbatrol®) THERAPEUTIC USES One of most widely used AEDs in world! (available in USA since 1974) 1) highly effective first choice for all partial seizures (simple and complex, secondarily generalized, cryptogenic and symptomatic) 2) effective first choice for tonic-clonic seizures (not effective for other generalized seizures – may aggravate absences and myoclonic seizures). 3) trigeminal neuralgia 4) occasionally used in manic-depressive patients.

PHENYTOIN (PHT) (Dilantin®) Available in USA since 1938 (formerly called diphenylhydantoin) also has Ca2+ channel blocking activity.

THERAPEUTIC USES 1) highly effective first choice for all partial seizures (simple and complex, secondarily generalized, cryptogenic and symptomatic) – first choice of seizure prophylaxis in head injury! 2) effective first choice for tonic-clonic seizures (not effective for other generalized seizures*) 3) status epilepticus 4) some antiarrhythmic properties *may even worsen absence and myoclonic seizures! not generalized CNS depressant, but does produce some degree of drowsiness without progression to hypnosis. contraindication – bradyarrhythmias.

GABAA receptor agonists

BENZODIAZEPINES - safest and most free from severe side effects of all AEDs!!! Chronic treatment – CLONAZEPAM, CLOBAZAM, CLORAZEPATE; Terminating status epilepticus – DIAZEPAM (drug of choice), LORAZEPAM.

CLONAZEPAM (KLO) (Klonopin®) – potent chronic treatment of absence and myoclonic seizures; – effective against all other types of seizures (generalized seizures and, to lesser extent, partial seizures); also effective for subcortical myoclonus. – useful in patients with concomitant anxiety disorder. very high affinity for GABAA receptors. plasma levels and antiepileptic effects are not correlated. acetylated in liver (metabolic rate depends on genetic acetylator function); metabolites have no clinical relevance; [KLO] is decreased by CBZ, PHB. T1/2 = 20-80 hrs. available as tablets (0.5 mg, 1 mg, 2 mg), also can be given IV or rectally. administered × 1-3/d. dosage 0,25-12 mg/d (start at 1.5 mg/d divided TID, increase by 0.5-1 mg q 3 d; max 20 mg/d) therapeutic blood level: 10–80 ng/mL. major ADVERSE EFFECT is sedation + rapid tolerance. children tolerate much better! (pediatricians use it most often) drug usually works very well for several months, and then tends to become less effective, leaving only sedating effects many cases have

been reported of seizures during withdrawal, including status epilepticus (even in patients with no history of status). Taper drug over 3-6 months!

DIAZEPAM (Valium®), LORAZEPAM (Ativan®), MIDAZOLAM (Versed®, Nayzilam®) - drugs of choice in status epilepticus.

 long term use is limited due to rapid tolerance development.

Nayzilam® - nasal spray CIV, FDA approved for the acute treatment of seizure clusters in patients ≥ 12 years. contraindicated in patients with acute narrow-angle glaucoma approval based on randomized, double-blind, placebo-controlled trial (Study 1; NCT01390220) – 5 mg nasal spray was superior to placebo in providing rapid, sustained seizure control when administered to patients experiencing an seizure clusters in the outpatient setting and was associated with a favorable safety profile:

– termination of seizure(s) within 10 minutes after initial dose of study drug (80.6 versus 70.1%). – absence of seizure recurrence between 10 minutes and 6 hours after the initial dose of study drug (58.2 versus 37.3%). – smaller proportion of Nayzilam-treated patients experienced the next seizure within 24 hours after the initial blinded dose of study drug (37.3% versus 46.3%).

GABA transaminase inhibitors

VIGABATRIN (VGB) (Sabril®) - irreversibly inhibits extracellular GABA transaminase. GABA transaminase requires 3-6 days to be resynthesized. not licensed in USA because of visual toxicity.

THERAPEUTIC USES - refractory complex partial seizures; very effective in infantile spasms (esp. in tuberous sclerosis). less effective against primarily generalized tonic-clonic seizures. may worsen myoclonic and absence seizures (can cause absence status!).