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ANTI EPILEPTIC DRUGS: A REVIEW

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ABATRACT

Epilepsy is a central nervous system (neurological) disorder in which brain activity becomes abnormal, causing seizures or periods of unusual behavior, sensations, and sometimes loss of awareness. A "seizure" is a paroxysmal alteration of neurologic function caused by the excessive, hyper synchronous discharge of neurons in the brain. Considering 5 cases that I have studied all these patients are using long term medication for their seizures and these people have adverse effects during their first line treatment. Drugs used during first line are sodium valproate, carbamepazine, lamitrogen. Carbamepazine and lamitrogen are the drugs used in the treatment of focal seizures and these are prolonged used drugs. These drugs act on inhibiting the presynaptic release of excitatory amino acid neurotransmitters. Sodium valoprate. This medication is used to treat seizure disorders, mental/mood conditions (such as manic phase of bipolar disorder).

KEYWORDS: Sodium valproate, carbamepazine, lamitrogen.

INTRODUCTION

EPILEPSY

Epilepsy is a group of neurological disorders characterized by epileptic seizures. These are episodes that can vary from brief and nearly undetectable to long periods of vigorous shaking and neural discharges. It effects 0.5 to 1% of the population approximately 50million people worldwide.

Types of Epilepsy

Two major types of epilepsy:

(a) Partial seizures (localized to part of the brain)

b) Generalized seizures (involved the whole brain)

a) Partial seizures: In which the discharge begins locally and often remains localized. The symptoms depend on the brain region or regions involved and include involuntary muscle contractions, abnormal sensory experiences or autonomic discharge on mood and behavior often turned psychomotor epilepsy which may arise from a focus within a temporal lobe. Partial seizures can often be attributed to local cerebral lesions and their incidents increases with age. An epileptic focus in the mortar cortex results in attacks sometimes called Jacksonian epilepsy.

b) Generalized seizures: It involves the whole brain including the reticular system thus producing abnormal electrical activity throughout both hemispheres. Immediate loss of conscious ness is characteristic of generalized seizures.

These are two types

- Tonic clonic seizures
- Absent seizures

Tonic clonic seizures: these consist of an initial strong contraction of the whole musculature casein a rigid extension spasm and involuntary cry.

Absent seizures mostly occur in children they are much less dramatic but may occur more frequently than tonic clonic seizures.

Causes

- Low oxygen during birth
- Head injuries that occur during birth or from accidents
- Brain tumors
- Genetic conditions that result in brain such as tuberous sclerosis
- Infections such as meningitis or encephalitis
- Stroke or many other types of damage to the brain
- Abnormal levels of substances such as sodium or blood sugar.
- Alcohol consumption
- Missing medication doses
- Cocaine and other narcotics

- Lack of sleep.

Drugs used in treatment of epilepsy

Sodium channel blockers: carbamepazine, phenytoin, lamitrogen, sodium valoprate, Felbimite, Topiramate, Zonisamide, Rufinamide, Nacozamide.

Calcium channel blockers: Sodium valoprate, Ethosucimmide, GABA pentin, Pregabalin, Zonisamide.

GABA Receptors: Phenobarbital, Benzodiazepines (clonazepam, diazepam, lorazepem). Felbimite.

Mechanism of action

The major antiepileptic drugs are thought to act by three main mechanisms

1. Reducing electrical excitability of cell membranes namely through use –dependent block of sodium channels.
2. Enhancing GABA mediated synaptic inhibition: this may be achieved by and enhanced post synaptic action of GABA, by inhibiting GABA TRANS AMINASE of the in habiting GABAup take into neurons and glial cells.
3. Inhibiting T type calcium channels.

Adverse Effects: Sedation, dizziness, ataxia, Blurred vision, hypersensitivity reactions, leukopenia, vertigo nausea, hair loss, weight gain, foetalmal formation, depression, behavior and mood changes, rashes, vomiting.

Review on Adverse effects of Epileptic drugs

Carbamazepine

The most important pharmacological effect of carbamazepine is its strong induction of the hepatic cytochrome P450 enzyme system. Hence, carbamazepine reduces efficacy or blood levels of many other medications. This effect is a major problem in treating patients with other medical conditions, such as the elderly. It is also a major problem in treating bipolar disorder, since most such patients are treated with multiple psychotropic medications.

Carbamazepine 9,10-epoxide metabolite can be neurotoxic (producing delirium or confusion), and may be produced in greater amount in combination treatment with valproate.

Consequently, the valproate-carbamazepine, though safely used in many patients, should be avoided on a routine basis.

Side effects of carbamazepine include: ataxia, dizziness, drowsiness, nausea, and vomiting. Pruritus, speech disturbance, amblyopia. See below for a comprehensive list of adverse effects. Along with its needed effects, carbamazepine may cause some unwanted effects. Although not all of these side effects may occur, if they do occur they may need medical attention.

Blurred vision or double vision, continuous back-and-forth eye movements. Actions that are out of control, behavioral changes (especially in children), confusion, agitation, or hostility (especially in the elderly), diarrhea (severe), discouragement, drooling, fear, feeling of unreality, feeling sad or empty, headache (continuing), increase in seizures, irritability, lack of appetite, loss of balance control, loss of interest or pleasure, muscle trembling, jerking, or stiffness, nausea (severe), Black, tarry stools, blood in the urine or stools, bone or joint pain, chest pain, cough, darkening of the urine, difficulty with speaking or slurred speech, fainting, frequent urination, hoarseness, irregular, pounding, or unusually slow heart beat, over back or side pain, mental depression with restlessness and nervousness or other mood or mental changes, muscle or stomach cramps, nosebleeds or other unusual bleeding or bruising.

LAMOTRIGINE

Its biochemical effect involves inhibiting the presynaptic release of excitatory amino acid neurotransmitters such as glutamate and aspartate; this effect may or may not explain its psychotropic properties. Lamotrigine is metabolized by the liver and is moderately (over 50%) protein-bound. Its half-life is 25 hours, which allows for simple once daily dosing.

Since it can be somewhat stimulating, and its effect is on glutamate, which is not normally part of the biology of sleep, PL editors have come to the conclusion that Lamotrigine is best given in the morning, not in the evening, as is commonly the case. This will prevent impairment of the normal stages of sleep.

Adverse effects: Commonly reported side effects of Lamotrigine include: ataxia, skin rash, headache, insomnia, and nausea. Other side effects include: infection, dyspepsia, abnormal gait, constipation, and drowsiness. See below for a comprehensive list of adverse effects.

Along with its needed effects, Lamotrigine may cause some unwanted effects. Although not all of these side effects may occur, if they do occur they may need medical attention.

Blurred vision, changes in vision, clumsiness or unsteadiness, double vision, poor coordination, skin rash, Anxiety, chest pain, confusion, continuous, uncontrolled back and forth or rolling eye movements, depression, increase in seizures, infection, irritability, Blistering, peeling, or loosening of the skin, chills, cough, dark urine, diarrhea, fever, general feeling of discomfort or illness, headache, itching, joint pain, loss of appetite, memory loss, muscle cramps, pain, or weakness, nausea, red or irritated eyes, runny nose, shivering, small red or purple spots on the skin, sore throat, sores, ulcers, or white spots on the lips or in the mouth.

SODIUM VALPROATE

Proposed mechanisms include affecting GABA levels, blocking voltage-gated sodium channels, and inhibiting histone deacetylases. Valproic acid is a branched short-chain fatty acid (SCFA) made from valeric acid. Valproate is included in the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system.

Side effects: Diarrhea, dizziness, drowsiness, hair loss, blurred/double vision, change in menstrual periods, ringing in the ears, shakiness (tremor), unsteadiness, weight changes may occur. A small number of people who take anticonvulsants for any condition (such as seizure, bipolar disorder, pain) may experience depression, suicidal thoughts/attempts, or other mental/mood problems. Tell your doctor right away if you or your family/caregiver notice any unusual/sudden changes in your mood, thoughts, or behavior including signs of depression, suicidal thoughts/attempts, thoughts about harming yourself. Severe (sometimes fatal) brain disorder (encephalopathy) has rarely occurred, particularly in patients with certain metabolic disorders (urea cycle disorders). Tell your doctor right away if you develop unexplained weakness, vomiting, or sudden mental/mood changes (such as confusion). A very serious allergic reaction to this drug is rare, including: fever, swollen lymph nodes, rash, itching/swelling (especially of the face/tongue/throat), severe dizziness, trouble breathing.

PHENYTOIN

Phenytoin is believed to protect against seizures by causing voltage-dependent block of voltage gated sodium channels. This blocks sustained high frequency repetitive firing of action potentials. This is accomplished by reducing the amplitude of sodium-dependent action potentials through enhancing steady state inactivation. Sodium channels exist in three main conformations: the resting state, the open state, and the inactive state. Phenytoin binds preferentially to the inactive form of the sodium channel. Because it takes time for the bound drug to dissociate from the inactive channel, there is a time dependent block of the channel. Since the fraction of inactive channels is increased by membrane depolarization as well as by repetitive firing, the binding to the inactive state by phenytoin sodium can produce voltage-dependent, use-dependent and time-dependent block of sodium-dependent action potentials.

The primary site of action appears to be the motor cortex where spread of seizure activity is inhibited. Possibly by promoting sodium efflux from neurons, phenytoin tends to stabilize the threshold against hyper excitability caused by excessive stimulation or environmental changes capable of reducing membrane sodium gradient. This includes the reduction of post-tetanic potentiation at synapses which prevents cortical seizure foci from detonating adjacent cortical areas. Phenytoin reduces the maximal activity of brain stem centers responsible for the tonic phase of generalized tonic-clonic seizures.

Side effects: Headache, nausea, vomiting, constipation, dizziness, feeling of spinning, drowsiness, trouble sleeping, or nervousness may occur. May cause swelling and bleeding of the gums. unusual eye movements, loss of coordination, slurred speech confusion, muscle twitching, double or blurred vision, excessive hair growth, increased thirst or urination, unusual tiredness, bone or joint pain, changes in mood thoughts, behavior and signs of depression, susidal thoughts.

PHENOBARBITOL

It acts on $GABA_A$ receptors, Phenobarbital increases the flow of chloride ions into the neuron which decreases the excitability of the post-synaptic neuron. Hyperpolarizing this post-synaptic membrane leads to a decrease in the general excitatory aspects of the post-synaptic neuron. By making it harder to depolarize the neuron, the threshold for the action potential of the post-synaptic neuron will be increased. Phenobarbital stimulates GABA to accomplish this hyper polarization. Direct blockade of excitatory glutamate signaling is also believed to contribute to the hypnotic/anticonvulsant effect that is observed with the barbiturates.

Side effects: Dizziness, drowsiness, problem with memory or concentration, excitation, irritability, aggression, confusion, loss of coordination or balance, loss of appetite, head ache tiredness, nausea, vomiting, constipation and hangover. Somnolence, hyperventilation, apnea, bradycardia, hypotension, megaloblastic anemia.

REFERENCES

1. Anti-epileptic drugs Rang and Dale's pharmacology Elsevier ltd 8th Edison.
2. Anti-epileptic drugs principles of pharmacology KD Tripathijaypee publications seventh Edison.
3. Fisher RS, van Emde Boas W, Blume W, Elger C, Genton P, et al. (2005) Epileptic seizures and epilepsy: definitions proposed by the International League against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia, 46: 470-472.
4. Hauser WA, Annegers JF, Rocca WA (1996) Descriptive epidemiology of epilepsy: contributions of population-based studies from Rochester, Minnesota. See comment in PubMed Commons below Mayo Clin Proc, 71: 576-586.
5. Giussani G, Cricelli C, Mazzoleni F, Cricelli I, Pasqua A, et al. (2014) Prevalence and Incidence of Epilepsy in Italy Based on a Nationwide Database. See comment in PubMed Commons below Neuroepidemiology, 43: 228-232.
6. Begley CE, Famulari M, Annegers JF, Lairson DR, Reynolds TF, et al. (2000) The cost of epilepsy in the United States: an estimate from population-based clinical and survey data. See comment in PubMed Commons below Epilepsia, 41: 342-351.
7. Begley CE, Beghi E (2002) The economic cost of epilepsy: a review of the literature. See comment in PubMed Commons below Epilepsia, 43 Suppl 4: 3-9.
8. Hitiris N, Mohanraj R, Norrie J, Brodie MJ (2007) Mortality in epilepsy. See comment in PubMed Commons below Epilepsy Behav, 10: 363-376.
9. Sillanpää M, Shinnar S (2010) Long-term mortality in childhood-onset epilepsy. See comment in PubMed Commons below N Engl J Med, 363: 2522-2529.
10. Mohanraj R, Brodie MJ (2006) Diagnosing refractory epilepsy: response to sequential treatment schedules. European journal of neurology: the official journal of the European Federation of Neurological Societies, 2006; 13: 277-82.
11. Sinha S, Siddiqui KA (2011) Definition of intractable epilepsy. See comment in PubMed Commons below Neurosciences (Riyadh), 16: 3-9.

12. Perry MS, Duchowny M (2013) Surgical versus medical treatment for refractory epilepsy: outcomes beyond seizure control. See comment in PubMed Commons below Epilepsia, 54: 2060-2070.
13. Baker GA, Taylor J, Aldenkamp AP; SANAD group (2011) Newly diagnosed epilepsy: cognitive outcome after 12 months. See comment in PubMed Commons below Epilepsia, 52: 1084-1091.
14. Baxendale S, Heaney D, Thompson PJ, Duncan JS (2010) Cognitive consequences of childhood-onset temporal lobe epilepsy across the adult lifespan. See comment in PubMed Commons below Neurology, 75: 705-711.
15. Bell GS, Sinha S, TisiJd, Stephani C, Scott CA, et al. (2010) Premature mortality in refractory partial epilepsy: does surgical treatment make a difference? See comment in PubMed Commons below J Neurol Neurosurg Psychiatry, 81: 716-718.
16. Dupont S, Tanguy ML, Clemenceau S, Adam C, Hazemann P, et al. (2006) Long-term prognosis and psychosocial outcomes after surgery for MTLE. See comment in PubMed Commons below Epilepsia, 47: 2115-2124.
17. Shackleton DP, Kasteleijn-Nolst Trenité DG, de Craen AJ, Vandenbroucke JP, Westendorp RG (2003) Living with epilepsy: long-term prognosis and psychosocial outcomes. See comment in PubMed Commons below Neurology, 61: 64-70.
18. Stavem K, Guldvog B (2005) Long-term survival after epilepsy surgery compared with matched epilepsy controls and the general population. See comment in PubMed Commons below Epilepsy Res., 63: 67-75.
19. Taylor J, Baker GA (2010) newly diagnosed epilepsy: cognitive outcome at 5 years. See comment in PubMed Commons below Epilepsy Behav, 18: 397-403.
20. Trinka E, Bauer G, Oberaigner W, Ndayisaba JP, Seppi K, et al. (2013) Cause-specific mortality among patients with epilepsy: results from a 30-year cohort study. See comment in PubMed Commons below Epilepsia, 54: 495-501.
21. Helmstaedter C, Aldenkamp AP, Baker GA, Mazarati A, Ryvlin P, et al. (2014) Disentangling the relationship between epilepsy and its behavioral comorbidities - the need for prospective studies in new-onset epilepsies. Epilepsy & behavior: E&B, 31: 43-47.
22. Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, et al. (2010) Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. See comment in PubMed Commons below Epilepsia, 51: 676-685.

23. Shneker BF, Fountain NB (2003) Epilepsy. See comment in PubMed Commons below Dis Mon, 49: 426-478.
24. Bien CG (2013) Value of autoantibodies for prediction of treatment response in patients with autoimmune epilepsy: review of the literature and suggestions for clinical management. See comment in PubMed Commons below Epilepsia, 54 Suppl 2: 48-55.
25. Chen SJ (2013) Immune-mediated limbic encephalitis-tip of the iceberg in childhood autoimmune epilepsy. See comment in PubMed Commons below Pediatr Neonatol, 54: 217-218.
26. Davis R, Dalmau J (2013) Autoimmunity, seizures, and status epilepticus. See comment in PubMed Commons below Epilepsia, 54 Suppl 6: 46-49.
27. Weber YG, Nies AT, Schwab M, Lerche H (2014) Genetic biomarkers in epilepsy. See comment in PubMed Commons below Neurotherapeutics, 11: 324-333.
28. Pandolfo M (2013) Pediatric epilepsy genetics. See comment in PubMed Commons below Curr Opin Neurol, 26: 137-145.
29. Irani SR, Bien CG, Lang B (2011) autoimmune epilepsies. See comment in PubMed Commons below Curr Opin Neurol, 24: 146-153.
30. Bien CG, Scheffer IE (2011) Autoantibodies and epilepsy. See comment in PubMed Commons below Epilepsia, 52 Suppl 3: 18-22.
31. Craven I, Griffiths PD, Hoggard N (2011) Magnetic resonance imaging of epilepsy at 3 Tesla. See comment in PubMed Commons below Clin Radiol, 66: 278-286.
32. Bronen RA, Fulbright RK, Spencer DD, Spencer SS, Kim JH, et al. (1996) Refractory epilepsy: comparison of MR imaging, CT, and histopathologic findings in 117 patients. See comment in PubMed Commons below Radiology, 201: 97-105.
33. Scott CA, Fish DR, Smith SJ, Free SL, Stevens JM, et al. (1999) Presurgical evaluation of patients with epilepsy and normal MRI: role of scalp video-EEG telemetry. See comment in PubMed Commons below J Neurol Neurosurg Psychiatry, 66: 69-71.
34. Cascino GD (2004) surgical treatment for epilepsy. See comment in PubMed Commons below Epilepsy Res., 60: 179-186.
35. Henry TR, Babb TL, Engel J Jr, Mazziotta JC, Phelps ME, et al. (1994) Hippocampal neuronal loss and regional hypometabolism in temporal lobe epilepsy. See comment in PubMed Commons below Ann Neurol, 36: 925-927.
36. O'Brien TJ, So EL, Mullan BP, Hauser MF, Brinkmann BH, et al. (1998) Subtraction ictal SPECT co-registered to MRI improves clinical usefulness of SPECT in localizing

the surgical seizure focus. See comment in PubMed Commons below Neurology, 50: 445-454.

37. Chassoux F, Rodrigo S, Semah F, Beuvon F, Landre E, et al. (2010) FDG-PET improves surgical outcome in negative MRI Taylor-type focal cortical dysplasias. See comment in PubMed Commons below Neurology, 75: 2168-2175.
38. Chandra PS, Salamon N, Huang J, Wu JY, Koh S, et al. (2006) FDG-PET/MRI coregistration and diffusion-tensor imaging distinguish epileptogenic tubers and cortex in patients with tuberous sclerosis complex: a preliminary report. Epilepsia, 47: 1543-1549.
39. Salamon N, Kung J, Shaw SJ, Koo J, Koh S, et al. (2008) FDG-PET/MRI coregistration improves detection of cortical dysplasia in patients with epilepsy. See comment in PubMed Commons below Neurology, 71: 1594-1601.
40. Rubí S, Setoain X, Donaire A, Bargalló N, Sanmartí F, et al. (2011) Validation of FDG-PET/MRI coregistration in nonlesional refractory childhood epilepsy. See comment in PubMed Commons below Epilepsia, 52: 2216-2224.
41. Stefan H, Rampp S, Knowlton RC (2011) Magnetoencephalography adds to the surgical evaluation process. See comment in PubMed Commons below Epilepsy Behav, 20: 172-177.
42. Glauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Guerreiro C, et al.(2013) Updated ILAE evidence review.