

Seizure

- An occasional excessive and disordered discharge of nerve tissue
- Manifestation of transient hypersynchronous abnormal neuronal behavior

Definition

- Seizure – transient manifestation of abnormal hypersynchronous discharges of cortical neurons
- Epilepsy – disorder characterized by the occurrence of at least 2 unprovoked seizures
- Epileptic syndrome – a disorder consisting of a cluster of signs and symptoms plus its typical EEG
-

Pathophysiology of Epilepsy

- Cellular level
 - Sodium channels
 - Calcium channels
 - Potassium channels
- Synaptic level
 - Glutamate (excitatory)
 - GABA (inhibitory)

Mechanism of Seizure Generation

Possible Causes of Seizures in Young People

- Infant (0-2 years old)
 - Genetic
 - Hypoxia
 - Congenital Anomalies
- Child (2-12 years old)
 - Head trauma
 - Acute Infection
- Adolescent (12-18 years old)
 - Head trauma
 - Drug and alcohol
 - use/withdrawal

Possible causes of seizures in Adults

- Young adults
 - Head trauma
 - Alcoholism
 - Brain tumor

electrical discharge
from a specific or
single focus

Simple Partial Seizures

- With motor symptoms
- Focal motor without march
- Focal motor with march (Jacksonian)
- Versive
- Postural
- Phonatory (vocalization or arrest of speech)

Simple Partial Seizures

- With somatosensory or special sensory symptoms
- Somatosensory
- Visual
- Auditory
- Olfactory
- Gustatory
- Vertiginous

Simple Partial Seizures

- Epigastric sensation
- Pallor
- Sweating
- Flushing
- Piloerection
- Pupillary dilatation
- Apnea
- Arrhythmias/bradyarrhythmia
- Chest pain
- Cyanosis
- Erythema
- Genital sensations/orgasm
- Hyperventilation
- Lacrimation
- Miosis/mydriasis
- Palpitations
- Pilomotor excitation
- Tachycardia
- Urinary urgency/incontinence
- Vomiting

Simple Partial Seizures

- With psychic symptoms
 - Dysphasic
 - Dysmnestic (déjà vu, jamais vu, memory recall, memory gaps/amnesia)
 - Cognitive (dreamy states, distortions of time sense)
 - Affective (fear, anger, sadness, pleasure, sexual emotion, emotional distress)
 - Illusions (macropsia)
 - Structured hallucinations (music, scenes, visual, auditory, olfactory)
 - Other (change in reality, depersonalization, feeling of a presence (“as if someone is nearby”), forced thinking, distortion of body image)
- SIMPLE PARTIAL EPILEPSY

Simple Partial Seizure

Simple Partial Seizure

COMPLEX PARTIAL EPILEPSY

- Appears to be in a dream like state.
- Unaware or unresponsive to questioning
- May perform unusual actions such as picking of clothing's, grimacing, contorting to one side, chewing
- Feel confused for several minutes
- No recollection of the event

COMPLEX PARTIAL SEIZURES

Complex Partial Seizure

PARTIAL EPILEPSY with secondary GENERALIZATION

Partial with secondary generalization

Generalized Seizures

- Begin throughout both hemispheres, more or less simultaneously
 - Do not have localized onset
 - Reflect generalized disturbance of cortical function
- “Generalized Epilepsy”

Generalized Seizures

- Tonic – clonic seizures
- Clonic seizures
- Tonic seizures
- Atonic seizures (astatic)
- Absence seizure
- Myoclonic seizures

Generalized Tonic Clonic Seizures

Absence Seizure

3hz Spike Wave

Absence Seizure

Myoclonic

Criteria for starting antiepileptic drug therapy

- Diagnosis of epilepsy must be firm
- Risk of recurrence of seizures must be sufficient
- Seizures must be sufficiently troublesome
- Types of seizures
- Frequency of seizures
- Severity of seizures
- Timing of seizures
- Precipitation of seizures
- Good compliance must be likely
- Patient has been fully counseled

Selection of An Antiepileptic Drug: Factors to Consider

- Control of Seizures
- Tolerability
- Pharmacokinetic properties
- Patient Characteristics
- Drug interactions
- Cost

The “Older” Anticonvulsants

Why is there a need for “new” anticonvulsants?

- More effective
- Different mechanism of action: more selective
- Better tolerated: less side effect(s)
- Safer
- Better for women: less teratogenicity
- Less interactions with other drugs

Newer antiepileptic drugs

Gabapentin (Neurontin)

- US FDA approval early in 1994
- Molecular structure resembles GABA but it does not bind to the GABA-Receptor
- It increases GABA levels in CNS and reduces glutamate

Gabapentin: Kinetics

- Absorption: 60% of 600 mg*
- Water soluble
- T_{max}: 2 - 4 hrs
- Half life ~ 6 hrs
- Protein binding: 0%
- No hepatic metabolism, pure renal excretion
- No interactions with other drugs

Gabapentin: Current Usage

- It is a very safe and easy to use
- Rapid titration
- Most new prescriptions are for non epileptic conditions - pain, psychiatric illnesses, sleep disorders
- Currently it is almost always used as add-on drug except in certain clinical situations - elderly, porphyria, multidrug allergies

Gabapentin: Side Effects

- Most people tolerate the drug very well, most common side effects are drowsiness and ataxia
- About 20% of patients gain weight
- About 10% of patients become “aggressive” or have behavioral issues
- Rash is almost unheard of

Lamotrigine (Lamictal)

- US FDA approval 1994
- Phenyltriazine derivative
- Inhibits voltage gated Na⁺ channels

Lamotrigine (Lamictal)

- Half life: 24 hours
- Broad spectrum of activity
- May be used as monotherapy
- Rapidly and completely absorbed
- Protein binding is 55%

Lamotrigine

- Hepatic conjugation and LTG does not change the clearance of other drugs
- Inducers: Carbamazepine, phenobarbital, and phenytoin increase LTG clearance

- Valproic acid **significantly** reduces the LTG clearance

Lamotrigine: Current Usage

- Used as anticonvulsant and in bipolar disorder
- Effective against multiple seizure types, including absence and in Lennox-Gastaut syndrome
- As monotherapy:
 - Very well tolerated
 - Not associated with an increased incidence of teratogenicity

Lamotrigine: Current Usage

- Initial adult dose is 25 to 50 mg/day with gradual titration upwards to 200 mg-600 mg/day
- If the patient is taking valproic acid, initial adult dose is 25 mg QOD with slow titration up to 200 to 300 mg/day

Lamotrigine: Toxicity

- Diplopia, dizziness (common)
- Less sedating than many AEDs and is not associated with weight gain or cognitive dysfunction
- Organ toxicity is very rare
- Incidence of rash is elevated if patient is given high initial doses/rapid titration; with slow titration, the rash rate is lower than either phenytoin or carbamazepine

Lamotrigine discontinuation over one year

Topiramate (Topamax)

- Fructopyranose sulfamate derivative
- Inhibits voltage gated Na^+ channels, enhances GABA activity, and blocks AMPA receptor at higher levels

Topiramate: Kinetics

- Well absorbed
- T_{max} : 1-4 hrs
- Not significantly metabolized, excreted unchanged in urine in monotherapy
- Half life ~20 hrs
- Protein binding ~15%

Topiramate (Topamax)

- Broad spectrum anticonvulsant effective in:
 - Partial/focal epilepsy
 - Generalized epilepsy including myoclonic seizures
 - Lennox-Gastaut syndrome

Topiramate: Drug Interactions

- TPM has no significant effect on CBZ or VPA blood levels
- TPM decreases PHT clearance by $\leq 20\%$ in some patients
- TPM decreases ethinyl estradiol level (BCP) 33%
- PHT, CBZ, PB decrease TPM level up to 50%
- VPA has no significant effect on TPM level

Topiramate: Side Effects

- Dizziness, ataxia, somnolence, and fatigue are the most common AEs
- Weight loss in 25%
- Paresthesias in 10%
- Nephrolithiasis in 1.5%
- Metabolic acidosis
- Cognitive symptoms, which may develop insidiously, seen in 10 to 30%, less likely with slow titration

Topiramate: Current Usage

- In addition to epilepsy, used for migraine prophylaxis and weight loss
- Under evaluation for psychiatric conditions, pain, and neuroprotection
- Used as monotherapy and add-on for multiple seizure types

Topiramate discontinuation over one year

Levetiracetam (Keppra)

- Related to piracetam (used in Europe)
- The mechanism(s) of action largely unknown
- In animals: prevents kindling
- Inactive in maximal electroshock and pentylenetetrazol seizure models in mice and rats
- Inactive in convulsions induced by GABAergic chemoconvulsants in mice

Levetiracetam (Keppra)

- US FDA approval 2000
- It is approved for add-on treatment of:
 - Partial seizures
- It does appear to have a broad spectrum of activity against multiple seizure types including myoclonic seizures and generalized epilepsies
- Successfully used as monotherapy
- May be rapidly titrated and clinical onset of action is very rapid

Levetiracetam: Kinetics

- Rapid and complete absorption
- Low protein binding
- Clearance is renal not hepatic
- Half life is approximately 8 hour
- No drug interactions

Levetiracetam

(Pooled data from 3 efficacy studies, n=904)

Levetiracetam: Toxicity

- Most common side effects are fatigue, drowsiness, ataxia
- Weight neutral
- No rash
- No organ toxicity
- About 15% of patients have behavioral changes:
 - Elderly
 - Mentally retarded

Levetiracetam: Most common side effects

Levetiracetam: Reason for discontinuation

15% of patients taking levetiracetam

11% of patients taking Placebo

Oxcarbazepine: Metabolism

Oxcarbazepine (Trileptal)

- Plasma half-life of MHD 9.3 ± 1.8 hours
- Anticonvulsant activity similar to CBZ
- Approved for monotherapy
- Some patients who “fail” CBZ may do well on OxCBZ
- 30% of patients with CBZ rash will have rash with OxCBZ

Oxcarbazepine: Kinetics

- Complete absorption
- Protein binding 40% (CBZ = 70%)
- Hepatic glucuronidation, not oxidation
- No active epoxide
- No auto-induction
- Fewer drug interactions than CBZ
- Induce CYP 3A4:

– Other drugs metabolized by CYP3A4 (eg BCPs) may have lower blood levels

Oxcarbazepine: Mechanisms of action

- Probably similar to carbamazepine
- Block voltage-sensitive Na⁺ channels
- Modulation of voltage-activated Ca⁺⁺ currents
- No significant interactions with brain neurotransmitters or modulation of receptor sites
- Increases K⁺ conductance

Oxcarbazepine: Side Effects

• Dizziness and diplopia are fairly common especially if an individual dose is large and taken on an empty stomach

• Slow titration reduces side effects

• Hyponatremia less common than with CBZ but may occur, especially in the elderly

General Guidelines in AED Management

- Start with single (preferably old) drug appropriate for seizure types and patient; give QD or BID if possible
- Educate the patient about the drug, its side effects and interactions, and that it helps to control but not “cure” seizures
- Start slow and low: Begin with low dose and slowly increase

Blood Levels in AED Management

- “Therapeutic level” is a misnomer!
- A “good” level is one in which the patient has no seizures and no side effects
- The quoted ranges for PB (20-40 mcg/ml), phenytoin (10-20 mcg/ml), carbamazepine (6-12 mcg/ml), and valproic acid (50-100 mcg/ml) are rough guides at best

When to Get AED Levels?

- After initiation of treatment
- After dose changes (up or down) of phenytoin
- When there are questions of compliance, toxicity, or drug interactions
- When there are breakthrough seizures
- Routine every 6 - 24 months
- I do it when filling out driver’s forms for BMV

Do we have the ideal anticonvulsant?

- Do we have effective AEDs?
- Do we have more selective AEDs?
- Do we have non teratogenic AED?

- Do we have AEDs that do not interact with other medications?
- What next???

-

Conclusion

- New AEDs may represent advances over the old in terms of pharmacokinetics, side effects
- Efficacy differences have not been established
- Each new AED will be the “magic bullet” for some patients

Report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society

Background and Justification

- Age-adjusted epilepsy prevalence of 6.8/1,000 population
- Cumulative incidence through age 74 was 3.1%

In the last 10 years, the following drugs were approved by the US FDA

- Felbamate
- Gabapentin
- Lamotrigine
- Topiramate
- Tiagabine
- Oxcarbazepine
- Levetiracetam
- Zonisamide

Prior to 1990s, six major AEDs were available for the treatment of epilepsy

- Carbamazepine
- Phenobarbital
- Phenytoin
- Primidone
- Valproic acid
- Ethosuximide

•The older drugs, while effective in patients with newly-diagnosed epilepsy share some characteristics:

–Phenytoin, carbamazepine, phenobarbital, and primidone are hepatic enzyme inducers

Advantages of older AEDs

- Broad familiarity
- Lower cost
- Known efficacy
- Wide availability
- Long term experience

The Analytical Process

- Literature search (MEDLINE, CURRENT CONCEPTS) for relevant articles published between Jan '87 – Sept 2001
- Manual search by panel members covering Sept 2001 – May 2002
- A manual search for Class I articles are updated to include those published through March 2003
- Cochrane library search for randomized controlled trials in epilepsy in Sept 2002

Criteria for Selection of Articles

- Relevance to the clinical questions of efficacy, safety, tolerability or mode of use
- Human subjects only
- Type of studies: randomized controlled trials, cohort, case control, observational or case series
- All languages for randomized controlled trials not available in English
- Relevant to patients with newly-diagnosed epilepsy

Exclusion Criteria

- Articles classified as reviews, meta-analyses and articles related to non-epilepsy uses of AEDs unless adverse reactions are disclosed based on AED mechanism of action

- Total # of articles – 1464
 - Gabapentin – 240
 - Lamotrigine – 433
 - Topiradeate – 244
 - Tiogabine – 177
 - Zonisamide – 146

- Question 1

–How does the efficacy and tolerability of the new AEDs compare with that of older AEDs in patients with newly diagnosed epilepsy?

Summary of Findings

- Efficacy in newly diagnosed patients

–GBP is effective in the treatment of newly diagnosed patient epilepsy

—LTG, TPM, & OXC are effective in mixed population of newly diagnosed and generalized tonic-clonic seizures

—At present there is insufficient evidence to determine effectiveness in newly diagnosed patients for TGB, ZNS, & LEV

Recommendation

- Newly diagnosed epileptic patients maybe initiated in standard AEDs (CBZ, PHY; VPA, PB) or new AEDs (LTG, GBP, OXC, TPM)
- Choice of AED will depend on individual patient characteristics (Level A)

CONCLUSION

•All of the drugs have proved efficacies as add-on therapy in patient with refractory partial epilepsy.

Partial Seizure in Adults

- GBP (600-1800mg/day);
- LTG (300-500mg/day);
- LEV (1000-3000mg/day);
- OXC (600-2400mg/day);
- TGB (16-50mg/day);
- TPM (300-1000mg/day)
- are effective in reducing frequency as adjunctive therapy in refractory partial seizures.

- GBP, LTG, TGB, TPM, OXC AND ZON are more effective at higher doses
- and ZON (100-400mg/day)
- LEV evidence for a dose response is less clear but more patient responded at 3000mg/day
- Side effects and drop-outs increase in a dose dependent manner for all drugs
- Slower titration reduces side effects for GBP and TPM

Recommendation

•It is appropriate to use GBP, LTG, TGB, TPM, OXC, ZON, LEV as add-on therapy in patients with refractory epilepsy

Summary of Evidence

(Monotherapy for refractory partial epilepsy)

- LTG 500mg/day is superior to 100mg/day of VPA (acting as pseudoplacebo)**
- OXC 2400mg/day is superior to 300mg/day**
- TPM 1000mg/day is superior to 100mg/day**

- There is insufficient evidence at present to determine the efficacy of LEV, TGB or ZON

- In one trial, GBP 1200mg and 2400mg were not more effective than a pseudoplacebo dose of 600mg in this population

Recommendation

- OXC and TPM can be used as monotherapy in patients with refractory partial epilepsy

- LTG can be used (Level B downgraded due to drop-outs)

- There is insufficient evidence to recommend use of GBP, LEV, TGB or ZON in monotherapy of refractory partial epilepsy (Level U)

IDIOPATHIC EPILEPSY IN ADULTS

What is the evidence that the new AEDs are effective for the seizures seen in patients at the refractory idiopathic generalized epilepsy?

CONCLUSION

- Trials for refractory generalized epilepsy has been criticized due to the fact that not all patients were required to have an EEG demonstrating a generalized pattern.

SUMMARY OF EVIDENCE

(Refractory primary generalized epilepsy)

- TPM 6mg/kg/day is effective for the treatment of refractory generalized tonic clonic convulsions +/- other seizure types

- GBP 1200mg is not effective in refractory GTCS in patients with primary or secondary generalized epilepsy

RECOMMENDATIONS

- TPM may be used in the treatment of refractory GTCS in children and adults (Level A)

- There is insufficient evidence to recommend GBP, LTG, OXC, TGB, LEV or ZON for the treatment of refractory generalized tonic-clonic seizures in adults and children (Level U)

What is The Evidence That The New AEDs are effective as monotherapy in children with refractory partial seizures?

*no monotherapy trials have been performed in this population

CONCLUSION

- An NIH consensus conference... partial seizures in children are similar in pathophysiology to those in adults.

- An AED with demonstrable efficacy in adults will demonstrate the same efficacy or adjunctive therapy in children >2 years of age.

Summary of Evidence

- GBP; LTG; TPM; OXC are effective in reducing seizure frequency as adjunctive therapy in children with refractory partial seizures

What is the Evidence that the new AEDs are effective in children and/or adults with Lennox-Gestaut Syndrome?

CONCLUSION

- Patients with Lennox-Gestaut syndrome are difficult to treat and are most susceptible to exacerbation by AEDs.

- TPM and LTG appear to be effective in this population and should be considered for use.

SUMMARY OF EVIDENCE

- LTG at doses adjusted for weight and VPA use reduces seizure associated with Lennox-Gestaut syndrome.

- TPM 6mg/kg/day is effective in reducing drop attacks (tonic-clonic seizures) in patients with Lennox-Gestaut syndrome.

- To date, there is no Class I or II evidence that GBP, TGB, OXC, LEV or ZON are effective.

- In case reports, LTG and GBP worsened myoclonic seizures in some patients.

What Is the Risk of Teratogenicity with new AEDs compared to the old AEDs?

- Category D - drugs (AEDs) with known teratogenicity in both animal and human pregnancies

e.g. Phenytoin, Carbamazepine, Valproic Acid

- Category C – drugs (AEDs) with demonstrable teratogenicity in animals but not in humans

e.g. newer AEDs