Anticonvulsant Therapy

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Outline

- Introduction
- Why do we treat seizures
- How do we select anticonvulsant medications
- Adverse Effects
- Drug Interactions
- Anticonvulsants and Pregnancy
Epidemiology of Epilepsy

- 1-2% of Canadians
  - 40,000 people in BC

- Cerebral Palsy – 20%
- Autism – 20-30%
- Developmental Delay - >20%

- 3rd most common neurologic disorder
  - After Stroke and Alzheimer’s
Seizure Manifestations
Seizure Classification

Partial (seizure activity originates in one part of the brain)
- Simple
- Complex

Generalised (seizure activity involved entire brain)
- Absence
- Myoclonic
- Tonic clonic
- Tonic
- Atonic
Seizure Occurrence

- Up to 10% of the population will experience a single seizure during their lifetime
  - majority due to an acute reversible cause: fever, metabolic changes, drug intoxication/withdrawal.

- Since seizures don’t recur in these patients after the provoking factor has been corrected, they don’t have a diagnosis of epilepsy.

- A **diagnosis of epilepsy** is made after a patient has had 2 or more **unprovoked** seizures.
What was the cause of the seizure?

- Epileptic seizures are symptoms due to a variety of causes.

- Determining the underlying cause has implications for both treatment and prognosis.
Causes epileptic seizures

**Idiopathic (Genetic) - 50% of cases**
- Childhood and Juvenile absence epilepsy
- Benign rolandic epilepsy of childhood
- Juvenile myoclonic epilepsy (JME)

**Symptomatic - 50% of cases**
- Malformations of brain developmental
- Tuberous Sclerosis
- Brain Infection
- Stroke
- Traumatic brain injury
- Tumor
Clinical Factors Associated With Genetic Versus Symptomatic Epilepsy

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<th>Idiopathic Epilepsy</th>
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<td>(e.g. head trauma, meningitis)</td>
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<td>• Characteristic EEG abnormalities</td>
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Why Do We Treat Seizures?

- Prevent Falls & Injuries
- Employment & Education
- Psychosocial well-being
  - Anxiety
  - Embarrassment
  - Loss of self-control
  - Driving
  - Life-style restriction
Medications

- Very Old
  - Bromides (1861)

- Old
  - Phenobarbital (1912)
  - Phenytoin (Dilantin\textsuperscript{R})(1936)
  - Diazepam (Valium\textsuperscript{R})(1960’s)
  - Carbamazepine (Tegretol\textsuperscript{R}) (1974)
  - Valproic Acid (Depakote\textsuperscript{R}) (1978)

- New
  - Clobazam (Frisium\textsuperscript{R})
  - Lamotrigine (Lamictal\textsuperscript{R})
  - Topiramate (Topamax\textsuperscript{R})
  - Viganabrin (Sabril\textsuperscript{R})

- Even Newer
  - Levetiracetam (Keppra\textsuperscript{R})
  - Oxcarbazepine (Trileptal\textsuperscript{R})

- The Newest
  - Lacosamide (Vimpat\textsuperscript{R})
  - Rufinamide (Banzel\textsuperscript{R})
  - Ezogabine (Potiga\textsuperscript{R})
    - (Retigabine in Europe)
When do you consider starting treatment?

- After first unprovoked seizure 50% of patients will have a 2\textsuperscript{nd} seizure. This needs to be balanced against the potential side-effects and cost of medication.

- In general treatment is started after the 2\textsuperscript{nd} seizure.
How effective are medications?

- 70% of patients will respond
  - (1\textsuperscript{st} or 2\textsuperscript{nd} drug)

- If 2 appropriate drugs fail
  - 3\textsuperscript{rd} drug: approximate 5% success rate

- If 3\textsuperscript{rd} drug fails: “refractory epilepsy”
  - Other treatments
    - Ketogenic diet
    - Epilepsy Surgery
Goals of Treatment

- Complete Suppression of Seizures
  - with NO side-effects

- Maintain/Restore patients lifestyle
Case #1

- Mark is a 7-year-old boy seen in the neurology clinic accompanied by his mom. Teachers have noticed “staring spells” at school.
Principles of AED therapy

1. Select most appropriate drug
   • Seizure type
   • Epilepsy Syndrome
   • Individual patient factors
     □ adverse effect, cost, patient-lifestyle
     □ dosing schedule
     □ Co-morbidities
Principles of AED therapy

2. Optimize Dosage
   - start low dose, titrate up to maximum dose
   - Minimize initiation related side-effects
   - End Point:
     - seizures controlled or side-effects occur
Principles of AED therapy

- Drug level monitoring
  - Target blood drug level
    - Helpful in guiding dose adjustments
  - Treat the INDIVIDUAL
    - NOT the therapeutic range
Adverse Effects
Adverse Effects

- Initiation & Dose related adverse effects
- Idiosyncratic “allergic” reactions
Case #1 continued

- Mark’s mom calls your office 2 weeks later. Patient has been increasing the medication every 5 days but noticing that she is more “sleepy” during the day.
Adverse Effects

- Initiation & Dose related adverse effects
  - Important to recognize
  - Seldom are serious – reversible
    - Decreasing medication
    - Discontinuing medication
Valproic Acid (Depakote®)

**Advantages**
- Well tolerated
- Broad spectrum
- No effect on BCP

**Disadvantages**
- Weight gain
- Tremor
- Hair thinning
- Platelet dysfunction
- Drug interactions
- “allergic” reactions
- Avoid in Pregnancy
Case # 2

- Sarah 14 year old girl. She has experience 2 brief generalized tonic-clonic seizures.

- Decision is made start anticonvulsant medication.

- She is started on lamotrigine (Lamictal®)
Lamotrigine (Lamictal\textsuperscript{R})

- **Advantages**
  - Effective
  - Well-tolerated
  - Twice daily

- **Disadvantages**
  - Allergic Rash
  - Titrate Slowly
Case #2 continued

- Sarah returns to your office 3 weeks later.
- She has developed a rash and fever.
Idiosyncratic “allergic” reactions

- Unpredictable
- NOT dose-dependent
- Usually occur early in the course of treatment
- Range: Mild-> severe
- Rare: 1 in 20,000 – 50,000
Idiosyncratic “allergic” reactions

- **Skin Rash**
  - Usually within 4 – 6 weeks
  - Titrate dose up slowly
  - Mild - Severe
    - Reversible if discontinued early!!

- AED: lamotrigine 1:1000-2000

- Others: phenytoin, carbamazepine, phenobarbital
Idiosyncratic “allergic” reactions

- Liver
  - Usually occurs early in treatment
  - Can be reversible if medication is stopped early

- Blood
  - Symptoms:
    - Bleeding, bruising, persistent infections
Carbamazepine (Tegretol™)

- **Advantages**
  - Effective
  - Well tolerated

- **Disadvantages**
  - Dizziness/unsteady
  - "allergic" reaction
  - Drug Interactions
  - May exacerbate seizures
    - Myoclonic, absence
Carbamazepine

- Rare serious & potentially fatal skin reactions:
  - 1 to 6 per 10,000 patient

- Asian Ancestry: risk 10 times higher
Carbamazepine

- Genetic Marker
  - Inherited variant of a gene (HLA-B 1502 allele), an immune system gene
  - Patients with this variant are at a higher risk
  - It is possible to screen: blood test

- Asian Ancestry: prevalence of this allele
  - High Risk: (10-15%)
    - China (Han Chinese), Thailand, Malaysia, Indonesia, Philippines, Taiwan
  - Moderate Risk: (5-10%)
    - South Asia
  - Low Risk: (<1%)
    - Japanese or Korean
Carbamazepine

- Note:
  - If already on carbamazepine for months
    - Unlikely to experience serious reaction
  - Patients with positive results may not get this reaction
  - Serious skin reactions can still occur in patients who test negative
  - Regardless of ethnicity
    - Monitor for signs and symptoms
Review of Drugs
Phenytoin (Dilantin®)

- Advantages
  - Effective
  - Broad spectrum
  - Chew tabs, capsules
  - Intravenous
  - Inexpensive
  - Once daily

- Disadvantages
  - Therapeutic levels
  - Drug interactions
  - “Allergic” reactions
Topiramate (Topamax<sup>R</sup>)

- **Advantages**
  - Effective
  - “off label”
    - Migraine
  - No “allergic” reactions
  - Twice daily

- **Disadvantages**
  - Cognitive effects
  - Kidney Stones
  - Weight Loss
Levetiracetam (Keppra\textsuperscript{R})

- **Advantages**
  - Effective
  - No drug interactions
    - Including OCP
  - Well tolerated
    - No “allergic” reactions
  - Can titrate fast

- **Disadvantages**
  - Mild fatigue
  - Psychosis (0.6%)
  - Cost
Clobazam (Frisium\textsuperscript{R})

- Advantages
  - Effective
  - Well tolerated
  - Once or twice daily

- Disadvantages
  - Drowsiness
  - Unsteadiness
  - Rare
    - Behavior changes
Lacosamide (Vimpat\textsuperscript{R})

- **Advantages**
  - Effective for focal seizures
  - Well tolerated

- **Disadvantages**
  - Drowsiness
  - Headache
  - Unsteadiness
  - Rare
    - Heart arrhythmia
    - Rash
    - Suicidal behavior
Rufinamide (Banzel®)

**Advantages**
- Effective in Lennox-Gastaut Syndrome
- Well tolerated

**Disadvantages**
- Drowsiness
- Headache
- Unsteadiness
- Loss of appetite
- Rare
  - Heart arrhythmia
  - Rash
  - Suicidal behavior
Ezogabine (Potiga\textsuperscript{R})

- **Advantages**
  - Effective for focal seizures
  - Well tolerated

- **Disadvantages**
  - Three times daily dosing
  - Drowsiness
  - Dizziness
  - Urinary Retention
  - Rare
    - Bluish Pigmentation
      - Skin
      - Sclera
      - Retina
Drug Interactions
Why do drug interactions occur?

- Increase breakdown of other drugs
- Decrease breakdown of other drugs
Drug Interactions: Birth Control Pill

- Reduce Effectiveness
  - Carbamazepine
  - Oxcarbazepine
  - Phenobarbital
  - Phenytoin
  - Topiramate

- Lamotrigine

- No Effect
  - Clobazam
  - Clonazepam
  - Ethosuximide
  - Gabapentin
  - Levetiracetam
  - Valproic Acid
Stopping AED Therapy

- Need to continue AED therapy should be re-evaluated after 2 years seizures free.

- Factors favoring low risk recurrence
  - Minimum 2 years seizure free
  - Normal EEG
  - Normal Neurological Examination
  - Ease of controlling seizures

- Slow withdrawal of medications:
  - over 2-3 months
Anticonvulsant Medication and Pregnancy
Anticonvulsants and Pregnancy

- > 90% of women with epilepsy will have a healthy baby

- Slightly higher risk for congenital malformations
  - General population: 2-3%
  - Untreated epilepsy: 2-5%
  - All anticonvulsant drugs: 4-7%
Anticonvulsants and Pregnancy

- Planned Pregnancy
  - Talk to doctor

- Ideally one drug at lowest possible dose
  - Monotherapy: 4.5% vs polytherapy 7%

- Folic Acid
  - 0.4mg/day all women of child bearing age
  - Higher dose (4-5mg/day): women with epilepsy of child bearing age
Conclusion

- Epilepsy is common
- We treat seizures to prevent injury and maintain active lifestyle
- We select anticonvulsant medications
  - Seizure types, drug profile, individual factors
- Adverse Effects
- Drug Interactions
- Anticonvulsants and Pregnancy