Pharmacology 101: Anti-Epileptic Drugs

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Objectives

• Receive Practical Advice Regarding Prescription Medications

• Understand the Absorption, Distribution, Metabolism and Excretion of Drugs

• Understand Mechanisms AED Interactions and Adverse Reactions

• Gain better understanding of how to avoid interactions and adverse reactions and how to discuss pharmacology of AEDs with healthcare providers
Practical Advice

• Follow through with monitoring blood levels when appropriate (*ADME*)

• Weekly pill boxes may reduce medication administration errors

• Know what tablets can be crushed or split (*absorption*)

• Pay attention to recommended storage conditions AND DO not pre-fill any liquid medications into smaller containers, vials or syringes unless stability information is available from a physician, pharmacist, or manufacturer (*stability*)

• If the medication is in an amber colored bottle or is contained in a foil wrapper, there is a reason (*stability*)

• The taste of medications can often be masked
Practical Advice

• Using syringe adapters on bottles may decrease the risk of contamination

• Watch carb content when on ketogenic diet (good time to switch from liquids to tablets or capsules)

• Have an emergency seizure treatment protocol that includes what drugs to avoid signed by the neurologist

• Discuss creating a “sick protocol” with the neurologist

• Rectal acetaminophen suppositories are great for fever when patients have GI illness

• Strive to be open minded to returning to drug that previously didn’t give the anticipated response, as long as it is not contraindicated
Seizure Activity: A Delicate Balance

Excitation (lots of firing)
Na+ and Ca++ inside cell

GLUTAMATE RELEASE

Inhibition (balancing the firing)
Cl− inside cell; K+ outside cell

GABA RELEASE
Stomach to Brain – Pharmacokinetics and Pharmacodynamics of Anti-epileptic drugs (AEDs)

Pharmacokinetics = What body does to drug

Pharmacodynamics = What drug does to body
Pharmacokinetics of AEDs

- Absorption
- Distribution
- Metabolism
- Elimination
Useful Terms

- \( \text{Tmax} \): time to maximum drug concentration
- \( \text{Cmax} \): maximum drug concentration
- \( \text{AUC} \): amount of drug under the time/concentration curve
- \( \text{Half life (t} \frac{1}{2}) \): Time it takes for \( \frac{1}{2} \) of drug to be eliminated from body
- \text{Steady state}: Absorption = Elimination
Clinical Pearl:
How long does drug stay in system?

• Common question – how long will it take for the drug to get out of his system?

• It typically takes about 5 half lives to clear a drug from the body after discontinuation of the drug

• “Steady state” pharmacokinetics occur in the same amount of time

Example:
Phenobarbital $t_{\frac{1}{2}} = 2 - 7$ DAYS

Lamotrigine $t_{\frac{1}{2}} = 13.5$ HOURS
Pharmacokinetics

Day 1

Peak: Side Effects

Day 2

Zone of Seizure Control

Trough: Seizures

Clinical Pearl: What if she throws up?

First step: Look at emesis

Think about: Liquid versus tablet or capsule, outside coating, how often drug is taken
Bioequivalence of Drugs: FDA Accepted Parameters

• Single dose of reference drug and test drug given to healthy adults in a crossover design. Bioequivalence accepted when the 90% confidence interval of the ratios
  – AUC
  – $C_{\text{max}}$
  – $T_{\text{max}}$

• The bioequivalence interval falls between 0.8 and 1.25 (log-transformed data)
Testing for Bioequivalence

Test product low nonequivalent

Test product high nonequivalent

Test product bioequivalent
Bioequivalence: Generic/Generic

Brand Product

Generic #1

Generic #2
Generic AEDs

• Speak to the pharmacist about the importance of using the same generic manufacturer for each refill

Drug Stability

• Stability tests are conducted during drug development based on various conditions. It is important to follow manufacturers' recommendation on storage conditions and expiration.
Mechanisms of Drug Interactions

- Absorption Inhibition
- Metabolic Enzyme Inhibition
- Metabolic Enzyme Induction
- Additive Pharmacodynamic Effects
- Antagonistic Pharmacodynamic Effects
Absorption Inhibition

- Binding to cations such as aluminum, magnesium, iron, calcium (multi-vitamins, supplements)

- pH dependent absorption – pH in stomach changed by drug or food (dairy, acidic fruits or vegetables)

- Full or empty stomach?
Pharmacogenomics

• Genetic variability (also known as polymorphism) influences metabolism

• POLG DNA testing prior to use of valproic acid

• 1/5 people of Asian decent are poor metabolizers of drugs dependent on CYP2C19 enzyme for metabolism (phenytoin, phenobarbital)

• The future of pharmacotherapy…..
Enzyme Inhibition

- Resource to check for drug interactions
  
  www.drugs.com/drug_interactions.html

- Use with caution and consult prescriber or pharmacist
Enzyme Induction

• Enzyme inducers increase the activity of certain metabolizing enzymes, thereby decrease effect of drugs dependent on these enzymes for metabolism
  – Carbamazepine, phenytoin, primidone (Mysoline), phenobarbital
Pharmacodynamic Interactions

• Antagonistic Interactions (increases risk of seizures)
  – Giving drugs that can decrease seizure threshold to person with epilepsy
    • Propofol (anesthetic)
    • Certain high dose antibiotics
    • Aminophylline (bronchodilator)
    • Cyclosporin
    • Oral contraceptives
    • Stimulants
    • Anti-psychotics
Pharmacodynamic Synergy

- Polytherapy required for Dravet Syndrome

- Classic synergistic drug cocktail for Dravet Syndrome: stiripentol, clobazam, valproic acid

- All medication changes (including OTC or herbal therapy) should be under the supervision of the treating neurologist

- Consideration of continued need of AED should be made as new drugs are added
Food and Herbs that Alter Drug Metabolism

- St John’s Wort
- Milk Thistle
- Garlic
- Ginseng
- Licorice
- Grapefruit
Herbal Pharmacodynamic Interactions

- Herbs that can decrease seizure threshold
  - Gingko biloba
  - Star fruit
  - Star nise
  - Sage
  - Ephedra
  - Eucalyptus
  - Pennyroyal
  - Shankhappusphi
Conclusion

• Understanding fundamental pharmacology may help facilitate discussion with healthcare providers and make informed decisions

• Herbs are not necessarily benign and may interact with AEDs – any use of herbal therapy should be discussed with neurologist before use
Questions?