Introduction to Pharmacology: Pearls and Tidbits for the Dravet Community

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Objectives

• Understand basic principles of pharmacokinetics and pharmacodynamics

• Discuss Bioequivalence of Generic Drugs

• Understand Mechanisms of AED Interactions and Adverse Reactions

• Discuss foods and supplements that may interact with AEDs and / or cause a pharmacodynamic interaction
Pharmacokinetics / Pharmacodynamics
Pharmacokinetic Terminology

- $C_{\text{max}}$: Maximum plasma concentration
- $T_{\text{max}}$: Time to reach maximum plasma concentration
- $C_{\text{min}}$: Minimum plasma concentration
- AUC: Area Under the Curve
- Absorption Phase
- Elimination Phase ($T_{1/2}$)

Graph showing the relationship between plasma concentration and time.
Pharmacokinetics

Steady State Pharmacokinetics

- Repeated fixed dosing at intervals equal to half-life
- Equivalent dosage curve (continuous iv infusion)
- Steady-state concentrations attained after three to five half-lives
How long does drug stay in system?

- It typically takes 3 - 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 when the drug is continuously administered

Example:

- Phenobarbital $t_{1/2} = 2 – 7$ DAYS
- Valproic Acid = 4-16 hours
- Depakote ER = 18 hours
What if she throws up?
Bioequivalence of Drugs: FDA Accepted Parameters

• Single dose of reference drug and test drug given to healthy adults in a crossover design. Bioequivalence accepted if the ratio of the mean of Tmax, Cmax and AUC is within 80% - 125%, with 90% assurance.
Generic Drug Approval Process - FDA
Testing for Bioequivalence

Test product low nonequivalent

Test product high nonequivalent

Test product bioequivalent
Bioequivalence: Generic/Generic

Brand Product

Generic #1

Generic #2
Drug Interactions Mechanisms

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

• 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?
Enzyme Inhibition

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

- Use with caution and consult prescriber or pharmacist

Example: stiripentol / clobazam interaction (synergistic)
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
  – 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

• Multiple drugs for Dravet Syndrome – Should I take off all drugs and start all over?
• Make all changes under supervision and agreement of neurologist
• Consideration of continued need of AED should be made as new drugs are added
Clinical Pearl: Practical Tips

- Weekly pill box
- Know what can be crushed or broken
- Disguise taste when possible
- Watch carb content when on keto diet (good time to switch from liquids)
- Follow through with monitoring blood levels when appropriate
- Have a sick plan
Food and Supplements that Alter Drug Metabolism

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

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

- Understanding pharmacology concepts 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.

- Patients with Dravet syndrome most often require multiple drugs to get adequate seizure control, and utility of drug may need revisiting before new drug is added.