Pharmacology and pharmacokinetics in epilepsy care

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Financial disclosure

None

Learning objectives

1. Discuss the classification of antiepileptic drugs (AEDs)
2. Discuss and compare the mechanisms of action and adverse reactions of the antiepileptic drugs
3. Review pharmacokinetics of AEDs and understand the detailed mechanism of how the serum concentration of AEDs can be altered by changes in drug formulations and concomitant medications
4. Compare two rescue benzodiazepine agents for prolonged seizures
5. Understand the use of herbal products in the United States
6. Analyze the mechanism of drug-herb interactions among epilepsy patients
7. Discuss cannabis use for epilepsy treatment

Outline

1. Overview of antiepileptic drugs (AEDs)
2. Classification of AEDs
3. Pharmacokinetics – ADME of AEDs
4. Topic discussion
   - Midazolam intranasal administration
   - Herbal medication and epilepsy
     - Drug-herb interactions
     - Hemp oil use for epilepsy

Antiepileptic drugs – overview

- More than 20 antiepileptic drugs are available in the United States
- Epilepsy treatment with antiepileptic drugs (AEDs)
  - Antiepileptic drugs
    - First treatment approach before nonpharmacotherapy (e.g., surgery, diet, VNS, DBS, RNS, etc.)
    - Long-term exposure
  - Dilemma
    - Necessary for adequate seizure control but may be harmful

Antiepileptic drugs – overview

- Epilepsy treatment with AEDs
  - Ultimate treatment goal
    - Seizure free
  - Treatment goal when using AEDs
    - Seizure free <u>with minimal adverse outcomes</u>

Pharmacology of AEDs

- Classification of AEDs
  - Older agents vs. newer agents
  - Indications
    - Generalized seizures vs. focal onset seizures
  - Enzyme-inducing AEDs vs. nonenzyme-inducing AEDs
  - Drug class: channel or receptor functions
    - Na channel blockers
    - Ca channel blockers
    - GABA enhancers
    - K channel agonist
    - AMPA receptor antagonist
    - NMDA receptor antagonist
    - Combinations
    - Others/MOA unknown

Classification of AEDs

Older agents (before 1993)

- Phenobarbital (1912)
- Phenytoin (1938)
- Primidone (1954)
- Ethosuximide (1960)
- Carbamazepine (1974)
- Valproic acid (1978)
- Divalproex Na (1979)

Newer agents (1993 ~)

- Felbamate (1993)
- Gabapentin (1993)
- Lamotrigine (1994)
- Topiramate (1996)
- Tiagabine (1997)
- Levetiracetam (1999)
- Oxcarbazepine (2000)
- Zonisamide (2000)
- Pregabalin (2004)

Classification of AEDs

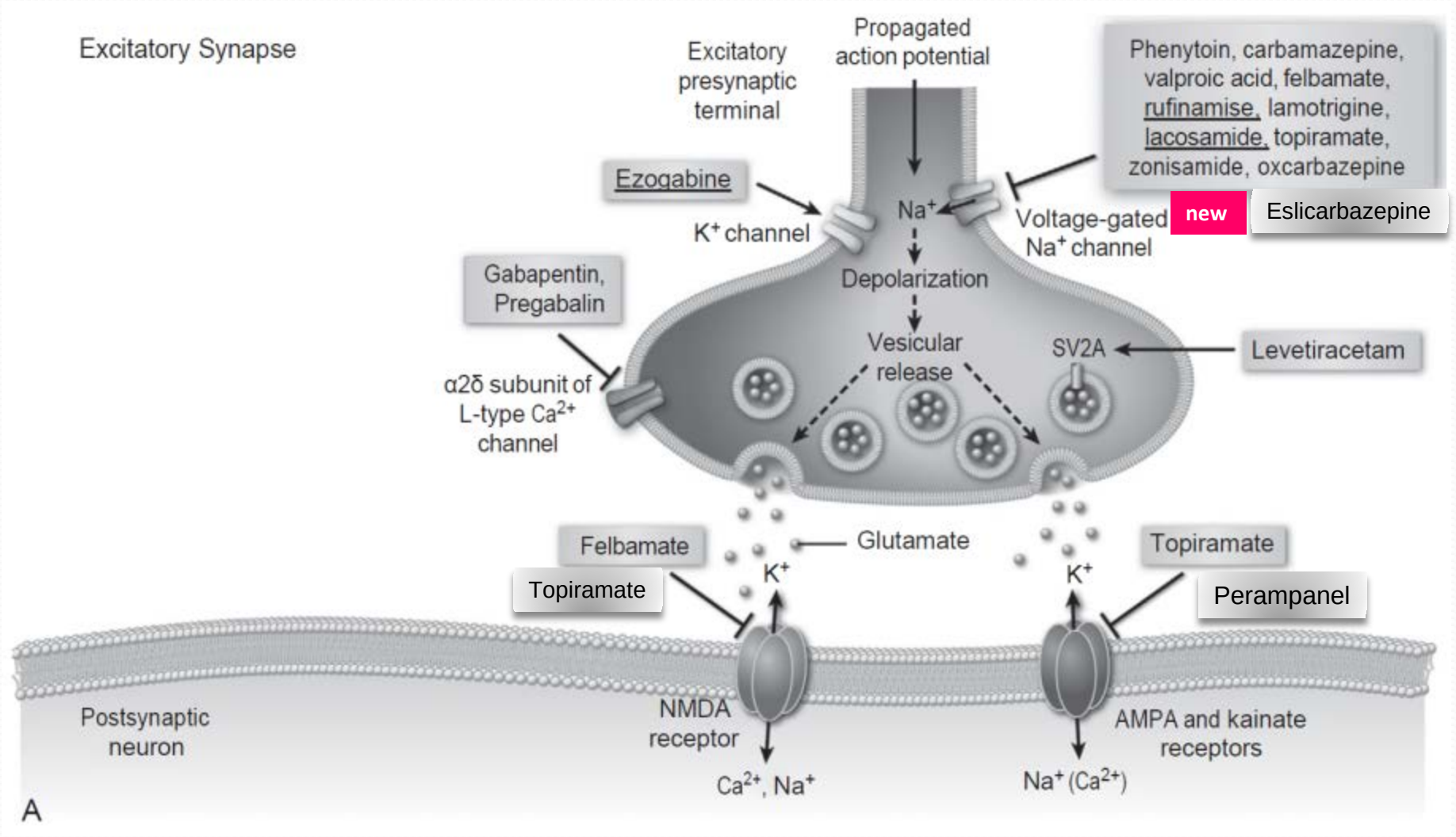
- Very new
  - Lacosamide (2008)
  - Rufinamide (2008)
  - Vigabatrin (2009)
  - Clobazam (2011)
  - Ezogabine (2011)
  - Perampanel (2012)
  - Eslicarbazepine (2013)

Classification of AEDs

- Indications of AEDs
  - Effective for both generalized and focal seizures
    - Lamotrigine, levetiracetam, topiramate, valproic acid
  - Effective only for generalized or focal seizures
    - Ethosuximide (only for absence seizure)
    - Newer/very new AEDs

Antiepileptic drugs – overview

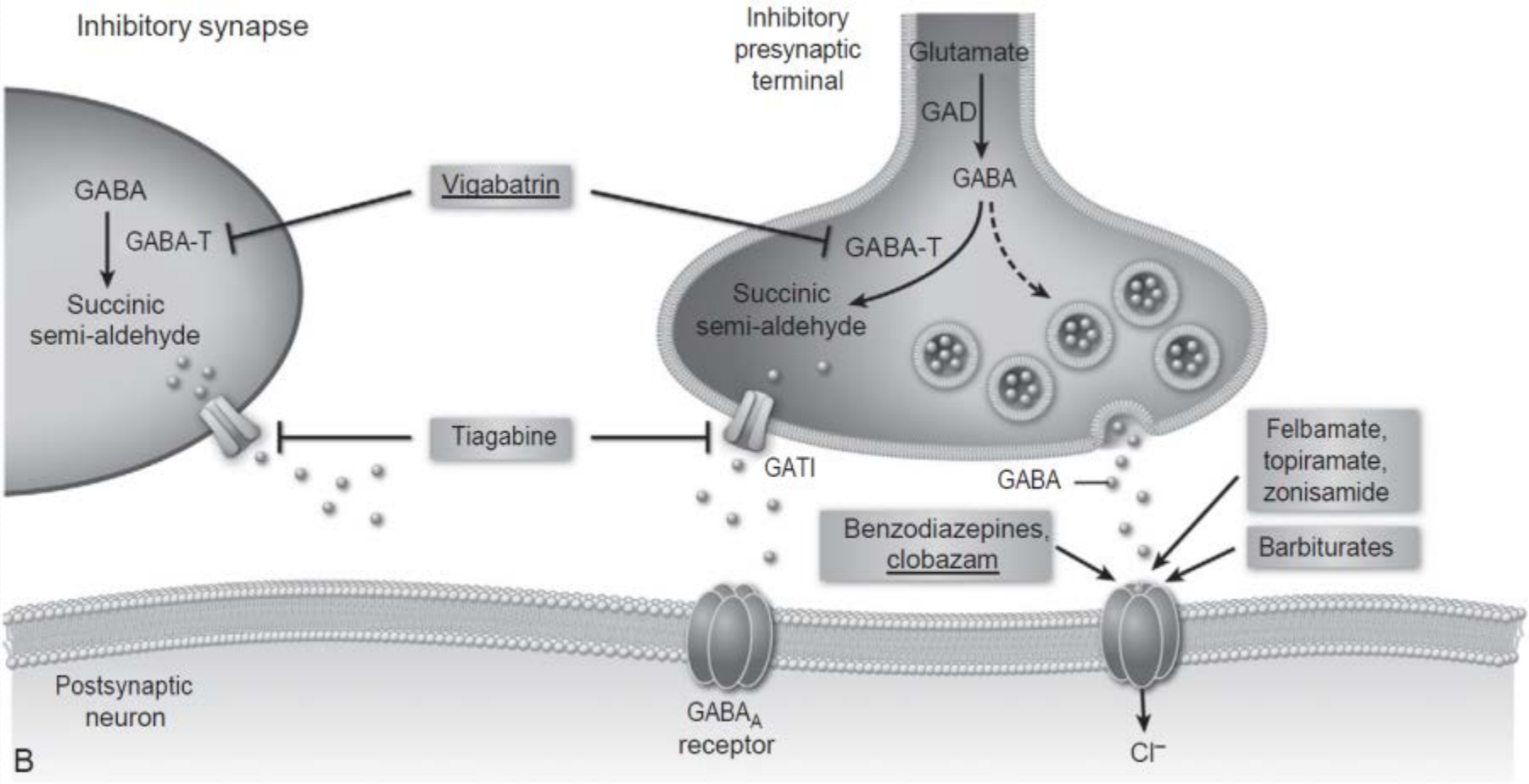
- MOA of AEDs



Joseph I. Sirven et al. Antiepileptic Drugs 2012: Recent Advances and Trends Mayo Clin Proc. 2012;87(9):879-889

Antiepileptic drugs – overview

- MOA of AEDs



Joseph I. Sirven et al. Antiepileptic Drugs 2012: Recent Advances and Trends Mayo Clin Proc. 2012;87(9):879-889

Pharmacology of AEDs

- MOA of AEDs
  - ↑ Inhibitory transmission
    - Increase Cl- current (inward)
      - Benzodiazepines, barbiturates, felbamate
    - Neurotransmitter: GABA
      - Vigabatrin: inhibit gamma-aminobutyric acid transaminase (GABA-T)
      - Tiagabin: binds to GABA uptake carrier (GATI) and increases available GABA into presynaptic neurons

Pharmacology of AEDs

- MOA of AEDs
  - ↓ Excitatory transmission
    - Decrease Na, Ca currents (inward)
      - Na channel blockers
        - Phenytoin, carbamazepine, oxcarbazepine, valproic acid, felbamate, rufinamide, lamotrigine, lacosamide, topiramate, zonisamide
      - Ca channel blockers
        - Gabapentin, pregabalin (nothing to do with GABA)
      - Increase M currents (inhibit epileptic-form activity)
      - K channel agonist
        - Ezogabine
    - Neurotransmitter: glutamate
      - NMDA receptor antagonists: felbamate, topiramate
      - AMPA receptor antagonists: perampanel, topiramate

Complications with AEDs

- Adverse reactions
  - Common
    - Sedation, drowsiness, nausea, GI discomfort, incoordination, vertigo, headache, dizziness, blurred vision, ataxia
    - Drug specific:
      - Phenytoin: nystagmus, gingival hyperplasia
      - Valproic acid: tremor
      - Levetiracetam: psych-related issues – e.g., agitation
      - Acetazolamide, topiramate, zonisamide: kidney stones
      - Carbamazepine and oxcarbazepine: hyponatremia
        - Frequency: oxcarbazepine > carbamazepine

Complications with AEDs

- Adverse reactions
  - Serious
    - Hypersensitivity reactions
      - Lamotrigine, clobazam: rash (SJS/TEN) – slow titration
      - Carbamazepine: rash – HLA-B*1502
    - Hepatotoxicity
      - Felbamate: fulminant hepatitis and aplastic anemia (BW)
      - Valproic acid: hepatotoxicity (BW)
    - Vision
      - Vigabatrin: permanent vision loss
    - Suicidal ideation
      - All AEDs increase risk of suicidal thoughts/behavior
      - Incidence rate: 0.43% treated patients vs. 0.24% of patients receiving placebo

Complications with AEDs

- Adverse reactions: others
  - Hematologic effects
    - Thrombocytopenia (valproic acid), aplastic anemia (felbamate), leukopenia (carbamazepine)
  - Endocrinologic effects
    - Metabolic disorders:
      - Weight gain (valproic acid, gabapentin, pregabalin)
      - Weight loss (topiramate, zonisamide)
      - Risk of osteoporosis/osteopenia (almost all AEDs)
  - Teratogenicity
    - Pregnancy category: C or D

Complications with AEDs

- Monitoring parameters
  - Medication compliance
    - Poor compliance exacerbates seizure disorder
    - Know the reasons for noncompliance/poor adherence
  - Efficacy
    - Seizure frequency
      - Increased, same, decreased
    - Seizure symptoms
      - New symptoms?
    - Duration of seizure
      - Prolonged, same, shorter
  - Safety
    - Adverse reactions
      - Monitor lab values
    - TDM – therapeutic drug monitoring
      - Therapeutic range, consistent with previous level, acute toxicity

Complications with AEDs

- Monitoring parameters
  - Labs
    - CBC, chemistry, LFTs, ammonia levels, vitamin D
  - TDM
    - Drug levels
  - Physical and cognitive functions
  - Drug interactions
  - Mental status
    - Depression, suicidal thoughts and/or ideation

Pharmacokinetics of AEDs

- ADME
  - Absorption
  - Distribution
  - Metabolism
  - Excretion

Pharmacokinetics of AEDs

- Absorption of AEDs
  - Routes
    - PO, IV, IM, intranasal (IN), PR
  - Selection of formulations (IR, DR, ER)
    - Alter absorption process
    - May improve medication compliance
      - e.g., lamotrigine IR (twice daily) vs. ER (once daily)

Pharmacy question

- ✓Sprinkles?
- ✓Delayed release?
- ✓Extended release?

- ✓Interchangeable?

Formulations

- Sprinkles? Delayed release? Extended release?

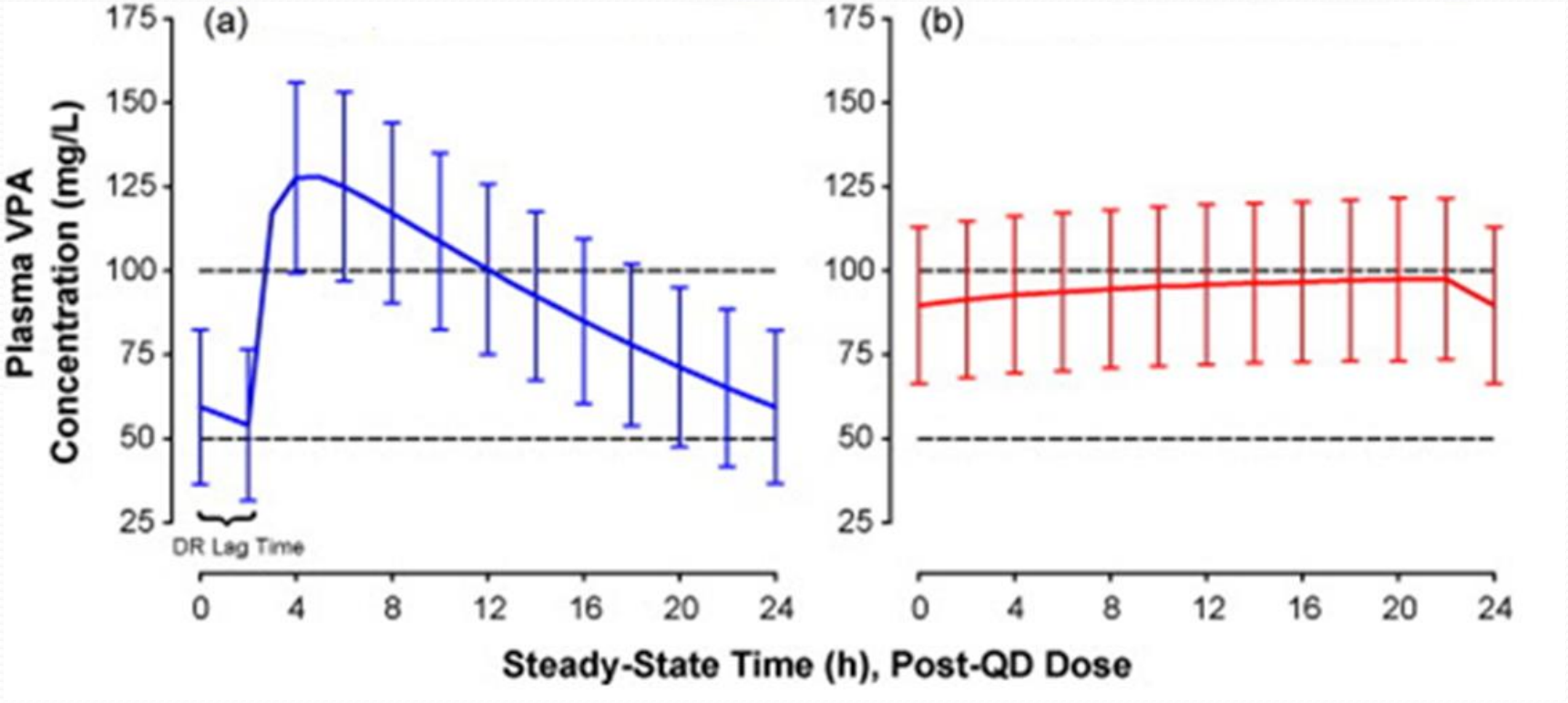
Product(s)/strength	Formulation	FDA approval date
Depakote 250 mg, 500 mg	Enteric-coated delayed-release	1983
Depakote 125 mg	Enteric-coated delayed-release	1984
Depakote 125 mg	Sprinkle delayed-release	1989
Depakote ER 250 mg, 500 mg	Enteric-coated extended-release	2002

- Interchangeable?
  - No
    - When switching from IR to ER, may increase 8% to 20% of daily dose to maintain similar level

http://www.fda.gov/downloads/Drugs/DrugSafety/MedicationErrors/UCM180426.pdf

Formulations

- Delayed release versus extended release



Epilepsy Research, Volume 87, Issues 2–3, December 2009, Pages 260–7

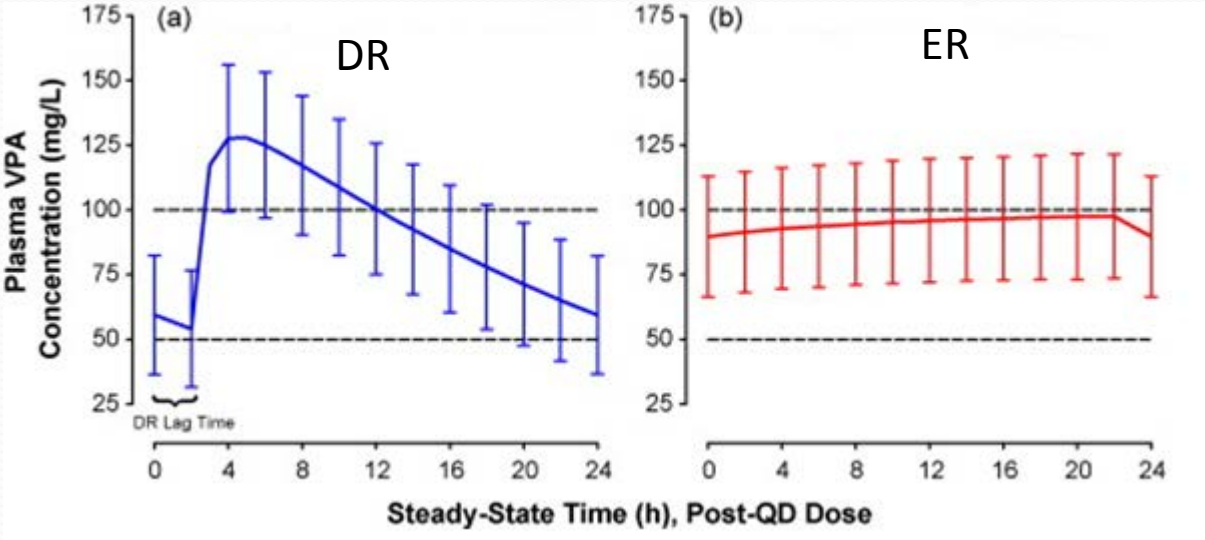
Case 1

- A 13-year-old Hispanic male was diagnosed at age 5 with generalized epilepsy. He has been on valproic acid for about two months, and his seizures are well controlled. However, his mother mentioned that the boy feels dizzy and sleepy at about noon, which significantly makes it difficult for him to concentrate on his classes.

- Medications
  - Valproic acid delayed-release 500 mg po bid
    - Takes 7 a.m. and 7 p.m.
    - Latest serum valproic acid level: 125 (four hours after the dose)
      - Valproic acid: 50-100 mcg/mL

Case 1

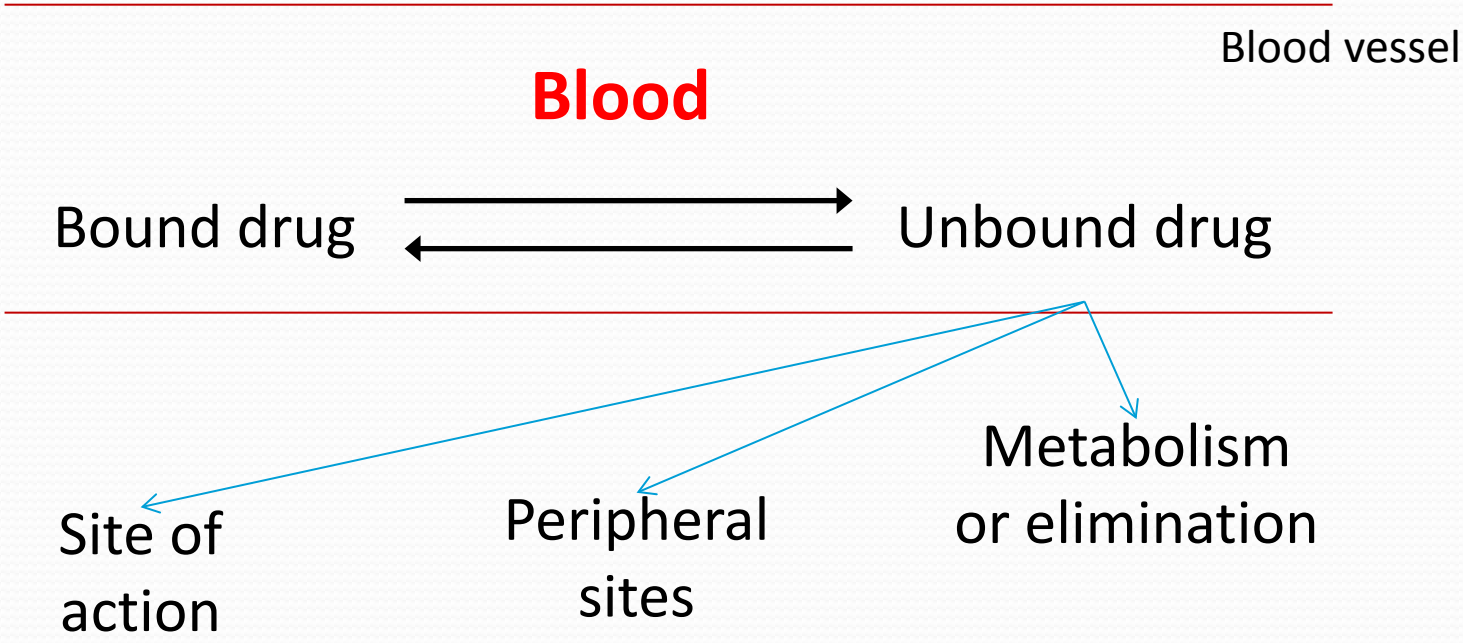
- Pharmacokinetics of valproic acid
  - Delayed release versus extended release



  - Intervention
    - Switching to extended release
      - Less fluctuation of serum concentration of valproic acid

Pharmacokinetics of AEDs

- Distribution of AEDs
  - Distribution: protein binding



Pharmacokinetics of AEDs

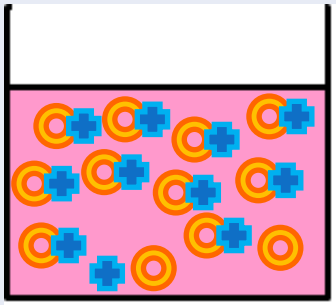
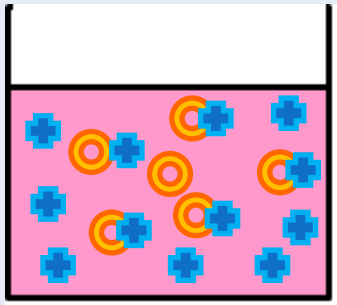
- Distribution: protein binding (cont'd)
  - High protein binding AEDs
    - Phenytoin
      - e.g., warfarin: protein binding-99%, phenytoin-90%
        - Increase PT and INR
    - Valproic acid
  - Altered due to
    - Age
      - Neonates and elderly – lower protein binding
    - Nutrition
    - Liver/renal disease
    - Pregnancy – lower protein binding

Pharmacy question

- ✓Does drug distribution affect serum concentration of AED?

Pharmacokinetics of AEDs

- Drug distribution and protein binding (cont'd)
  - Example:

	Patient A	Patient B
Condition	Otherwise healthy	Third degree burn
Alb	4.4 g/dL	2.2 g/dL
Total PHT level	10 mg/L	10 mg/L
Adjusted PHT level Free PHT Albumin Bound PHT		
Adjusted PHT level	?	?
Estimated free PHT level	?	?

Pharmacokinetics of AEDs

- Drug distribution and protein binding (cont'd)

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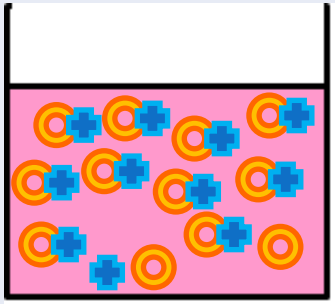
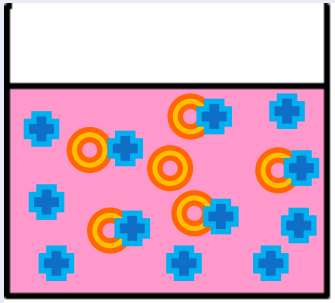
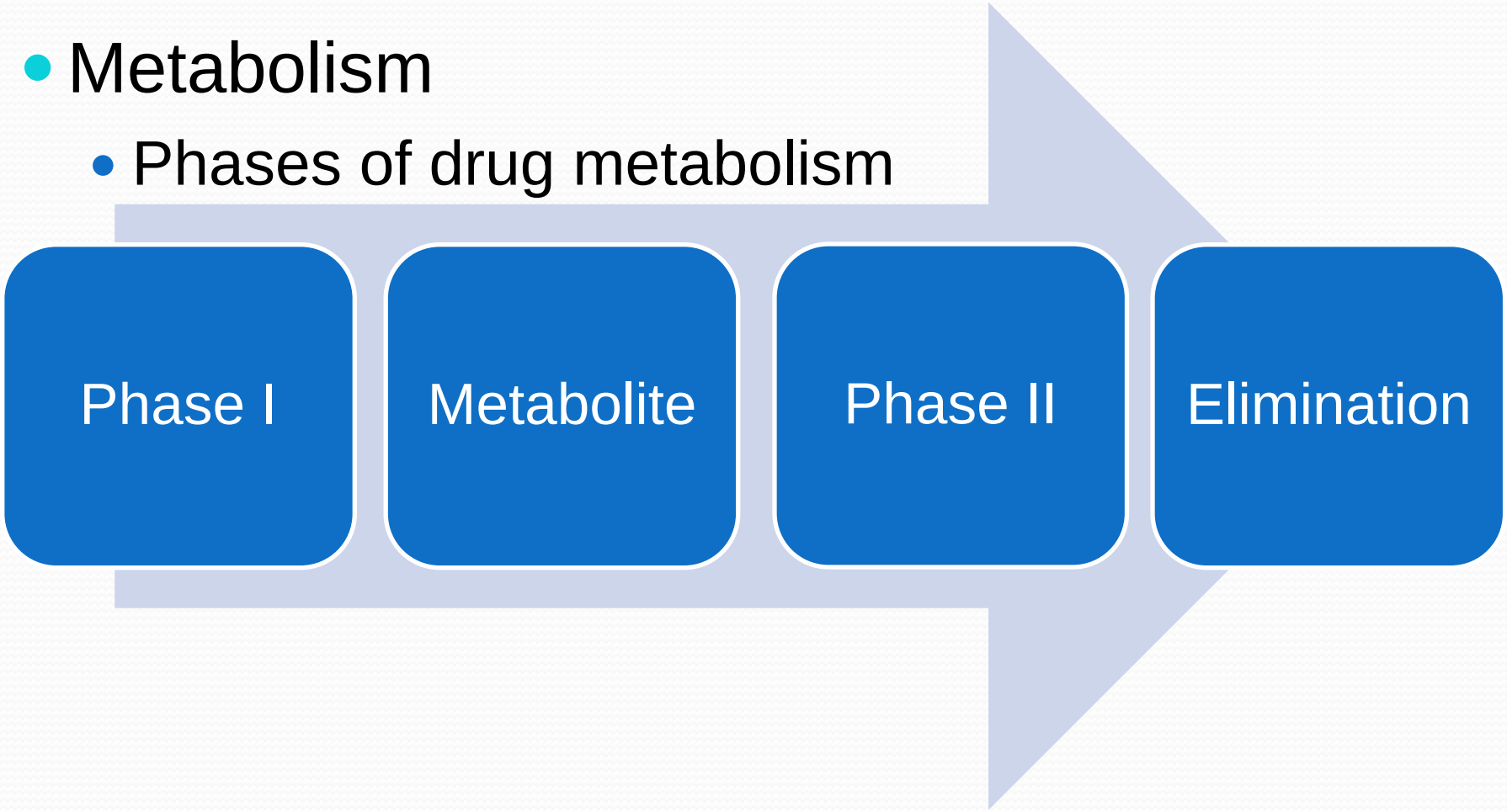
Adjusted PHT level Free PHT Albumin Bound PHT		
Adjusted PHT level	$\frac{10\ mg/L}{(0.9 \times \frac{4.4\ g/dL}{4.4\ g/dL}) + 0.1} =$ 10 mg/L	$\frac{10\ mg/L}{(0.9 \times \frac{2.2\ g/dL}{4.4\ g/dL}) + 0.1} =$ 18.2 mg/L
Estimated free PHT level	1 mg/L	1.8 mg/L

Pharmacokinetics of AEDs

- Metabolism
  - Phases of drug metabolism



Pharmacokinetics of AEDs

- Metabolism
  - Phases of drug metabolism
    - Phase I
      - Primary enzyme system is **Cytochrome P450 (CYP)**
      - Often produces active metabolites
    - Phase II
      - Makes drug molecules water soluble for elimination in urine
      - Most studied enzyme is **UDP-glucoronosyltransferases (UDP/UGT)**

Pharmacokinetics of AEDs

- Metabolism
  - Enzyme systems
    - Substrates, inducers, inhibitors
  - Drug interactions
    - Enzyme-inducing AEDs
      - Phenytoin: CYP2C9, CYP2C19
      - Carbamazepine: **CYP3A4**, CYP2C8, CYP1A2
      - Lamotrigine: UGT1A4 (weak)
      - Phenobarbital (primidone): **CYP3A4**

Pharmacy question

- ✓Enzyme-inducing AEDs?
- ✓Substrate? Inducer? Inhibitor?

Metabolism of AEDs

- Drug interactions
  - Substrate? Inducer? Inhibitor?
    - Substrate: a drug metabolized by specific enzyme
    - Inhibitor: a drug that inhibits specific enzyme activity
    - Inducer: a drug that induces specific enzyme activity

Drug A	Drug B	Mechanism	Serum concentration of Drug A
Substrate of CYP3A4	Inhibitor of CYP3A4	Drug B decreases the metabolism of Drug A	Increased
Substrate of CYP3A4	Inducer of CYP3A4	Drug B increases the metabolism of Drug A	Decreased

Metabolism of AEDs

- Drug interactions
  - Example: co-administration of carbamazepine and oral contraceptives (OC)
    - OC: substrate of CYP3A4
    - Carbamazepine: inducer of CYP3A4
      - What would the serum concentration of OC be?
        - Decreased

Pharmacokinetics of AEDs

- Metabolism
  - Drug interactions
    - Interactions between AEDs and other medications
      - e.g., induction: warfarin and CBZ
    - Interactions between AEDs
      - e.g., valproic acid and lamotrigine
        - Increase lamotrigine concentration (UGT)

Pharmacokinetics of AEDs

- Metabolism
  - **Autoinduction**
    - Induces its own drug metabolism
      - e.g., CBZ
        - Metabolism of CBZ typically increases after first month of therapy

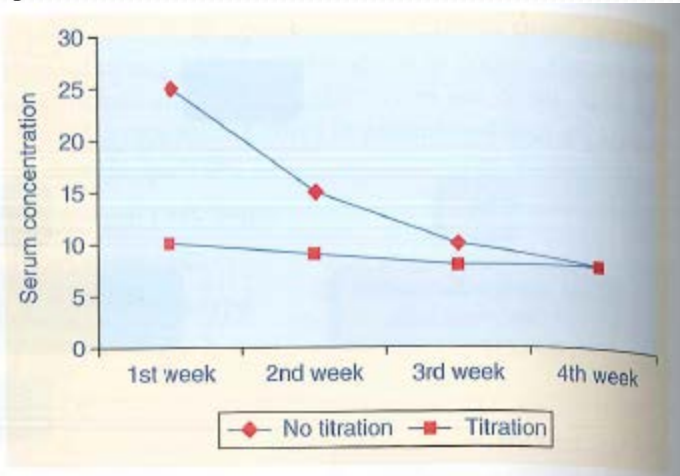


FIGURE 31–3. Serum concentrations of carbamazepine in the presence and absence of appropriate dose titration.

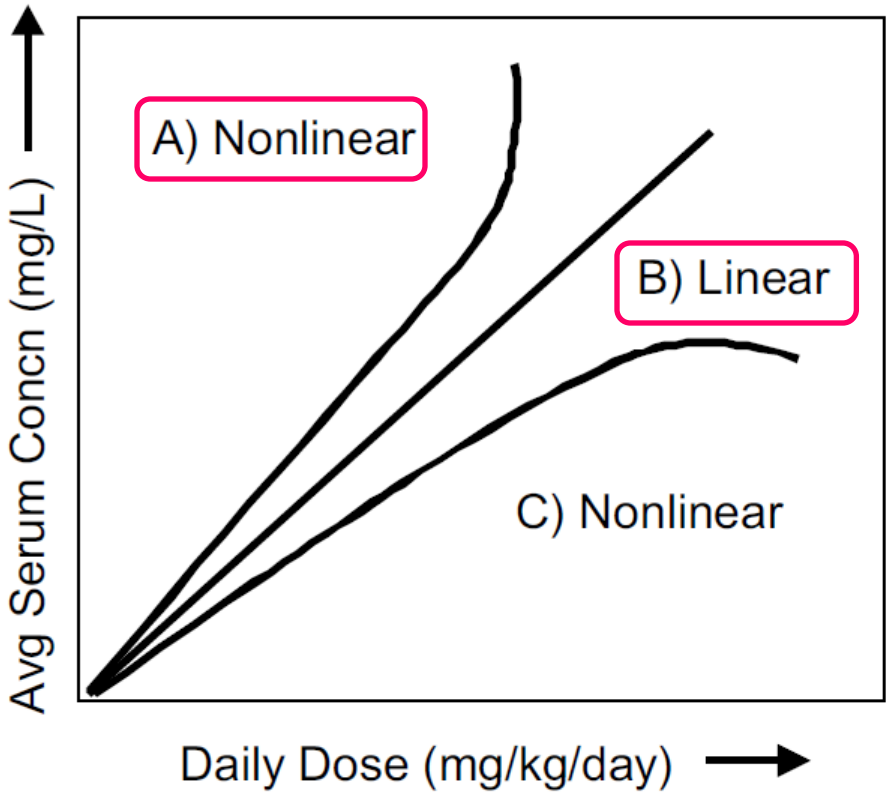
Pharmacokinetics of AEDs

- Excretion/elimination
  - Drug elimination routes
    - Hepatic elimination
    - Renal elimination
    - Others: sweat, saliva, breast milk, etc.
      - Total clearance = hepatic clearance + renal clearance+ others
  - Disease states may alter AED clearance
    - e.g., CHF patient with gabapentin/pregabalin

More pharmacokinetics

- Relationship between
  1. Dose and serum concentration
  2. Dose and clearance

Dose and serum concentration



A) Nonlinear pharmacokinetics (Michaelis-Menten type): Clearance decreases as dose increases
PHT

B) Linear pharmacokinetics: Clearance remains constant as dose increases
PB, VPA (unbound)

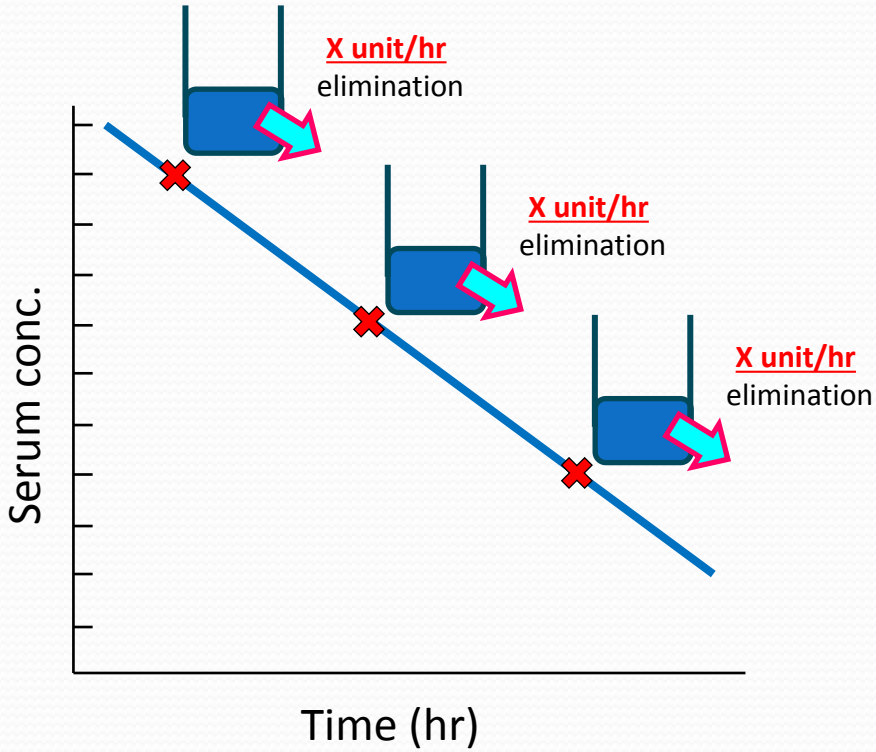
C) Nonlinear pharmacokinetics: Clearance increases with dose
CBZ, VPA (total)

Figure 1. Effects of dose on the steady-state concentrations of classic AEDs. PHT = phenytoin; PB = phenobarbital; VPA = valproic acid; CBZ = carbamazepine.

Cloyd JC, Remmel RP. Antiepileptic drug pharmacokinetics and interactions: impact on treatment of epilepsy. Pharmacotherapy. 2000 Aug;20(8 Pt 2):139S-151S.

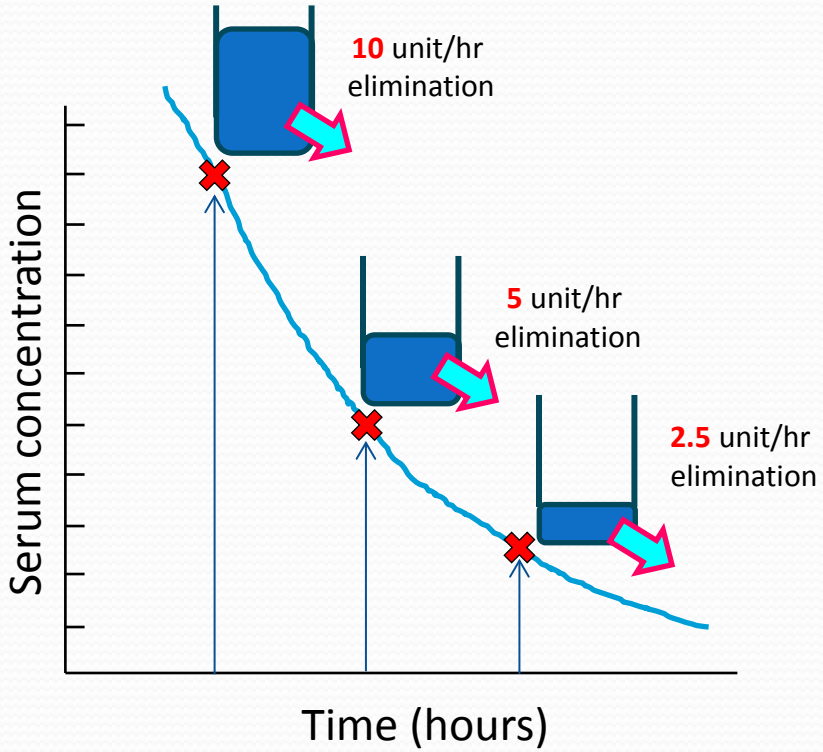
Dose and clearance

- Zero-order elimination
  - Rate of elimination
    - Constant
  - Serum concentration
    - Decreases linearly with time
  - Elimination half-life
    - $t_{½} = \frac{A_0}{2kz}$



Dose and clearance

- First-order elimination
  - Rate of elimination
    - Proportional to drug concentration
  - Serum concentration
    - Decreases exponentially with time
  - Elimination half-life
    - $t_{1/2} = \frac{0.693}{k_f}$



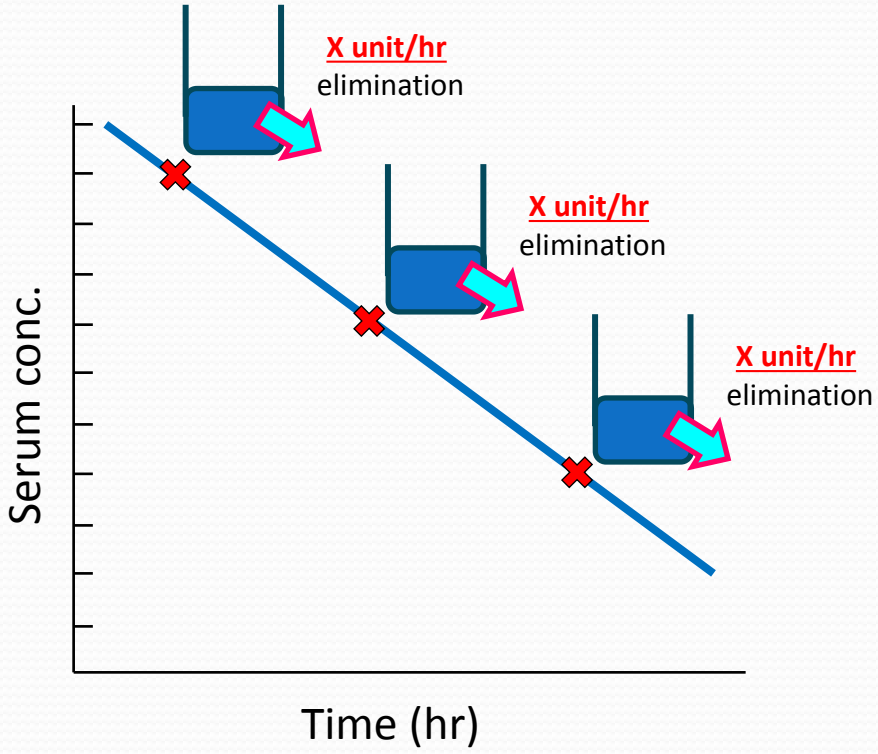
Pharmacy question

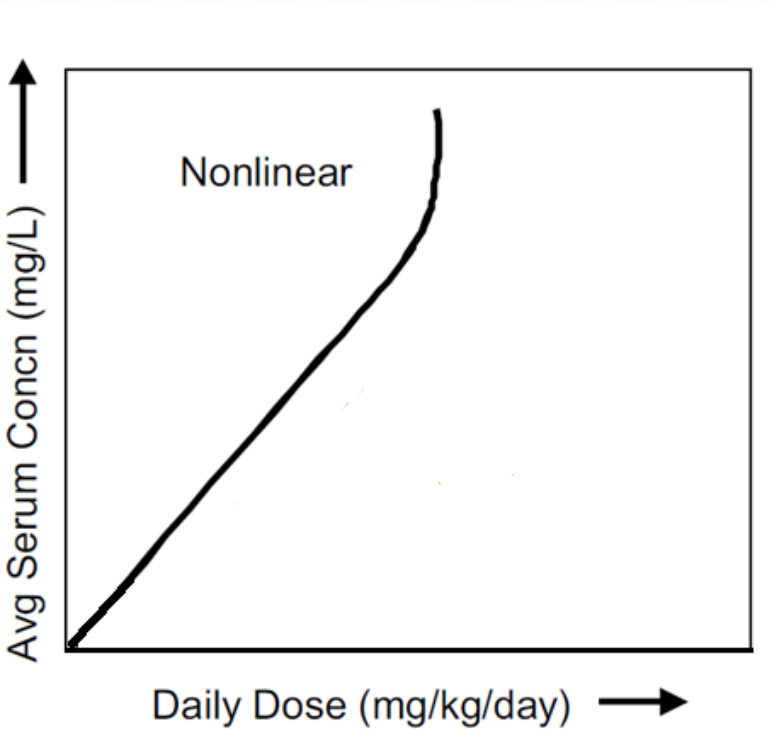
- ✓Why does serum concentration of phenytoin increase rapidly?

Dose and clearance

- Zero-order elimination
  - Example
    - A 45-year-old male patient with moderate renal insufficiency (CrCL = 40 mg/L) was transferred to neuro ICU. He had an MVA and required brain surgery.
    - Phenytoin was given for the prophylaxis of seizures due to post traumatic brain injury.
    - Today is Day 3 at neuro ICU, and his PHT levels are creeping up.
    - His nutrition status is nothing by mouth for four days.

Dose and clearance



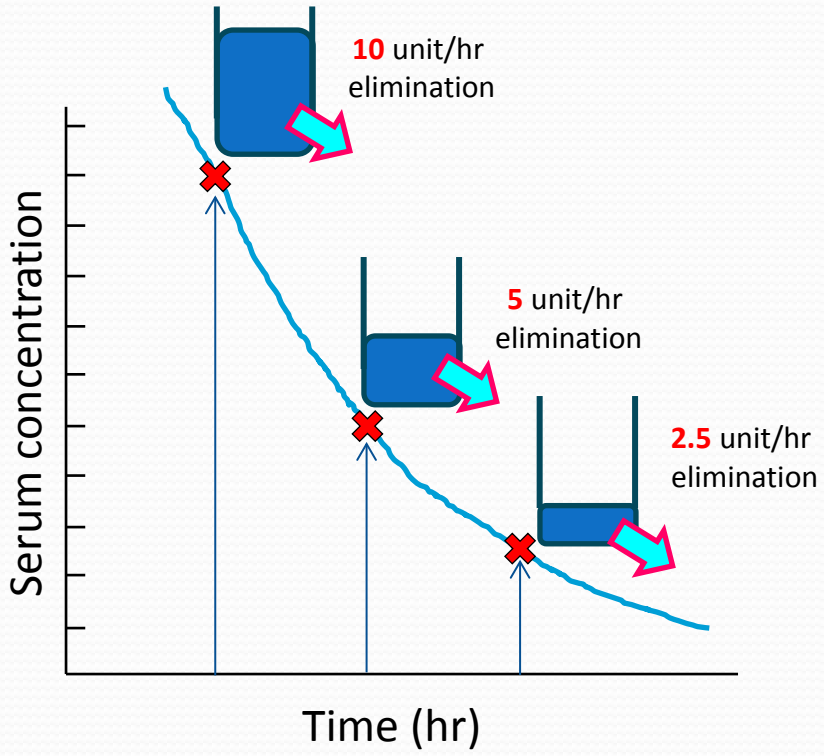


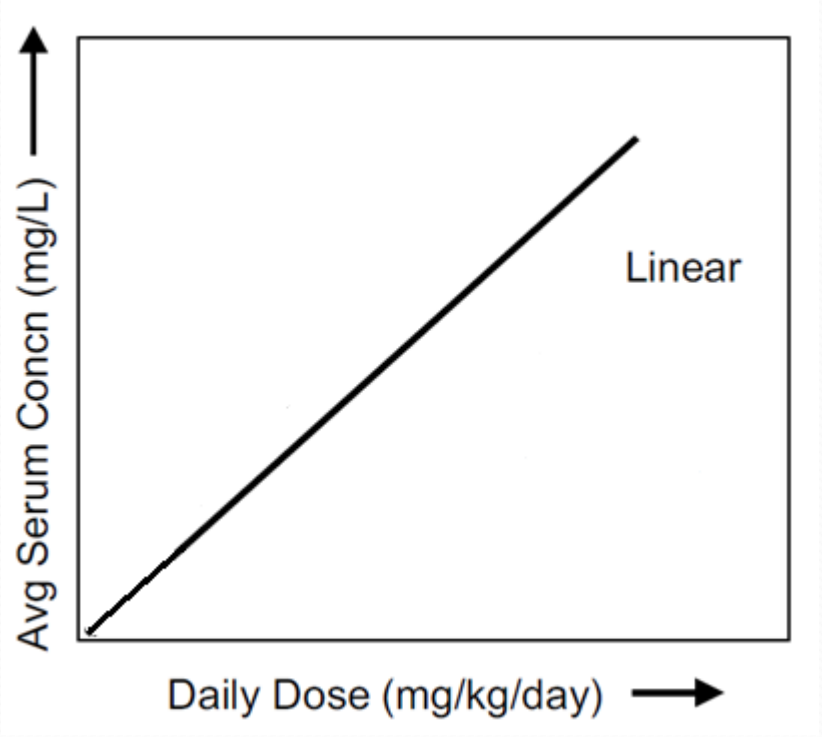
- PHT is eliminated by the same rate constantly
- The kidneys are not able to eliminate PHT due to renal insufficiency
- PHT will accumulate in the body
- Difficult to estimate PHT levels, unlike AEDs, which follow first-order elimination
- It mimics that PHT is given at higher dose
- PHT follows nonlinear pharmacokinetics

Dose and clearance

- Phenytoin case
  - Cautious for patients with renal insufficiency, liver failure (clearance of phenytoin)
  - Cautious for patients with low albumin (distribution of phenytoin – protein binding)
  - Monitor free phenytoin levels

Dose and clearance





- Rate of elimination is proportional to drug concentration
- Serum concentration is decreased exponentially with time
- This AED follows linear pharmacokinetics

Topic discussion

- Midazolam intranasal administration
- Herbal medication and epilepsy
  - Drug-herb interactions
  - Hemp oil use for epilepsy

Case 1

- A 15-year-old female diagnosed at age 1 with generalized epilepsy has been on valproic acid for about three years. Her seizures are well controlled. Since this morning, she has had three seizures, and each seizure lasts about a minute. The interval between each seizure is 30 minutes.

- Questions
  - What abortive agent would you recommend if a seizure last more than three minutes?

Abortive agents – overview

- Benzodiazepines for a prolonged seizure
  - FDA-approved medications among benzodiazepines

Benzodiazepine	FDA approved for status epilepticus	FDA approved for treatment of seizures
Clonazepam	No – off-label use	Yes
Diazepam	Yes (rectal gel)	Yes
Lorazepam	Yes; parenteral only	No – off-label use (complex partial seizures)
Midazolam	No – off-label use	No – only for sedation

http://online.lexi.com.libproxy.unm.edu/lco/action/home

Abortive agents – overview

- Benzodiazepines for a prolonged seizure
  - MOA of benzodiazepines
    - Binds to GABA receptor and reduces excessive excitation in the brain
  - Administration routes
    - Oral, intravenous, intramuscular, rectal, intranasal, buccal

http://www.sec.gov/Archives/edgar/data/946840/000119312512399193/d414342dex991.htm
http://online.lexi.com.libproxy.unm.edu/lco/action/home

Midazolam

- Administration route: IM or IN
- Formulation
  - Solution for IV, IM, IN (preservative free)*, buccal*
  - Syrup
  - Buccal (UK)
- Dose for prehospital treatment
  - 13-40 kg: 5 mg once
  - >40 kg: 10 mg once
- Cost
  - 5 mg/mL (1 mL, preservative free): $1.056

http://www.hospira.com/products_and_services/drugs/MIDAZOLAM_HYDROCHLORIDE
http://online.lexi.com.libproxy.unm.edu/lco/action/doc/retrieve/docid/patch_f/7296

Midazolam

- Buccal
  - Formulation: solution (in European countries)

http://www.mims.co.uk/news/1106012/Buccolam-licensed-buccal-midazolam-product/
http://ascomed.sharepoint.com/Pages/VIROPHARMA.aspx
http://www.sec.gov/Archives/edgar/data/946840/000119312512399193/d414342dex991.htm

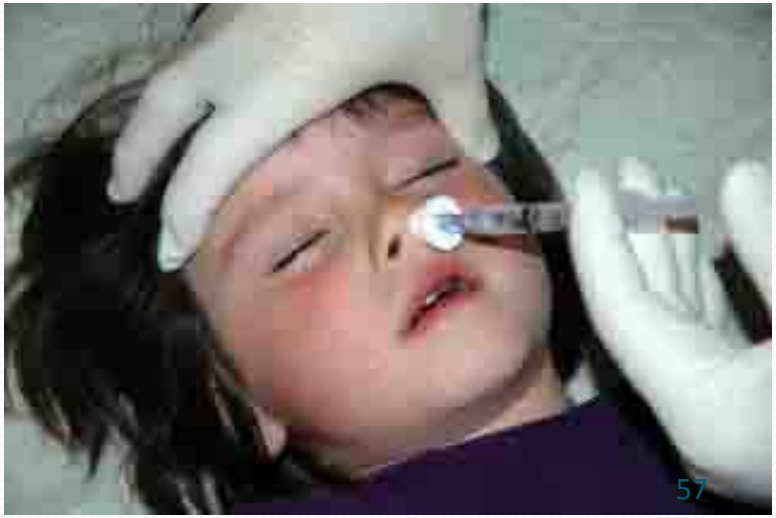
Midazolam

- Onset (adult data)
  - IM (adults): rapid; peak plasma effect in one hour
  - IN (children): rapid; onset four to eight minutes
- Duration
  - IM (adults): two hours
  - IN (children): 18-41 minutes
- Bioavailability (adult data): > 90%
- Half-life
  - Two to six hours

http://online.lexi.com.libproxy.unm.edu/lco/action/doc/retrieve/docid/patch_f/7296#f_pharmacology-and-pharmacokinetics

Midazolam

- IN administration



http://intranasal.net/Treatmentprotocols/default.htm

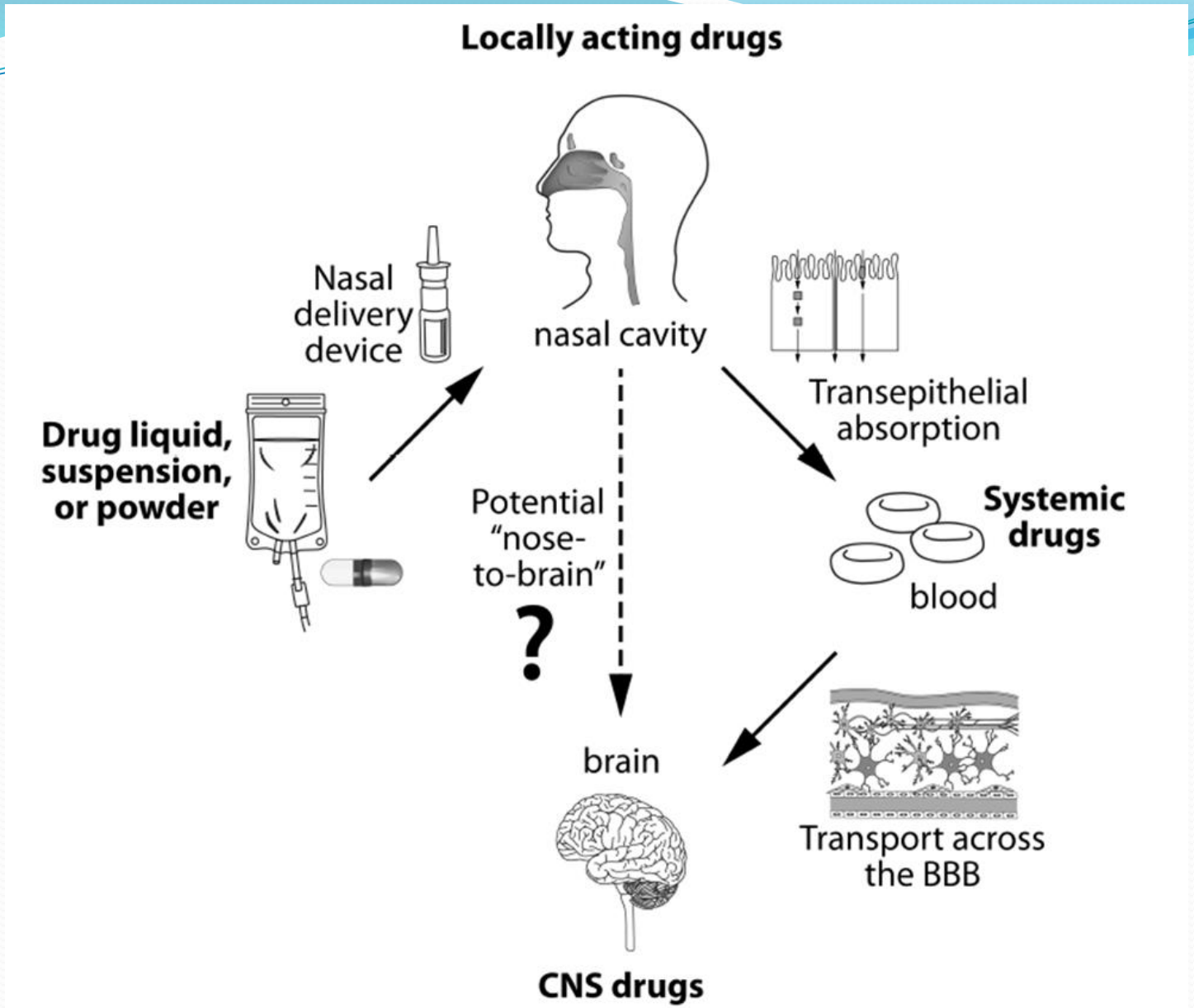


Figure. Drug delivery to the CNS from nasal formulations.
CNS, Central Nervous System; BBB, Blood Brain Barrier

Humphries LK, Eiland LS. Treatment of acute seizures: is intranasal midazolam a viable option? J Pediatr Pharmacol Ther. 2013 Apr;18(2):79-87.

Midazolam

- Veldhorst-Janssen et al. (2011)

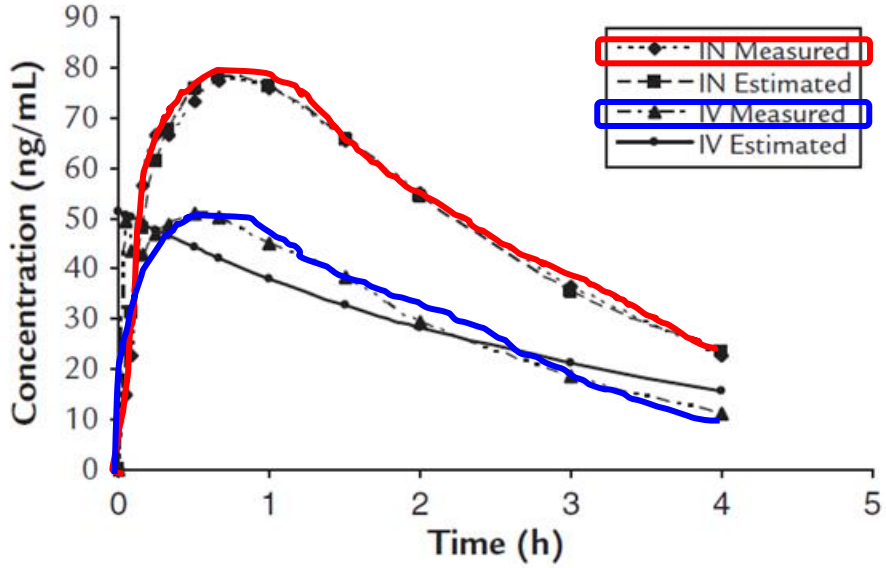


Figure 3. Mean estimated and measured concentration–time profile of intravenous (IV) (2.5 mg) and intranasal (IN) (5 mg) midazolam.

Veldhorst-Janssen NM, Fiddelers AA, van der Kuy PH, Theunissen HM, de Krom MC, Neef C, Marcus MA. Pharmacokinetics and tolerability of nasal versus intravenous midazolam in healthy Dutch volunteers: a single-dose, randomized-sequence, open-label, 2-period crossover pilot study. Clin Ther. 2011 Dec;33(12):2022-8.

Midazolam

- IN administration – dosing
  - 0.2–0.3 mg/kg

MIDAZOLAM (Versed) 5 mg/ml Pediatric Dose Chart
(For Indicated Seizures Only)

WEIGHT	GREY	PINK	RED	PURPLE	YELLOW	WHITE	BLUE	RED	GREEN	OTHER	OTHER
kg	3 –5	6–7	8–9	10–11	12–14	15–18	19–22	24–28	30–36	40	45
lbs	6–11	13–15	17–20	22–25	27–31	33–40	42–49	53–62	65–80	90	100
INTRAVENOUS / INTRAOSSEOUS / INTRAMUSCULAR											
0.1 mg/kg IV/IO/IM Dose	0.4 mg	0.65 mg	0.85 mg	1 mg	1.25 mg	1.75 mg	2 mg	2.5 mg	3.3 mg	4 mg	4.5 mg
0.1 mg/kg IV/IO/IM Volume	0.08 ml	0.13 ml	0.17 ml	0.2 ml	0.25 ml	0.35 ml	0.4 ml	0.5 ml	0.65 ml	0.8 ml	0.9 ml
INTRANASAL											
0.2 mg/kg IN Dose	0.75 mg	1.25 mg	1.75 mg	2 mg	2.5 mg	3.5 mg	4 mg	5 mg	5 mg	5 mg	5 mg
0.2 mg/kg IN Volume	0.15 ml	0.25 ml	0. 35 ml	0.4 ml	0.5 ml	0.7 ml	0.8 ml	1 ml	1 ml	1 ml	1 ml
USE A 1 ML SYRINGE FOR MIDAZOLAM ADMINISTRATION TO PEDIATRIC PATIENTS											

Alameda County Public Health Department. Available from http://www.acphd.org/layouts/containers/ems-ofm/ofm_pdf_13/SEIZURE_MIDAZOLAM_DRUG_CHART.pdf

Midazolam

- Gerrit-Jan de Haan et al. (2010)
  - Primary outcome: comparisons between diazepam (rectal) and midazolam (intranasal) in efficacy, safety, and preference
- Study population
  - Adults (N = 21) – patients with epilepsy
    - Male: 13 (61.9%)
- Dose
  - Diazepam (DZP): 10 mg
  - Midazolam (MDZ): 2.5 mg

de Haan GJ, van der Geest P, Doelman G, Bertram E, Edelbroek P. A comparison of midazolam nasal spray and diazepam rectal solution for the residential treatment of seizure exacerbations. Epilepsia. 2010 Mar;51(3):478-82.

Midazolam

- Gerrit-Jan de Haan et al. (2010)
  - Results
    - Success rate
      - DZP 89% vs. MDZ 82% (NS)
      - Time to stop seizures: NS
    - ADRs
      - No severe ADRs were observed
      - More CNS ADRs in DZP group; more local irritation in MDZ group
    - Preference (easy to use)
      - MDZ > DZP (p<0.001)

Table 2. Efficacy of DZP-r and MDZ-n in suppressing seizure exacerbations

	Success*	Failure	Unknown	Total events	Time until effect (min ± SD)**
DZP-r	56	6	1	63	4.3 ± 3.4
MDZ-n	50	8	3	61	4.6 ± 3.4
Total				124	

*p = 0.57 (not significant); **p = 0.6 (not significant). min, minutes; SD, standard deviation. DZP-r, diazepam rectal solution; MDZ-n, midazolam nasal spray.

de Haan GJ, van der Geest P, Doelman G, Bertram E, Edelbroek P. A comparison of midazolam nasal spray and diazepam rectal solution for the residential treatment of seizure exacerbations. Epilepsia. 2010 Mar;51(3):478-82.

Case 1

- A 15-year-old female diagnosed at age 1 with generalized epilepsy has been on valproic acid for about three years. Her seizures are well controlled. Since this morning, she has had three seizures, and each seizure lasts about a minute. The interval between each seizure is 30 minutes.

- Questions
  - What abortive agent would you recommend if a seizure lasts more than three minutes?

Case 1

- Suggested rational use:
  - What abortive agent would you recommend if a seizure lasts more than three minutes? Intranasal midazolam
    - Appropriate for older children and adults
      - May not be effective for cluster seizures due to shorter half-life

Pharmacy question

- ✓Cost of atomizer?
- ✓Buccal administration?
- ✓Where to send a prescription for midazolam intranasal?

Rx of midazolam

- Cost of atomizer
  - Range: $13.40 to $20/device at a pharmacy
  - Reusable if washed
- Other devices available?
  - Laryngo-tracheal mucosal atomization device
- Pharmacy
  - Compounding pharmacy

http://www.lmana.com/pwpcontrol.php?pwpID=6358

Case 2

- A 16-year-old male with generalized epilepsy showed a significant drop of serum valproic acid level. After ruling out other possible causalities (e.g., lifestyle changes, OTC medication use, timing of administration, medication compliance or adherence, weight changes, etc.), the parents of the patient said they gave their son a special energy drink twice daily. The energy drink contains multiple herbal products.

CAM use in the United States

- Herbal medicine – Herbal medicine facts
- Approximately 40% of U.S. adult population uses CAM
  - 50% of American Indians and Alaska Natives
  - 43% of Whites
  - 40% of Asian
  - 26% of African Americans
  - 28% of Hispanics
- Approximately 12% of U.S. child population uses CAM
  - Children whose parents are regular users of CAM are more likely to use CAM (24%) compared to children whose parents are not regular users of CAM (5%)

1. Barnes P. M., Bloom B., Nahin R. L. Complementary and alternative medicine use among adults and children: United States, 2007. National Health Statistics Reports. 2008;12:1–23.

CAM use in the United States

- Akins et al. survey data
  - CAM use among pediatric patients with neurological disorders (autism: ASD; developmental disabilities: DD)
    - Age: 2-5 years old
  - Methods: interview – self-reported
  - Results
    - Final sample size: 453
    - CAM use: 39% of ASD patients; 30% of DD patients

Akins RS, Krakowiak P, Angkustsiri K, Hertz-Picciotto I, Hansen RL. J Dev Behav Pediatr. 2014 Jan;35(1):1-10.

CAM use in epilepsy

- Herbal medicine
  - Possible issues of herbal medicine use among epilepsy patients
    - Poor medication compliance – rely on “natural” remedy
      - Need education
    - Unexpected drug-herb interaction
      - e.g., changes in metabolism – fluctuation in serum concentration of AED
      - e.g., increase risk of adverse outcomes – e.g., bleeding risk
    - Breakthrough seizures – e.g., stimulant-type herbs
    - Other serious adverse reactions
      - e.g., allergic reactions, abnormal liver/renal functions

CAM use in epilepsy - herb

- Herbal medicine
  - Pharmacist can provide evidence-based article analysis (if possible)
    - Assess safety and toxicity information on herb
    - Summary of an article with recommendations on therapeutic change
    - Education on herbal supplement use for caregiver/patient

CAM use in epilepsy - herb

- Medications for other disease states
  - Considerations
    - Safety
      - Drug-drug interactions ? Alter seizure threshold?
    - Efficacy

Case 2

- A 16-year-old boy with generalized epilepsy showed a significant drop of serum valproic acid level. After ruling out other possible causalities (e.g., lifestyle changes, OTC medication use, timing of administration, medication compliance or adherence, weight changes, etc.), the parents of the patient said they gave their son a special energy drink twice daily. The energy drink contains multiple herbal products.

- Facts
  - The energy drink contains more than 10 herbs
  - The majority of the herbs have a possibility to alter the metabolism and serum concentration of valproic acid
  - Some of the herbs may increase the risk of bleeding

Case 2

- Recommendations
  - Listen to patient and patient caregiver to understand the rationale of herbal use with respect to:
  - Obtain serum AED levels of AEDs
    - Baseline and with herb
  - Obtain lab values (e.g., LFTs, CBC, chemistry)
    - Baseline and with herb
  - Monitor seizure frequency, description, other CAM methods

Case 3

- A 6-year-old girl diagnosed with Lennox-Gastaut syndrome has multiple types of seizures, including drop seizures, myoclonic seizures, and tonic-clonic seizures. She failed five AEDs and has been on valproic acid, clobazam, lamotrigine, and topiramate. Despite using four AEDs, she experiences daily seizures. Today, the patient and her mother come to your clinic and ask if cannabis could be a good treatment option for the girl.

CBD for epilepsy

- Cannabis – species
  - *Cannabis sativa*
  - *Cannabis indica*

- Cannabis – active ingredients
  - Tetrahydrocannabinol (THC)
    - Psychoactive – stimulating (e.g., hallucinations)
  - Cannabinol (CBD)
    - Nonpsychoactive – sedating

Devinsky O, Cilio MR, Cross H, et al. Epilepsia. 2014 Jun;55(6):791-802.

CBD for epilepsy

- What is the difference between the two?
  - Cannabis sativa: higher THC/CBD ratio
  - Cannabis indica: lower THC/CBD ratio
    - Have potential to use as epilepsy treatment

Devinsky O, Cilio MR, Cross H, et al. Epilepsia. 2014 Jun;55(6):791-802.

CBD for epilepsy

- Historical use of cannabis
  - China: menstrual disorders, gout, rheumatism, malaria, constipation, absent-mindedness
  - Islamic countries: N/V, epilepsy, inflammation, pain, fever
  - Western world (in 19th century): analgesic

- Current use of cannabis
  - Glaucoma, pain (chronic pain*, HIV-associated sensory neuropathy*), N/V (chemotherapy-induced N/V*), muscle spasms (spasms in multiple sclerosis*), insomnia, anxiety, epilepsy

* Positive evidence

Devinsky O, Cilio MR, Cross H, et al. Epilepsia. 2014 Jun;55(6):791-802.

CBD for epilepsy

Why CBD?

- "Multitarget" drug
  - Binds to multiple receptors
    - Inhibits neuroexcitation
    - Enhances serotonin activity
    - Acts as an antioxidant

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CBD for epilepsy

Target population

- Epilepsy
  - Lennox-Gastaut syndrome
  - Dravet syndrome
- Neurological diseases
  - Neonatal hypoxic-ischemic encephalopathy
  - Psychosis
  - Anxiety disorders
  - Addictions

Devinsky O, Cilio MR, Cross H, et al. Epilepsia. 2014 Jun;55(6):791-802.

CBD for epilepsy

Issues surrounding CBD use

- Indications of CBD
- Few evidence-based analysis
- Strains of higher CBD/THC ratio
- Cost
- Pharmacokinetics of CBD

Devinsky O, Cilio MR, Cross H, et al. Epilepsia. 2014 Jun;55(6):791-802.

CBD for epilepsy

- Indication of CBD
  - Who can receive the benefits from CBD?
    - Not all types of seizures or epilepsy syndromes can be treated with CBD
      - Better evidence? – LGS and Dravet syndrome

Devinsky O, Cilio MR, Cross H, et al. Epilepsia. 2014 Jun;55(6):791-802.

CBD for epilepsy

- Few evidence-based analysis
  - Very few placebo-controlled studies
  - Older studies
  - Small sample size
  - Detailed study information is unclear

Devinsky O, Cilio MR, Cross H, et al. Epilepsia. 2014 Jun;55(6):791-802.

CBD for epilepsy

Table 1. Clinical trials of cannabidiol in epilepsy

Study	Treatments (subjects per group)	Duration	Outcome	Toxicity	Limitations
Mechoulam and Carlini, (1978)[72]	TRE – CBD 200 mg/day (4) TRE – Placebo (5)	3 months	CBD: 2 seizure free; 1 partial improvement; 1 no change	None	No baseline seizure frequency, no definition of improvement; unclear if AEDs were changed; small N/limited power; not truly randomized-blinded; unknown if groups were matched
Cunha et al. (1980)[73]	TRE-TLE CBD (7) [a] TRE-TLE Placebo (8)[a,b]	200–300 mg/day for 3–18 weeks	Last visit: 4 CBD, 1 placebo	Somnolence	Not clearly blinded, since one patient transferred groups and doses were adjusted in CBD, but no mention of this in placebo group and CBD group received had longer average treatment
Ames and Cridland (1986)[74]	IDD-TRE CBD (?6)[c] IDD-TRE Placebo (?6)[c] × 4 weeks	CBD 300/day × 1 week; 200/day × 3 weeks	No difference between CBD v. Placebo	Somnolence	This was a letter to the editor and details are lacking
Trembly and Sherman (1990)[75]	TRE (?10 or 12)[d]	3 months baseline; 6 months placebo: Randomized to either 6 months placebo v. CBD 100 t.i.d.; then crossover for 6 months on alternative treatment	No change in seizure frequency or cognitive/ behavioral tests	None	Only truly double blind study. Unclear why sample size differed in two reports. Data reported is incomplete

TRE, treatment-resistant epilepsy; TLE, temporal lobe epilepsy; IDD, intellectual/developmental disability.
[a]Frequent convulsions for ≥1 year; – 1 GTCSz per week.
[b]One patient transferred from placebo to treatment after 1 month.
[c]12 subjects were divided into two groups, but distribution uncertain.
[d]Abstract and subsequent book chapter have different N's (10 and 12).

Devinsky O, Cilio MR, Cross H, et al. Epilepsia. 2014 Jun;55(6):791-802.

CBD for epilepsy

- Strains of higher CBD/THC ratio
  - Standardization
    - Medical marijuana
      - *Cannabis indica*?
      - THC/CBD ratio?
    - Hemp oil
      - THC/CBD ratio?

CBD for epilepsy

- Cost
  - Expensive
    - Many caregivers refrain from using hemp oil due to cost
    - Effective dose (adult): 200-300 mg/day
      - e.g., Commercially available hemp oil
        - 1 oz (30 mL) costs $40
        - 80 servings in 30 mL; 1 serving = 15 drops (0.375 mL)
        - 15 drops × 80 servings = 1,200 drops
        - 1.25 mg of CBD in 15 drops (0.375 mL)
        - For a 200 mg of CBD,

1. $200\ mg \times \frac{0.375\ mL}{1.25\ mg} = 60$ mL/day = $80/day

2. $200\ mg \times \frac{15\ drops}{1.25\ mg} \times \frac{30\ mL}{1200\ drops} = 60$ mL/day = $80/day

Monthly cost = $80 × 30 days = $2,400

http://dixiebotanicals.com/products/dew-drops-hemp-oil-supplement/

Cilio MR, Thiele EA, Devinsky O. Epilepsia. 2014 Jun;55(6):787-90.

CBD for epilepsy

- Pharmacokinetics of CBD
  - Administration: po? inhaler?
    - PO: bad taste; bioavailability – approximately 6%
    - Inhaler: bioavailability – approximately 30%
  - Distribution
    - Highly lipophilic
      - Distributed mainly in the brain and adipose tissue
    - High protein binding (90%)

Devinsky O, Cilio MR, Cross H, et al. Epilepsia. 2014 Jun;55(6):791-802.

CBD for epilepsy

- Pharmacokinetics of CBD
  - Metabolism – liver
    - Substrate of CYP3A2, 3A4, 2C8, 2C9, 2C19
    - Inhibitor of CYP3A, 2C
    - Inducer of CYP2B
    - Concerns for drug interactions
      - e.g., carbamazepine and phenytoin may reduce serum concentration of CBD
  - Elimination
    - Mainly in feces; less in urine

Devinsky O, Cilio MR, Cross H, et al. Epilepsia. 2014 Jun;55(6):791-802.

Summary

1. AEDs are classified based on year of drug availability, mechanism of action, indications, and metabolism
2. Various mechanisms and adverse reactions of AEDs are known, and new AEDs are on the market
3. Understanding zero-order and first-order elimination is important to understand how serum concentration of AEDs is altered by changes in physical condition. Other pharmacokinetics factors, such as protein binding and drug metabolism, significantly affect efficacy and adverse reactions of AEDs
4. Intranasal and buccal administration are effective to treat prolonged seizures
5. Herbal products are frequently used in the United States, and analysis of drug-herb interaction is helpful to avoid serious adverse outcomes
6. Cannabis use for epilepsy is a hot topic; however, not all epilepsy patients will benefit from CBD