Narrow Therapeutic Index Medications in Older Adults

A presentation for HealthTrust Members
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Learning Objectives

Pharmacist & Nurse Objectives

- Define narrow therapeutic index medications
- Identify adverse effects suggestive of toxicity
- Describe therapeutic drug monitoring levels

Technician Objectives

- List narrow therapeutic index medications
- Identify potential filling errors associated with narrow therapeutic index medications
- Execute proper disposal of hazardous narrow therapeutic index medications

Definitions

Narrow Therapeutic Index Medication:

Medications where small differences in dose or blood concentration may lead to serious therapeutic failure and/or adverse drug reactions

- May be life-threatening
- May result in persistent or significant disability

Narrow Therapeutic Range:

- Less than twofold difference in the minimum toxic concentration and minimum effective concentration

Source: Midha K, et al. FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology. 2009
Yu LX, et al. FDA GPhA 2011 Fall Technical Workshop

Safety & Efficacy

Minimum Toxic Concentration

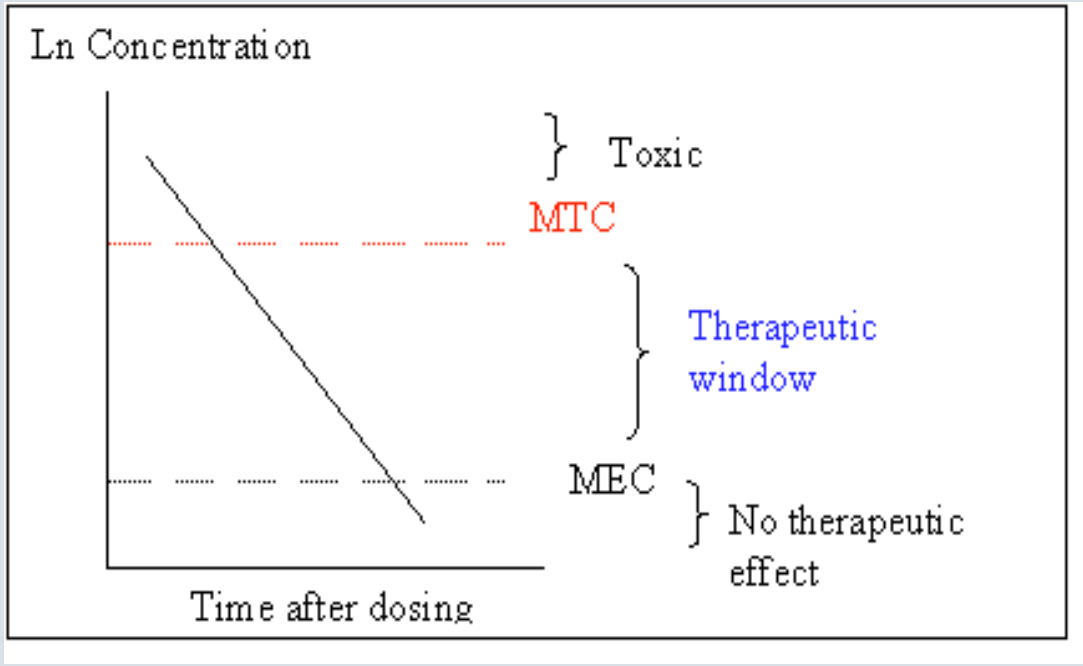
- Minimum concentration in which toxicity usually occurs

Minimum Effective Concentration

- Minimum concentration that is required for drug effect

Therapeutic Range

- Range of doses which optimize between safety and efficacy
- Achieves greatest therapeutic benefit



Source: Vo M, et al. PEOI. PK 1 D- Therapeutic window

Variations in Blood Concentrations

Medications may have:

- Product formulations that exhibit limited or erratic absorption
  - Carbamazepine
- Formulation-dependent bioavailability
  - Tacrolimus
- Wide interpatient pharmacokinetic variability
  - Warfarin

Pharmacokinetic/Pharmacodynamic Changes in Older Adults

Absorption

- Slowed transit time into small intestine

Distribution

- Decrease in total body water
- Increase in body fat

Metabolism

- Reduced function of enzymes

Elimination

- Reduced excretion
- Extended half-lives

Source: Hutchison LC, et al. *Fundamentals of Geriatric Pharmacotherapy*. 2015

Therapeutic Drug Monitoring

- Clinical practice of measuring specific drugs at designated intervals in the blood
- Maintain a constant concentration in a patient's bloodstream
- Optimizing individual dosage regimens

Geriatric Considerations:

- Start at lower doses
- Titrate up slowly to avoid adverse effects
- Closely monitor for safety and efficacy
- Anticipate a therapeutic response at the lower end of the therapeutic range

Common Narrow Therapeutic Index Medications

- Warfarin
- Tacrolimus
- Valproic Acid
- Digoxin
- Lithium carbonate
- Carbamazepine
- Phenytoin
- Theophylline
- Cyclosporine
- Levothyroxine

Assessment Q1- Pharmacist

A narrow therapeutic index medication is defined as:

A. Medications that need therapeutic drug monitoring
B. Medications where small differences in dose or blood concentration may lead to serious therapeutic failure and/or adverse drug reactions
C. Medications having more than three-fold difference in the MTC and MEC

Assessment Response 1- Pharmacist

A narrow therapeutic index medication is defined as:

A. Medications that need therapeutic drug monitoring

B. Medications where small differences in dose or blood concentration may lead to serious therapeutic failure and/or adverse drug reactions

C. Medications having more than three-fold difference in the MTC and MEC

Assessment Q2 - Technician

Which of the following is a narrow therapeutic index medication?

A. Morphine
B. Levetiracetam
C. Digoxin
D. Promethazine

Assessment Response 2- Technician

Which of the following is a narrow therapeutic index medication?

A. Morphine
B. Levetiracetam
C. Digoxin
D. Promethazine

Warfarin

- Mechanism of Action: Vitamin K antagonist (VKA) and reduces synthesis of clotting factors II, VII, IX, X as well as protein C + S
- Anticoagulant used in:
  - Venous thromboembolism treatment
  - Atrial fibrillation and/or cardiac valve replacement
  - Secondary prevention after myocardial infarction
- Adverse Effects:
  - Red or brown urine
  - Black stool
  - Epistaxis
  - Hematoma
  - Bruising

Sources: Whitlock RP, et al. *Chest* 2012;141(2 Suppl):e576S-600S
Nishimuria RA, et al. *Circulation* 2014;129:2440-92

Considerations with Dosing — Warfarin

- Geriatric patients are at an increased risk of bleeding due to:
  - Increased risk of falls
  - Drug interactions
  - Decreased dietary vitamin K intake
  - Impaired liver function
  - Comorbidities
  - Low albumin

Source: Hutchison LC, et al. *Fundamentals of Geriatric Pharmacotherapy*. 2015

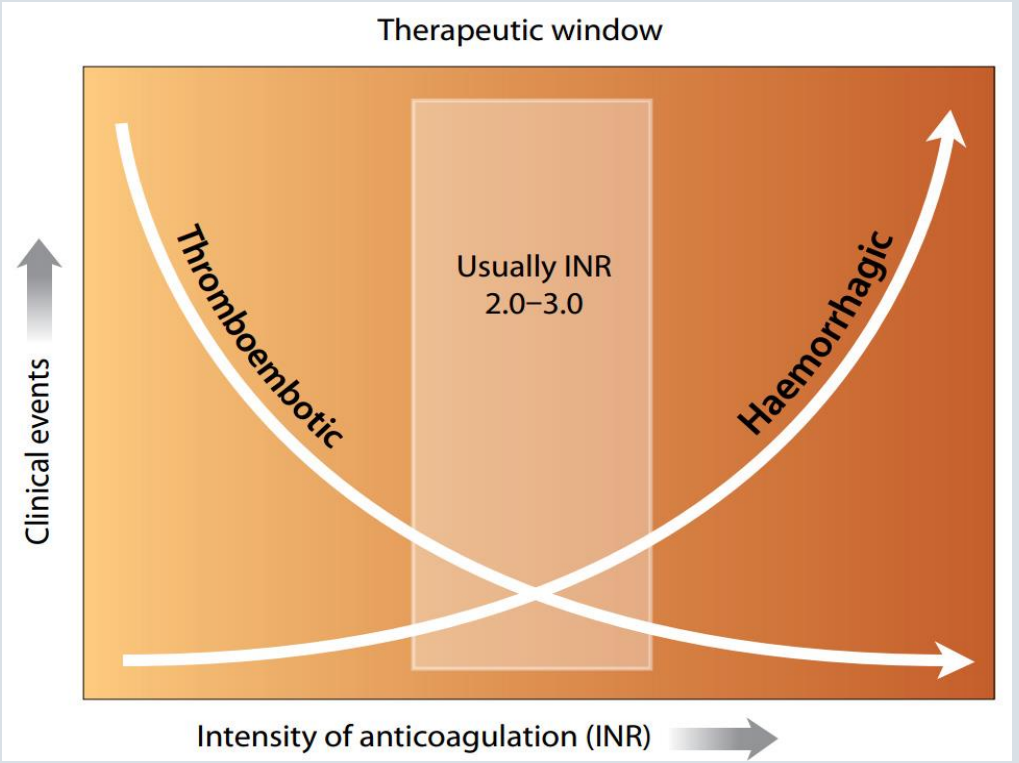
Safety & Efficacy — Warfarin

International Normalized Ratio (INR)

- Laboratory measurement of how much time it takes for a patient's blood to clot
- Normal INR without use of anticoagulant: 1.0

Why do we monitor the INR?

- Prevent excessive bleeding (INR > 4.5)
- Prevent thrombosis (INR < 2)
- Evaluate efficacy of dose



INR Monitoring

Indication	INR Goal
Mechanical aortic valve	2.0-3.0
Mechanical mitral valve	2.5-3.5
Bioprosthetic valve	2.0-3.0
Atrial fibrillation	2.0-3.0
Venous thromboembolism treatment	2.0-3.0
Thrombophilia (Antiphospholipid syndrome, Antithrombin deficiency, Protein C/S deficiency)	2.0-3.0

Sources: Whitlock RP, et al. *Chest* 2012;141(2 Suppl):e576S-600S
Nishimuria RA, et al. *Circulation* 2014;129:2440-92

Subtherapeutic INRs

- Subtherapeutic INRs can put the patient at risk of thrombosis
- Bridging is a technique of implementing simultaneous anticoagulation to counteract the delayed onset of warfarin
  - Ensure that full anticoagulation is achieved
  - Reduces risk of clot
- INR monitoring is usually performed daily until the therapeutic range has been achieved and maintained for at least 2 consecutive days
  - In outpatients starting VKA therapy, initial monitoring may be reduced to once every few days until a stable dose response has been achieved
  - Frequency of testing can be reduced to every 4 to 6 weeks when the INR response is stable

Sources: Whitlock RP, et al. *Chest* 2012;141(2 Suppl):e576S-600S
Nishimuria RA, et al. *Circulation* 2014;129:2440-92

Supratherapeutic INRs

	Kcentra (4F-PCC)	Vitamin K	Fresh Frozen Plasma (FFP)
Mechanism of Action	Repletes factors: II, VII, IX and X Repletes protein C and S	Repletes vitamin K	Repletes all coagulation factors
Doses	Bleeding: INR 2-3: 25 units/kg (max 2500) INR 4-6: 35 units/kg (max 3500) INR >6: 50 units/kg (max 5000)	Bleeding: Any INR: 10 mg IV x 1 over 1-2 mins	Bleeding: 15-30 ml/kg
	Low fixed-dose option: Non-ICH: 1000-1500 units ICH: 1500-2000 units	No Bleeding: INR 4.5-10: 1-2.5 mg PO x 1 INR > 10: 2.5-5 mg PO x 1	

Sources: Kcentra [package insert] Kankakee, IL. CSL Behring Pharmaceutricals. 2013
Tomaselli GF, et al. *J Am Coll Cardiol* 2017;70:3042-67

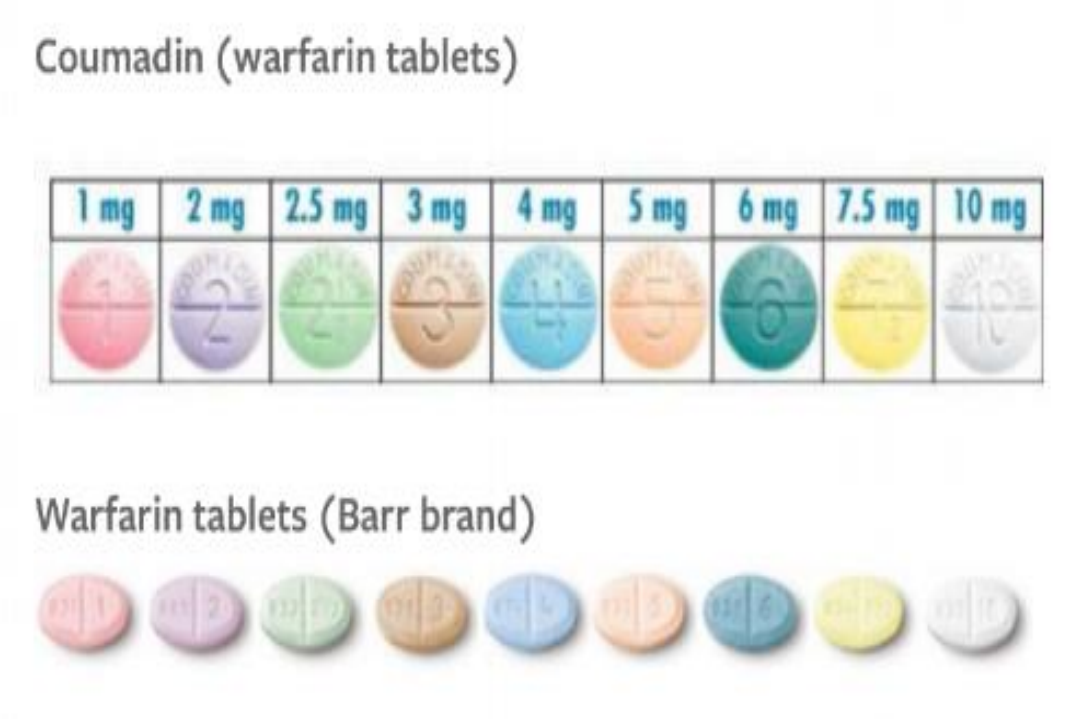
Considerations of Reversal Therapy

	Kcentra (4F-PCC)	Vitamin K	Fresh Frozen Plasma (FFP)
Pros	Repletes factors: II, VII, IX and X Repletes protein C and S Rapid reversal Rapid administration	Repletes vitamin K Multiple formulations Longer duration of action Inexpensive	Repletes all coagulation factors Inexpensive
Cons	Expensive Requires reconstitution Factor IX variability Modest duration of action	Anaphylactoid Reaction Warfarin resistance	Requires thawing Large volume May require repeat transfusions Slow modest reversal Slow administration

Prospective Evaluation of a Fixed-Dose 4-Factor Prothrombin Complex Concentrate Protocol for Urgent Vitamin K Antagonist Reversal

Background	Multi-center, non-inferiority, prospective cohort trial including 54 patients on warfarin and requiring rapid reversal
Methods	Primary Outcome: Post infusion INR < 2 Secondary Outcome: Post infusion INR < 1.5, mean 24h INR, 7 day mortality, and 7 day venous thromboembolic events Interventions: • INR ≤ 7.5 and weight ≤ 100 kg: 1500 units 4F-PCC • INR > 7.5 and weight > 100 kg: 2000 units 4F-PCC
Outcomes	Primary Outcome: 95 % achieved INR < 2 (p = 0.0035) Secondary Outcomes: • 90 % achieved INR < 1.5 (p = 0.4) • No significant differences in mean 24h INR, 7 day mortality, and 7 day venous thromboembolic events

Formulations — Warfarin



Tablet strength	Tablet color
1 mg	Pink
2 mg	Lavender (light purple)
2.5 mg	Green
3 mg	Tan
4 mg	Blue
5 mg	Peach (light orange)
6 mg	Teal (blue-green)
7.5 mg	Yellow
10 mg	White

Counseling — Warfarin

Caution	Counseling Point
Bleeding	Identification of: bleeding gums, hematuria, dark stool, epistaxis, hemoptysis Avoid activities that increase risk of falling
Diet	Eating an increased amount of foods rich in vitamin K can lower INR which can increase risk of blood clots Food with high vitamin K: broccoli, kale, spinach, kiwi, soybeans Limit alcohol consumption
Pill Identification	Color of medication correlates to warfarin dose
Concomitant medications, herbals or supplements	Acetaminophen for pain relief Avoid ginseng, garlic, gingko Check amount of vitamin K in multivitamins

Disposal — Warfarin

Stericycle P-Listed Hazardous Waste

- Non-antineoplastic drug that primarily has adverse reproductive effects
- FDA Pregnancy Category D
  - Waste must be unused
  - Must be in the form of a commercial product
  - Must be disposed with the correct paperwork, tracking and documentation of amount generated every month
- For both wrappers AND medication
  - All residue within bottle is considered toxic
  - Bottle is still hazardous waste after residue is discarded
  - It is discarded in a Stericycle bin (white bin)

Assessment Q3 — Technician

Which of following is NOT true regarding the proper disposal of Warfarin?

A. All residue within bottle is considered toxic
B. It is discarded in a Stericycle bin
C. The bottle is not considered hazardous waste once residue is discarded
D. It is listed as a P- or U-listed chemical by the EPA

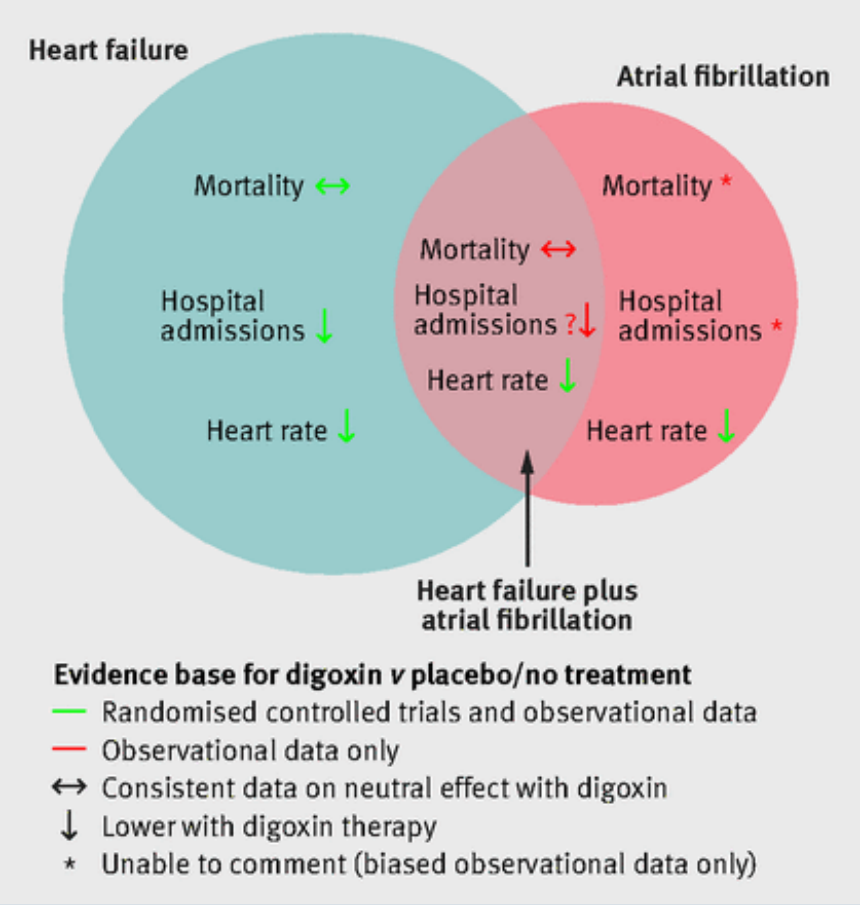
Assessment Response 3 — Technician

Which of following is NOT true regarding the proper disposal of Warfarin?

A. All residue within bottle is considered toxic
B. It is discarded in a Stericycle bin
C. The bottle is not considered hazardous waste once residue is discarded
D. It is listed as a P- or U-listed chemical by the EPA

Digoxin

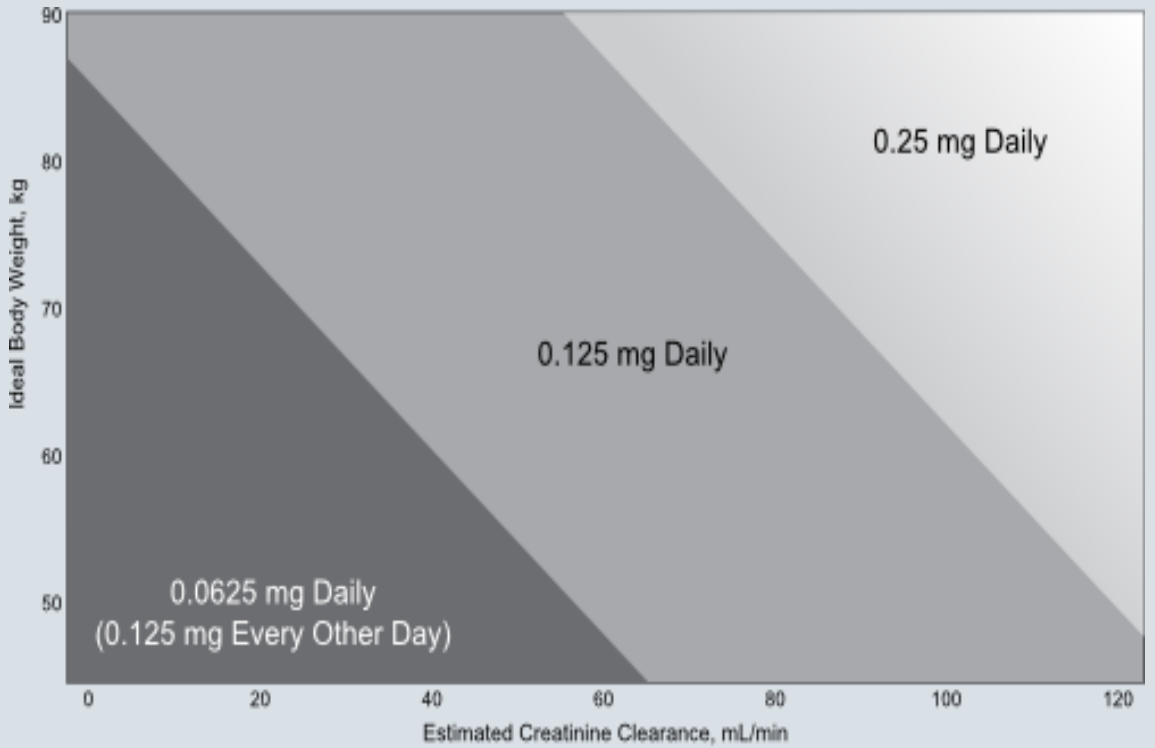
- Mechanism of Action: Positive inotrope which inhibits Na/K ATPase
- Used in:
  - Atrial fibrillation
  - Heart failure with reduced ejection fraction (HFrEF)



Considerations with Dosing — Digoxin

Geriatric patients are at increased risk of digoxin toxicity due to:

- Increased sensitivity of aged myocardium
- Reduced renal function
- Low lean body mass
- Drug interactions
- Comorbidities



Bauman JL, DiDomenico RJ, Viana M, Fitch M. *Arch Intern Med*. 2006 Dec 11-25;166(22):2539-45.

Source: Hutchison LC, et al. *Fundamentals of Geriatric Pharmacotherapy*. 2015

Adverse Effects and Toxicity — Digoxin

Adverse Effects

- Abdominal pain, Heart block, Bradycardia, Hypokalemia

Toxicity

- Nausea, Vomiting, Diarrhea, Headache, Blurred vision with yellow/green halos, Confusion, Dizziness

Therapeutic Drug Monitoring — Digoxin

Why do we obtain levels?

- Concern about compliance or inadequate digoxin history
- Drug interactions
- **Suspected toxicity**

Therapeutic ranges are dependent on indication:

- Atrial fibrillation: 0.5-1.2 ng/ml
- Heart failure: 0.5-0.9 ng/ml
- High risk of toxicity with levels > 2 ng/ml

Source: Ziff OJ, et al. *BMJ* 2015;351:h4451

Toxicity — Digoxin

- Digifab is recommended for life threatening poisoning presenting with:
  - Bradyarrhythmia, ventricular arrhythmias, hyperkalemia > 6 mmol/L, hemodynamic instability and digoxin levels > 2.6 ng/ml
  - Not indicated for mild cases or in the absence of signs/symptoms of toxicity
  - Digoxin bound to Fab fragments cannot result in toxicity

Drug	Mechanism of Action	Dose
Digifab (digoxin immune-fab)	Binds to molecules of digoxin and reduces free digoxin levels	Digoxin Immune Fab Dose (vials) = (serum digoxin concentration [ng/mL] x weight [kg]) / 100 Digoxin Immune Fab Dose (vials) = (Amount of digoxin ingested [mg])/ 0.5 mg of digoxin bound/vial

Source: Digifab [package insert] Nashville, TN. Protherics Inc. 2001

Digoxin Toxicity & Use of Digoxin Immune Fab

Background	Multi-center, retrospective, cohort trial including 24,547 patients with digoxin toxicity who did/did not receive digoxin immune fab (DIF)
Methods	Primary Outcome: Length of stay Secondary Outcome: Cost of hospitalization, in-hospital mortality, 180-day readmission rate Interventions • Digoxin Immune Fab • No treatment
Outcomes	Primary Outcome: • Longer mean length of stay in patients who received DIF ($p < 0.001$) Secondary Outcomes: • Increased overall hospital costs ($p < 0.001$) • Increased in-hospital mortality ($p < 0.001$) • Reduced 180-day readmission rate ($p < 0.001$) Subgroups: • 31% ≥85 years of age • 88% ≥65 years of age • DIF treatment- 85+ yrs vs 65-74 yrs (OR 0.88) ($p < 0.05$)

Formulations — Digoxin

Formulation	Doses	Bioavailability
Tablets	125, 250, 500 mcgs	60-80%
Capsules	50, 100, 200 mcgs	90-100%
Elixir	50 mcg/ml	70-85%
Parenteral Injection	100, 250 mcg/ml	100%

Source: Digoxin [package insert] Columbus, OH. Roxane Laboratories, INC. 2001

Disposal — Digoxin

- Regular disposal
  - For medications that have > 3% still intact
  - Doesn't fall into hazardous medication category
  - It is discarded in the Non-Hazardous Waste bin (blue bin)

Assessment Q4 — Pharmacist

Which of the following is not an expected side effect of digoxin toxicity?

A. Vomiting
B. Dizziness
C. Visual changes
D. Muscle pain

Assessment Response 4 — Pharmacist

Which of the following is not an expected side effect of digoxin toxicity?

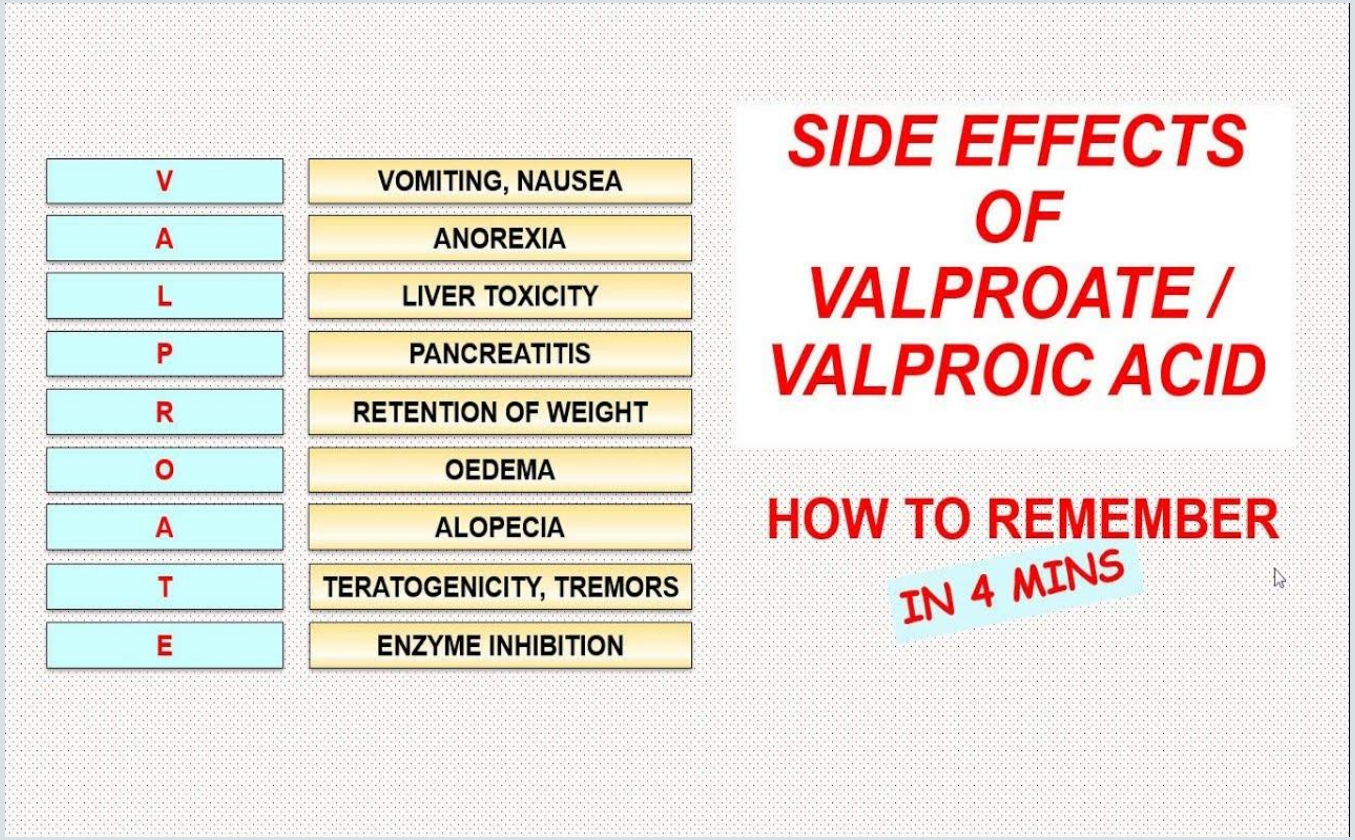
A. Vomiting
B. Dizziness
C. Visual changes
D. Muscle pain

Valproic Acid

- Mechanism of Action: increases availability of GABA to brain neurons and may enhance the action of GABA
- Used in:
  - Simple and complex absence seizure
  - Complex partial epileptic seizure
  - Bipolar Disorder
  - Migraine prophylaxis
- Off-label uses:
  - Chronic pain syndrome
  - Myoclonic seizure
  - Status epilepticus

Toxicity — Valproic Acid

- Adverse Effects:
  - CNS depression
  - Lethargy
  - Encephalopathy
  - Tremors
  - Hyperammonemia
  - Thrombocytopenia
  - Pancreatitis
  - Hepatoxicity



Considerations of Dosing — Valproic Acid

Geriatric patients are at an increased risk of toxicity due to:

- Various dosage forms
- Liver impairment
- Hypoalbuminemia

Source: Hutchison LC, et al. *Fundamentals of Geriatric Pharmacotherapy*. 2015

Therapeutic Drug Monitoring — Valproic Acid

- Therapeutic range: 50-100 mcg/ml
  - Mania: 50-125 mcg/ml
- Toxic level: > 100 mcg/ml
  - Moderate to severe toxicity: 450-850 mcg/ml
  - Coma: > 850 mcg/ml
- Activated charcoal may be useful
  - Especially in patients with delayed-release overdoses
- L-Carnitine is recommended is symptomatic patients with concentrations > 450 mcg/ml
  - 100 mg/kg administered over 30 mins, then 15 mg/kg Q6H over 20 mins

Source: Howland MA, et al. *Goldfrank's Toxicologic Emergencies*. 9th ed. New York, NY: McGraw-Hill Companies, Inc; 2011:711
EASL. *J Hepatol*. 2019;70(6):1222-126

Formulations — Valproic Acid

Drug (Brand)	Formulation	Doses	Conversion
Divalproex sodium delayed-release (Depakote sprinkle)	Capsule	125 mg	To Depakote ER: May require an increase in total daily dose between 8-20% ER formulation has reduced bioavailability
Divalproex sodium extended-release (Depakote ER)	Tablets	250, 500 mg	
Divalproex sodium enteric coated, delayed release (Depakote)	Tablets	125, 250, 500 mg	
Valproic acid immediate-release (Depakene)	Capsule Syrup	250 mg 250 mg/ 5ml	
Valproate sodium (Depacon)	Intravenous	100 mg/ml	

Filling — Valproic Acid

- Multiple formulations can lead to increased filling errors
- If incorrect medication reaches patient:
  - Suboptimal dosing
  - Overdose
  - Adverse effects

- Ways to reduce filling errors:
  - Match drug name
  - Match drug strength
  - Match drug formulation
  - Match prescription with stock bottle

Disposal — Valproic Acid

Stericycle Hazardous Waste

- Meets ≥ 1 of the NIOSH criteria for a hazardous drug
- Black Box warning for teratogenicity
  - FDA Pregnancy Category D
- For medication
  - All residue within bottle is considered toxic
  - It is discarded in a Stericycle bin (black bin)

Assessment Q5 — Technician

Which of the following techniques can be done to minimize potential filling errors?

A. Match drug name
B. Match drug strength
C. Match drug formulation
D. All of the above

Assessment Response 5 — Technician

Which of the following techniques can be done to minimize potential filling errors?

A. Match drug name
B. Match drug strength
C. Match drug formulation
D. All of the above

Tacrolimus

- Mechanism of Action: calcineurin inhibitor which suppresses cellular immunity by binding to FKBP-12 and calcineurin dependent proteins
- Immunosuppressant used in:
  - Maintenance immunosuppression post-transplant
- Adverse Effects:
  - Hypertension
  - Hyperglycemia
  - Anemia
  - Diarrhea
  - Hyperkalemia
  - Tremor
  - Chronic allograft nephropathy

Considerations of Dosing — Tacrolimus

Geriatric patients are at an increased risk of toxicity due to:

- Various dosage forms
- Hypoalbuminemia
- Nutrition status
- Drug interactions
- Race

Source: Hutchison LC, et al. *Fundamentals of Geriatric Pharmacotherapy.* 2015

Therapeutic Drug Monitoring — Tacrolimus

- Goal levels vary depending on patient risk factors, concomitant immunosuppression and time post-transplant

Why do we monitor levels?

- Prevent acute rejection or graft loss due to suboptimal dosing (< 5 ng/ml)
- Prevent toxicity with supratherapeutic levels (> 20 ng/ml)
- Evaluate efficacy of dose

Source: Scott LJ, et al. *Drugs* 2003;63:1247–97.

Therapeutic Drug Monitoring — Tacrolimus

Post-transplant Month	Trough Tacrolimus Level
First	8-15 ng/ml
Second	6-12 ng/ml
Third and subsequent	4-10 ng/ml

- Trough tacrolimus levels are drawn daily during initiation of therapy
  - Can be monitored less frequently as organ function stabilizes and the time after transplant increases
- Target range for tacrolimus concentrations varies with time after transplantation, the immunosuppressive regimen and the transplant type

Source: Scott LJ, et al. *Drugs* 2003;63:1247–97.

Counseling — Tacrolimus

- It is common to use of multiple doses of Tacrolimus based on drug level
  - Counsel points:
    - Different doses
    - Pill identification

Side Effect	Counseling Point
Tremors	Identification of new/worsening tremors in patients with Parkinsonian-like symptoms
Hyperglycemia	Identification of elevated BG and adjust antidiabetic regimen based on BG readings
Hypertension	Identification of HTN and adjust antihypertensive regimen based on BP readings

Formulations — Tacrolimus

Formulation	Doses	Bioavailability
Extended-release capsule (Astagraf XL)	0.5, 1, 5 mg	12-20%
Extended-release tablets (Envarsus XR)	0.75, 1, 4 mg	30%
Capsules (Prograf)	0.5, 1, 5 mg	17-20%
Granules (Prograf)	0.2, 1 mg	17-20%
Parenteral Injection	5 mg/ml	100%

Source: Tremblay S, et al. *Am J Transplant* 2017;17:432-42.

Disposal — Tacrolimus

Stericycle Hazardous Waste

- Meets ≥ 1 of the NIOSH criteria for a hazardous drug
- Increased risk of lymphomas and other malignancies
- FDA Pregnancy Category C
  - Excreted in breast milk
- For medication
  - All residue within bottle is considered toxic
  - It is discarded in a Stericycle bin (black bin)

Assessment Q6 — Pharmacist

When obtaining levels, what is the goal therapeutic range for tacrolimus?

A. 1-10 ng/mL
B. 5-20 ng/mL
C. 15-30 ng/mL
D. 10-25 ng/mL

Assessment Response 6 — Pharmacist

When obtaining levels, what is the goal therapeutic range for tacrolimus?

A. 1-10 ng/mL
B. 5-20 ng/mL
C. 15-30 ng/mL
D. 10-25 ng/mL

Conclusion

- Narrow therapeutic index medications are defined by small differences in dose or blood concentration leading to potentially serious therapeutic failure and/or adverse drug reactions
- PKPD changes associated with aging puts older adults at increased risk of adverse effects and reduced efficacy of medications
- Therapeutic drug monitoring is done to maintain a constant concentration in a patient's bloodstream
  - Ensure safety and efficacy
- When initiating a geriatric patient on narrow therapeutic index medications:
  - Start at lower doses and titrate up slowly to avoid adverse effects
  - Closely monitor for safety and efficacy
  - Anticipate a therapeutic response at the lower end of the therapeutic range

References

1. Midha K, et al. FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology.
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Thank you!

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