Valproate Case 3: Formulations 2-12-16

Jose de Leon, MD

3.Valproate Case 3

Described in J Clin Psychiatry 2004;65:724-5

http://www.ncbi.nlm.nih.gov/pubmed/15163266

*Pharmacological explanation provided 10 years later in Case Rep Psychiatry 2015;2015:*542862

http://www.ncbi.nlm.nih.gov/pubmed/26000191

Educational Objectives

At the conclusion of this presentation, the participant should be able to:

1. Think about pharmacological principles in the context of polypharmacy
2. Appreciate that for understanding valproate dosing, one must consider
   - 2.1. Pharmacokinetics and pharmacodynamics
   - 2.2. Genetic, environmental and personal variables
3. Understand that formulations influence pharmacokinetics
4. Show familiarity with valproate therapeutic drug monitoring

Abbreviations

- AED: antiepileptic drug
- β-oxidation: beta-oxidation
- C: concentration
- GI: gastrointestinal
- CYP: cytochrome P450
- ER: extended-release
- D: dose
- DDI: drug-drug interaction
- TDM: therapeutic drug monitoring
- UGT: uridine diphosphate glucuronosyltransferase

Definition

- Bioavailability = Biological Availability:
  "The extent to which
  - the active ingredient of a drug dosage form
  - becomes available
    - at the site of drug action or
    - in a biological medium believed to reflect accessibility to a site of action."

http://www.ncbi.nlm.nih.gov/mesh/?term=bioavailability

Warning

- Valproate C/D ratios are:
  - complex
  - non-linear (total C), vary with:
    - C (μg/mL or mg/L) and
    - D (mg/day)

    You can compare them at same Cs.
- Low values:
  - C=100 μg/mL and D=2000 mg/d
  - C/D ratio = 100/2000 = 0.050
  - C/D ratio x 1000 = 50 (easier notation)
- Dr. de Leon is learning about them.

Valproate Case 3

3.1. US Valproate Formulations

3.2. Valproate TDM

3.3. Valproate: Genetic, Environmental and Personal Variables

3.4. Case Description in 2004

3.5. Case Interpretation in 2015

3.6. Formulations in Psychiatry

Valproate Case 3

3.1. US Valproate Formulations
- 3.1.1. Equivalence
- 3.1.2. Half-lives
- 3.1.3. Absorption
- 3.1.4. Intake
- 3.1.5. Price

3.2. Valproate TDM
- 3.2.1. Non-Linear Kinetics
- 3.2.2. Measuring Cs
- 3.2.3. Recommended Cs

3.3. Valproate: Genetic, Environmental and Personal Variables
- 3.3.1. Genetic Variations
- 3.3.2. Environmental Factors
- 3.3.3. Personal Characteristics

3.4. Case Description in 2004

3.5. Case Interpretation in 2015
- 3.5.1. New Pharmacological Knowledge
- 3.5.2. Case Interpretation

3.6. Formulations in Psychiatry
- 3.6.1. Time-Release Formulations

3.1. US Valproate Formulations

3.1. US Valproate Formulations

3.1.1. Equivalence
3.1.2. Half-Lives
3.1.3. Absorption
3.1.4. Intake
3.1.5. Price

3.1.1. Equivalences

3.1.1. Valproate Case 3: Formulation Equivalence

- In the US, the following valproate formulations are considered equivalent:
  - Valproic acid: liquid, capsules or delayed-release capsules.
  - Divalproex sodium sprinkle capsules, delayed-release tablets, enteric-coated and delayed-release tablets.
- Divalproex sodium ER is **NOT** equivalent:
  - designed for once-a-day administration
  - provides 8-20% smaller trough and peak Cs

3.1.1. Valproate Case 3: Formulation Equivalence

- Studies in bipolar patients indicated that to keep the same Cs when changing from other formulations to divalproex sodium-ER, doses need to be increased by:
  - 250-500 mg/day
    http://www.ncbi.nlm.nih.gov/pubmed/17960970
  - 20% http://www.ncbi.nlm.nih.gov/pubmed/12832255

3.0.2. Half-Lives

3.1.2. Valproate Case 3: Half-Lives

	Half-lives in hours	
	ER	Other formulations
Normal	40	12-16
Induced patient	27	6-12

http://www.ncbi.nlm.nih.gov/pubmed/17274675

3.1.2. Valproate Case 3: Half-Lives

- Half-lives inform the clinician of the residual drug amount after discontinuation:
  - after 5 half-lives: 95% has been eliminated
  - after 7 half-lives: 99% has been eliminated
- Half-lives are important for TDM:
  - Rule of 5 half-lives:
    after a dose change, wait at least 5 half-lives to draw TDM.
  - It is safer to wait 7 half-lives.

For a comprehensive discussion of half-lives, see the presentation “Clozapine Case 6 Half-Lives”.

3.1.3. Absorption

3.1.3. Valproate Case 3: Absorption

- Peak Cs in hours:
  - 1-2: conventional formulations
  - 3-6: enteric-coated tablets
  - 10-12: delayed-release tablets

http://www.ncbi.nlm.nih.gov/pubmed/18397299

- ER provides a slow and constant absorption rate over 20 hours

3.1.4. Intake

3.1.4. Valproate Case 3: Intake

- All capsules should be swallowed as a whole and not chewed.
- Divalproex sodium sprinkles can be mixed with food for patients who have swallowing problems.
- Valproic acid solutions, tablets and capsules may cause GI upset. They should be taken with large amounts of water or food.

3.1.5. Price

3.1.5. Valproate Case 3: Price

- In the US, generic forms of valproate are usually cheaper than divalproex sodium (ask your pharmacist).
- In a large study, intolerance was only slightly more frequent in generics than in divalproex sodium. The authors (Wassef et al., 2005) recommend starting with the generic form and changing to the divalproex formulation if intolerance occurs. http://www.ncbi.nlm.nih.gov/pubmed/15677599

3.2. Valproate TDM

3.2. Valproate TDM

3.2.1. Non-Linear Kinetics
3.2.2. Measuring Cs
3.2.3. Recommended Cs

3.2.1. Non-Linear Kinetics

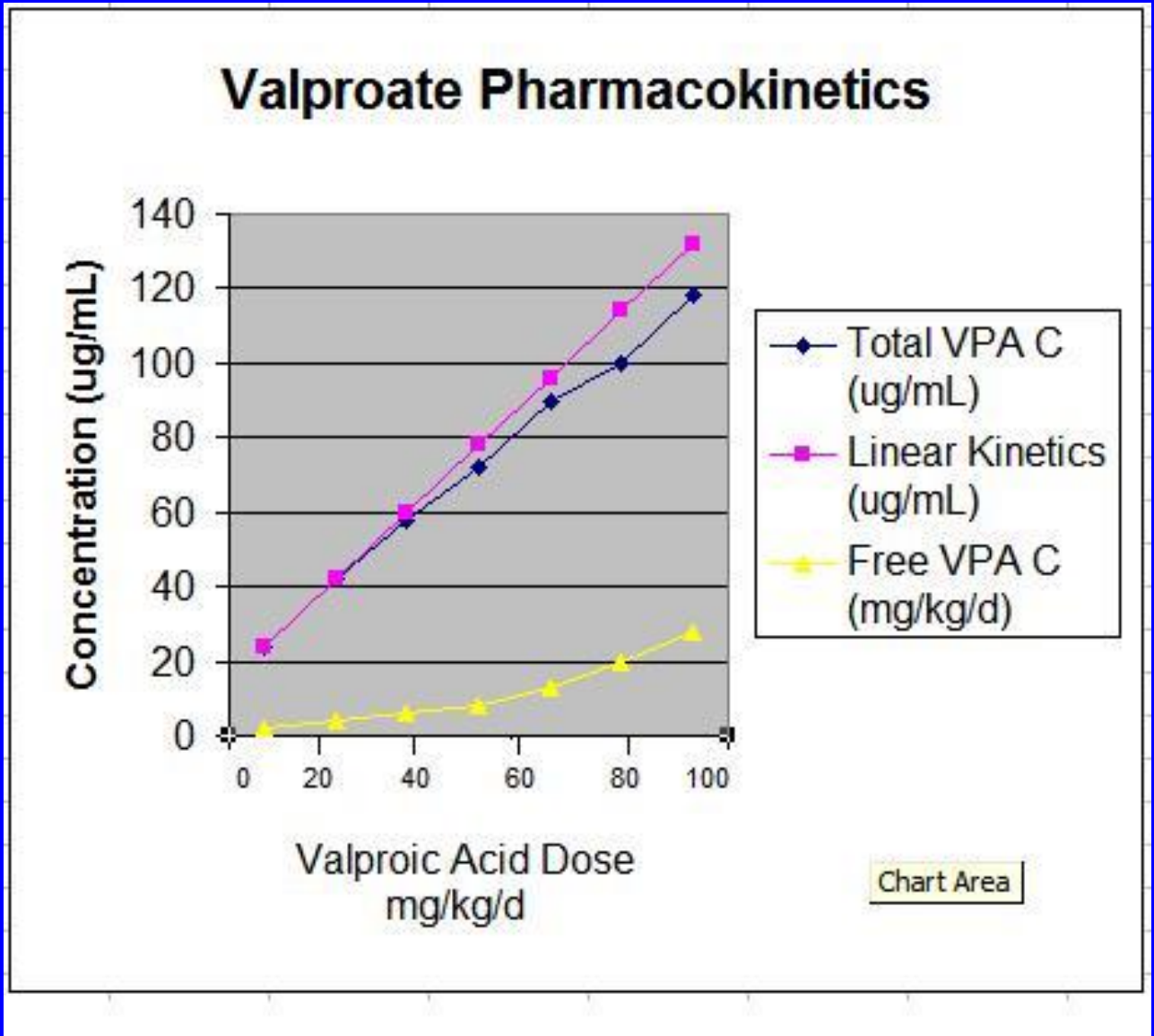
3.2.1. Valproate Case 3: Non-Linear Kinetics

- Total valproate C
  - does not ↑ proportionally with D
  - increases to a lesser extent due to saturable plasma protein binding (next slide: see black line below pink)
- As D ↑:
  - ↑ hepatic clearance due to ↑ free C
  - total C ↑ more slowly
- In therapeutic Cs
  - the free C ↑ in a linear fashion

Next slide: yellow curve from 55 to 100 mg/kg/day is linear.

3.2.1. Valproate Case 3: Non-Linear Kinetics

(modified from Figure 12-2) http://www.amazon.com/Clinical-Pharmacokinetics-Handbook-Larry-Bauer/dp/007142542X/ref=sr_1_6?s=books&ie=UTF8&qid=1291747683&sr=1-6



3.2.2. Measuring Cs

3.2.2. Valproate Case 3: Measuring Cs

- Using formulations that are not ER:
  - Steady state occurs in <5 days after changing dose.
    Highest half-life described: 16 hours,
    steady state: 5 x 16 hours= 80 hours
    = 3.3 days
  - Measure trough Cs in the
    early morning hours before first dose
    around 12 hours after last dose.

3.2.2. Valproate Case 3: Measuring Cs

- In ER formulations: wait >1 week (9 days) after changing dose to measure a C.
  Half-life = 40 hours,
  steady state: 5 x 40 hours=200 hrs or 8.3 days
- To interpret early morning C, consider the dosing pattern:
  - morning dosing:
    early morning C= trough C
  - evening dosing:
    early morning C=1.18-1.25 x trough C.
  - twice-daily dosing:
    early morning C= trough C
    and flatter Cs throughout the day.

3.2.3. Recommended Cs

3.2.3. Valproate Case 3: Recommended Cs

- Epilepsy: 50-100 µg/ml
  http://www.ncbi.nlm.nih.gov/pubmed/18397299
- Mania:
  - 45-125 µg/ml http://www.amazon.com/American-Psychiatric-Publishing-Psychopharmacology-Schatzberg/dp/1585623091/ref=sr_1_1?ie=UTF8&s=books&qid=1278966588&sr=1-1 Chapter by Bowden
  - 50-125 µg/ml
    http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=18697#nlm34068-7
  - 85-125 µg/ml http://www.amazon.com/Lexi-Comps-Drug-Information-Handbook-2010-2011/dp/1591952786/ref=sr_1_1?ie=UTF8&s=books&qid=1278707410&sr=1-1
  - Best: >94 µg/ml in a recent study
    http://www.ncbi.nlm.nih.gov/pubmed/16449481
- Other disorders: limited information

3.3. Valproate: Genetic, Environmental and Personal Variables

3.2. Genetic, Environmental and Personal Variables

3.2.1. Genetic Variations
3.2.2. Environmental Factors
3.2.3. Personal Characteristics

3.2.1. Valproate: Genetic Variations

3.2.1. Valproate Pharmacokinetics: Genetic Variations

3.2.1.1. Pharmacokinetic Gene Variations
3.2.1.2. Pharmacodynamic Gene Variations

3.2.1.1. Pharmacokinetic Gene Variations

3.3.1.1. Valproate Case 3: Pharmacokinetic Genes

- Too many metabolic enzymes:
  - glucuronidation by UGTs: more important in therapeutic Cs.
  - β-oxidation: more important in low Cs.
  - CYPs: minor
- Dr. de Leon described 3 patients (this one and 2 more) needing very high doses to get therapeutic Cs. They may be very sensitive to valproate auto-induction for genetic reasons.

http://www.ncbi.nlm.nih.gov/pubmed/26000191

3.2.1.2. Pharmacodynamic Gene Variations

3.3.1.1. Valproate Case 3: Pharmacodynamic Genes

- Pharmacodynamic genes have been associated with drug response in bipolar disorder:
  - in some studies
  - not in others

  Dr. de Leon believes that pharmacodynamic genes are not ready for clinical practice.

3.3.2. Valproate: Environmental Factors

3.3.2. Valproate: Environmental Factors

3.3.2.1. Pharmacokinetic DDIs

3.3.2.2. Pharmacodynamic DDIs

3.3.2.3. Complex DDIs

3.3.2.1. Pharmacokinetic DDIs

3.3.2.1. Pharmacokinetic DDIs

3.3.2.1.1. Inducers
3.3.2.1.2. Inhibitors

3.3.2.1.1. Inducer Effects on Valproate

3.3.2.1.1. Valproate Case 3: Inducers

- Rifampicin: UGT inducer
- AED inducers are UGT inducers, including
  - phenobarbital and primidone
- Mild AED inducers are mild UGT inducers:
  - lamotrigine, and oxcarbazepine

  They may not be clinically-relevant inducers.
- Ethinyl estradiol (oral contraceptives) is a valproate inducer via UGT induction.
- Carbanapem antibiotics:
  - major ↑ in valproate metabolism
  - induces by mechanisms not well understood

3.3.2.1.2. Inhibitors' Effects on Valproate

3.3.2.1.2. Valproate Case 3: Inhibitors

- Aspirin:
  - inhibits the β-oxidation pathway:
    ↑ total valproate C
  - displaces valproate from albumin:
    ↑ free valproate C
  - explains the high valproate C/D ratio in this case
- Felbamate:
  - inhibits the β-oxidation pathway
- Fluoxetine:
  - is a moderate inhibitor of CYP2C9

  It is possible that fluvoxamine has similar effects.

3.3.2.2. Pharmacodynamic DDIs

3.3.2.2. Valproate Case 3: Pharmacodynamic DDIs

- ↑ sedation by combining valproate with sedating:
  - drugs or
  - herbs
- Combining valproate with lithium may:
  - ↑ response in bipolar disorder and
  - ↑ neurotoxicity.
- Combining valproate with clonazepam may cause absence seizures.
- Additive weight gain effects by adding valproate to:
  - most antipsychotics
  - some antidepressants: TCAs
    mirtazapine
    paroxetine
  - lithium

3.3.2.3. Complex DDIs

3.3.2.3. Complex DDIs

3.3.2.3.1. Valproate-Carbamazepine DDI
3.3.2.3.2. Valproate-Topiramate DDI
3.3.2.3.3. Valproate-Phenytoin DDI

3.2.2.3.1. Valproate-Carbamazepine DDI

3.3.2.3.1. Valproate Case 3: Carbamazepine DDI

- Be very careful with this combination.
- It is safer to measure free Cs of both drugs.
- As a general rule,
  - use higher valproate Ds and
  - lower carbamazepine Ds.

http://www.amazon.com/American-Psychiatric-Publishing-Psychopharmacology-Schatzberg/dp/1585623091/ref=sr_1_1?ie=UTF8&s=books&qid=1278966588&sr=1-1 Chapter by Ketter et al.

3.3.2.3.1. Valproate Case 3: Carbamazepine DDI

- Pharmacokinetic DDIs:
  - Carbamazepine on valproate: mixed
    - ↓ total C (induction)
    - ↑ free C (competing for protein binding)
  - Valproate on carbamazepine: more toxicity
    - ↑ total C (inhibition)
    - ↑ free C (competing for protein binding)

3.3.2.3.1. Valproate Case 3: Carbamazepine DDI

- Pharmacodynamic DDIs are poorly understood.
  - Efficacy as an AED:
    - Carbamazepine blockades of voltage-gated sodium channels, and
    - Valproate have complex anti-convulsant effects.
  - Efficacy as a mood stabilizer:
    Possible additive effects by acting at the intracellular signaling system.
  - Safety:
    Textbooks usually report increased risk for neurological ADRs.

3.2.2.3.2. Valproate-Topiramate DDI

3.3.2.3.2. Valproate Case 3: Topiramate DDI

- Be very careful with this combination.
- Monitor closely:
  - Valproate C
  - ADRs

3.3.2.3.2. Valproate Case 3: Topiramate DDI

- Pharmacokinetic DDIs:
  - Topiramate effects on valproate Cs vary with topiramate Ds:
    - low Ds: ↓ valproate Cs (β-oxidation induction)
    - high Ds: ↑ valproate Cs (UGT inhibition)
  - Valproate effects on topiramate are not relevant.

3.3.2.3.2. Valproate Case 3: Topiramate DDI

- Pharmacodynamic DDIs:
  - Efficacy as AEDs: it is unknown whether combinations are more efficacious or not.
  - Safety in all patients:
    - ↑ risk of sedation: probably additive
    - weight: ↓ by topiramate & ↑ by valproate
  - Rare ADRs: this combination is associated with:
    - hypothermia
    - ↑ risk of hyperammonemia and hepatic encephalopathy

3.2.2.3.3. Valproate-Phenytoin DDI

3.3.2.3.3. Valproate Case 3: Phenytoin DDI

- Be very careful with this combination.
- Measure free Cs of both drugs.

3.3.2.3.3. Valproate Case 3: Phenytoin DDI

- Pharmacokinetic DDI:
  - Phenytoin on valproate: more toxicity
    - ↓ total C (induction)
    - ↑ free C (competing for protein binding)
  - Valproate on phenytoin: mixed
    - ↑ total C (inhibition)
    - ↑ free C (protein)
- AED pharmacodynamics: poorly understood

3.3.3. Valproate: Personal Characteristics

3.3.3. Valproate Case 3: Personal Factors

- Personal Factors: no well-understood
  - Hepatic impairment:
    - measuring free C are recommended
  - Renal impairment:
    - if low albumin: free C are recommended
  - Elderly condition:
    - lower initial D
    - consider free C: albumin may be low
  - ↓ food or fluid intake
    or excessive somnolence:
    - consider ↓ D or discontinuation
    (according to prescribing information)

3.4. Case Description in 2004

3.4. Case Description in 2004

The patient was followed > 4 years

AP treatment was first quetiapine,

second olanzapine and

third clozapine.

He arrived with 4 AEDs but was switched to only valproate, co-prescribed with antipsychotics.

<u>The same patient is used in several presentations:</u>

Quetiapine Case 2: Therapeutic Drug Monitoring

Quetiapine Case 3: Akathisia

Clozapine Case 2: Infection

Valproate Case 3: Formulation

3.4. Valproate Case 3: 2004

http://www.ncbi.nlm.nih.gov/pubmed/15163266

- The patient is a 34 yo Caucasian ♂ with schizophrenia.
- After 1 year on clozapine, he was doing very well and was being considered for discharge.
- He had no seizures and was stable on 5250 mg/d of valproic acid concentrate for 3 ½ years. Almost all levels have been 60-90 mg/L (one was > 100 mg/L).
- He began to complain about the valproate concentrate taste (a sign of ↓ in negative symptoms and disorganization).

3.4. Valproate Case 3: 2004

- Other medications:
  - Clozapine: 700 mg/day
  - Propranolol: 80 mg/day; used for akathisia
  - Benztropine: 1 mg/d was started for tremor and may help hypersalivation.
  - Docusate sodium: 250 mg/d for constipation

3.4. Valproate Case 3: 2004

- Recent valproate Cs=70-90 mg/dL.
- It was assumed that valproic acid concentrate and divalproex sodium are bioequivalent.
- Thus, the patient was converted
  - from valproic acid, 5250 mg/day
  - to divalproex sodium, 5250 mg/day

3.4. Valproate Case 3: 2004

Formulation	VPA D mg/day	VPA C mg/L
Concentrate	5250	70
Concentrate	5250	90
Divalproex	5250	145 (for 4 wks) (mild drowsiness)
Divalproex	3750	135
Divalproex	3000	127
Divalproex	2500	120
Divalproex	2000	70
Divalproex	2000	90

3.4. Valproate Case 3: 2004

- To get therapeutic valproate Cs:
  - valproic acid concentrate: 5250 mg/day
  - divaproex sodium: 2000 mg/day
- What this means for bioavailability:

	valproic acid concentrate	divalproex sodium
2-3 times	lower	higher

3.4. Valproate Case 3: 2004

What was the explanation?

3.4. Valproate Case 3: 2004

What was the explanation?

Dr. de Leon had no idea in 2004.

3.4. Valproate Case 3: 2004

- Divalproex **sodium** tablets are a delayed-release formulation comprised of sodium valproate and valproic acid in a 1:1 molar relationship.
- The drug manufacturer recommends the same D when switching.

3.4. Valproate Case 3: 2004

- One study suggested that switching from divalproex sodium to valproic acid resulted in ↓ Cs by 14%.
- This ↓ was considered irrelevant from the clinical point of view.

http://www.ncbi.nlm.nih.gov/pubmed/9779912

3.4. Valproate Case 3: 2004

Please remember always
that our
pharmacological understanding
is limited
even for well-studied drugs
such as valproate.

3.5. Case Interpretation in 2015

3.5. Case Interpretation in 2015

3.5.1. New Pharmacological Knowledge
3.5.2. Case Interpretation

3.5.1. New Pharmacological Knowledge

3.5.1. Valproate Case 3: New Knowledge

- Dr. de Leon has concluded that valproate is a mild inducer.
- Mild inducers:
  - can be obscured by their inhibitory properties,
  - may only be present in high doses, and
  - require even longer (months) to reach maximum effects or disappear.

http://www.ncbi.nlm.nih.gov/pubmed/25745819

See the presentation “Induction by Antiepileptic Drugs An Update for Clinicians”.

3.5.1. Valproate Case 3: New Knowledge

- Two other patients needed progressively higher valproate Ds to get therapeutic Cs. All three patients had low valproate C/D ratios multiplied by 1000.

http://www.ncbi.nlm.nih.gov/pubmed/26000191

3.5.1. Valproate Case 3: New Knowledge

- Case 2 (8 therapeutic valproate Cs):
  - D: ● initial: 1,500 mg/day
    ● discharge: 4,000 mg/day
  - Low C/D ratio x 1000: mean = 24
    range =17-33
- Case 3 (70 therapeutic Cs):
  - D: ● initial: 3,375 mg/day
    ● end: 10,500 mg/day
  - Low C/D ratio x 1000: mean = 9
    range = 5-18

3.5.2. Case Interpretation

3.5.2. Valproate Case 3: Interpretation

Formulation	VPA D mg/day	VPA C mg/L	C/D Ratio (x1000)
Concentrate	5250	70	0.013 (13)
Concentrate	5250	90	0.017 (17)
Divalproex	5250	145 (4 wks) (mild drowsiness)	0.028 (28)
Divalproex	3750	135	0.036 (36)
Divalproex	3000	127	0.042 (42)
Divalproex	2500	120	0.048 (48)
Divalproex	2000	70	0.035 (35)
Divalproex	2000	90	0.045 (45)

3.5.2. Valproate Case 3: Interpretation

- The C/D ratio x 1000:

	Valproic acid concentrate	Divalproex sodium
N	44	7
Mean	17	39
Range	10-21	28-48

According to an independent sample t-test calculated with equal variance not assumed, there was significant difference (t = −9.6; df = 6.3, p < 0.001).

3.5.2. Valproate Case 3: Interpretation

- Metabolic capacity:
  - higher in valproic acid concentrate
- D:
  - high in valproic acid concentrate 5,250 mg/day, and
  - average in divalproex sodium 2,000 mg/day.
- C/D ratios x 1000:
  - low in valproic acid concentrate: 10-21
  - normal in divalproex sodium: 28-48

3.5.2. Valproate Case 3: Interpretation

- This patient (case 1 of 3) has:
  - High metabolic capacity:
    - in a way similar to 2 other patients who show valproate auto-induction. Unusual genes may make them particularly sensitive to auto-induction.
    - in a way that is different from 2 other patients: auto-induction occurred in only one formulation.
- No explanation is known concerning why in this patient it occurred in only one formulation. Hypothesis: peculiar genetic variation

3.6. Formulations in Psychiatry

This is a short review based on an article by Andrade

J Clin Psychiatry 2004;65:724-5

http://www.ncbi.nlm.nih.gov/pubmed/26335096

3.6. Valproate Case 3: Formulations in Psychiatry

- The formulation of pills and capsules is classified according to release time:
  - Most are immediate-release; they release contents within minutes of ingestion.
  - Some are time-release formulations: they release contents
    - after a time lag, or
    - a little at a time, or
    - in some other predetermined way.

3.6. Formulations in Psychiatry

3.6.1. Time-Release Formulations

3.6.1. Time-Release Formulations

3.6.1. Time-Release Formulations

3.6.1.1. Goals

3.6.1.2. Advantages and Disadvantages

3.6.1.1. Time-Release Formulations: Goals

3.6.1.1. Valproate Case 3: Time-Release Formulation: Goals

- Goals of time-release formulations:
  - ↓ ADRs:
    - locally at GI tract (absorption site)
    - associated with peak Cs
  - ↑ half-life artificially

3.6.1.2. Time-Release Formulations: Advantages and Disadvantages

3.6.1.1. Valproate Case 3: Time-Release Advantages & Disadvantages

- Advantages of time-release formulations:
  - ↑ convenience of dosing & compliance
  - ↓ fluctuation in serum Cs throughout the day
- Disadvantages:
  - incomplete absorption may occur with intestinal speed changes that are:
    - acute, such as gastroenteritis, or
    - chronic, such as irritable bowel syndrome
  - greater expense

Questions

- Please review the 10 questions on the pdf entitled "Questions on the Presentation Valproate Case 3 Formulations".
- You will find the answers on the last slide after the "Thank you" slide. No peeking until you have answered all the questions.
- If you did not answer all the questions correctly, please review the PowerPoint presentation again to reinforce the pharmacological concepts.

Thank you

Answers

1. B
2. D
3. D
4. B
5. D
6. D
7. A
8. A
9. A
10. A