Valproate Case 1: Pharmacokinetics 2-12-16

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1. Valproate Case 1

J Clin Psychopharmacology 2009;29:509-11

http://www.ncbi.nlm.nih.gov/pubmed/19745660

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 safety, one must consider
   - 2.1. Personal, environmental and genetic factors
   - 2.2. Pharmacodynamics and pharmacokinetics
3. Show familiarity with other issues beyond the usual valproate therapeutic drug monitoring (to encourage original thinking, this objective will be fully disclosed at the end).

Abbreviations

- AED: antiepileptic drug
- C: concentration

  Valproate units: μg/mL (or mg/L)

  μ (micro) is 10^{-6}

  n (nano) is 10^{-9}
- CYP: cytochrome P450
- D: dose
- DDI: drug-drug interaction
- TDM: therapeutic drug monitoring
- UGT: uridine diphosphate glucuronosyltransferase

Warning

- Valproate C/D ratios:
  - were not used in the publication of this case and were first added to Dr. de Leon's articles in 2015.
  - are complex and non-linear. They vary with:
    - C, and
    - D.
  - are introduced at the end of this presentation.

Valproate Case 1

1.0. Introduction

1.1. Valproate Pharmacology

1.2. Case

1.3. Beyond Total Valproate Cs

1.4. Outcome

1.5. Valproate C/D Ratios

Valproate Case 1

1.0. Introduction

1.1. Valproate Pharmacology

1.1.1. Pharmacokinetics

1.1.2. Pharmacodynamics

1.2. Case

1.3. Beyond Total Valproate Cs

To encourage original thinking, subsections will be described at the end.

1.4. Outcome

1.4.1. Symptom Resolution

1.4.2. Final Explanation

1.5. Valproate C/D Ratios

1.5.1. Calculating Patient's C/D Ratio

1.5.2. High Valproate C/D Ratio

1.5.3. Effect of Other Drugs on Valproate

1.5.4. Conclusion

1.0. Introduction

1.0. Valproate Case 1: Introduction

- A 59-year-old Caucasian ♀:
  - Weight: 71.1 Kg (157 lbs)
  - Psychiatric diagnoses:
    - moderate mental retardation
    - schizoaffective disorder
  - Psychiatric diagnoses:
    - history of seizures
    - hypertension
    - diabetes mellitus Type 2
    - hypercholesterolemia
    - hypothyroidism

1.0. Valproate Case 1: Introduction

- As she had not had a recent seizure,
  - a neurologist recommended that 800 mg/day of carbamazepine be discontinued by tapering off for 2 months.
  - 1 ½ months after complete discontinuation, she had a seizure.

1.0. Valproate Case 1: Introduction

- After the seizure, she was started on divalproex sodium 1000 mg/day (500 mg twice a day) enteric-coated formulation in order to:
  - control seizures, and
  - possibly have a positive effect on the schizoaffective disorder.

1.1. Valproate Pharmacology

1.1. Valproate Case 1: Pharmacology

What do you know about the pharmacology of valproate?

1.1. Valproate Pharmacology

1.1.1. Pharmacokinetics
1.1.2. Pharmacodynamics

1.1.1. Valproate Pharmacokinetics

1.1.1. Valproate Case 1: Pharmacokinetics

What do you know about the pharmacokinetics of valproate?

1.1.1. Valproate Pharmacokinetics

1.1.1.1. Metabolism

1.1.1.2. DDI: Effects on Other Drugs

(DDI: Effects of Other Drugs On Valproate will be described in Section 1.4)

1.1.1.1. Valproate Metabolism

1.1.1.1. Case 1: Valproate Metabolism

- Complex metabolism:
  - UGTs
    - Hepatic (& intestinal): UGT1A3, UGT1A4, UGT1A6, UGT1A9 & UGT2B7
    - Intestinal: UGT1A8 and UGT1A10
  - β-oxidation as a fatty acid
    This is a mitochondrial enzyme.
  - CYPs: CYP2C9, CYP2C19 and CYP2A6
    small component
- It changes according to D:
  - In low Ds: β-oxidation is most important.
  - In therapeutic Ds: UGT is most important.

1.1.1.1. Case 1: Valproate Metabolism

- Auto-induction (not well-studied):
  - By UGTs in rats
  - β-oxidation in human volunteers
  - In Dr. de Leon's experience, some individuals are very sensitive.

    (See the presentation on Valproate Case 3 Formulation.)

1.1.1.1. Case 1: Valproate Metabolism

- Remember:

  Valproate metabolism is complex.

Doses:	Low	Therapeutic
β-oxidation	Most important	Second
UGTs	Second	First
CYPs	Minor	Minor

1.1.1.2. Valproate DDI: Effects on Other Drugs

1.1.1.2. Case 1: DDI Effects on Other Drugs

- Valproate is traditionally considered an inhibitor of:
  - CYP2C9: phenytoin
  - epoxide hydroxylase: carbamazepine
  - several UGTs: lamotrigine and lorazepam
  - N-glucosidation: phenobarbital
  - unknown mechanism: TCAs
  - unknown mechanism: paliperidone

1.1.1.2. Case 1: DDI Effects on Other Drugs

- Valproate may be an inducer of:
  - its own metabolism in some individuals
  - irinotecan (UGT1A1)
  - aripiprazole
  - vitamin D (in vitro study)

    This may explain why valproate can cause osteoporosis.
  - clozapine/olanzapine:
    - concentration-related
    - possibly influenced by smoking
    - confounded by competitive inhibition, so the net effect may be inhibition or induction.

1.1.1.2. Case 1: DDI Effects on Other Drugs

- Remember: VPA can be
  - an auto-inducer (replication needed), and
  - an inducer of other drugs:
    - olanzapine, and
    - clozapine.

1.1.2. Valproate Pharmacodynamics

1.1.2. Valproate Case 1: Pharmacodynamics

What do you know about the pharmacodynamics of valproate?

1.1.2. Valproate Case 1: Pharmacodynamics

- Pharmacodynamics:
  - an AED and
  - a mood stabilizer

http://www.ncbi.nlm.nih.gov/pubmed/25196459

1.1.2. Valproate Case 1: Pharmacodynamics

- AED with complex actions:
  - ↑ GABA neurotransmission

1.1.2. Valproate Case 1: Pharmacodynamics

- Antimanic and possibly a mood stabilizer
- Mechanism: not well-understood

  Hypothesized: at intracellular signaling system (inositol signaling)

  It is probably the same mechanism for:
  - lithium
  - carbamazepine
- Be careful: it may have pharmacodynamic additive effects with lithium and carbamazepine:
  - may ↑ the efficacy of the combination, but
  - may also ↓ the safety.

1.2. Case

1.2. Valproate Case 1: Case

- For almost two months:
  - confusion
  - dizziness
  - lethargy
  - hand tremor
  - incoherent speech

1.2. Valproate Case 1: Case

Confusion, dizziness, lethargy, hand tremor, and incoherent speech are signs of…?

1.2. Valproate Case 1: Case

Confusion, dizziness, lethargy, hand tremor, and incoherent speech are signs of…?

Drug toxicity.

1.2. Valproate Case 1: Case

Valproate was the most recently added drug.

How do we rule out valproate toxicity?

1.2. Valproate Case 1: Case

Valproate was the most recently added drug.

How do we rule out valproate toxicity?

By TDM.

In epilepsy, serum valproate Cs of 50-125 μg/mL are recommended.

1.2. Valproate Case 1: Case

Day	VPA D mg/day	VPA C μg/mL (50-125)	Toxicity
1	1000		
7	1000	112	
13	1000		Confused & dizzy
14	750		
17	750		Lethargic & incoherent
21	750	87	
22	500		
33	500	66	
47-53	500		Hand tremors
56	500	64	Hand tremors

1.2. Valproate Case 1: Case

Valproate Cs were not at toxic levels.

Can we rule out a valproate intoxication?

1.2. Valproate Case 1: Case

Valproate Cs were not at toxic levels.

Can we rule out a valproate intoxication?

No.

1.2. Valproate Case 1: Case

Might valproate intoxication occur at a low D of 500 mg/day and a low C of 64 μg/ml?

1.2. Valproate Case 1: Case

Might valproate intoxication occur at a low D of 500 mg/day and a low C of 64 μg/ml?

Yes, it is possible.

1.2. Valproate Case 1: Case

How is it possible?

1.3. Beyond Total Valproate Cs

1.3. Beyond Total Valproate Cs

1.3.1. Protein Binding
1.3.2. Free Valproate Cs
1.3.3. Aspirin’s Contribution
1.3.4. Other Contributing Factors

1.3.1. Protein Binding

1.3.1. Valproate Case 1: Protein Binding

- Valproate is highly protein-bound:
  - low doses: >90%
  - high doses: lower
- Valproate total C
  - does not follow linear kinetics
  - and this is due to saturation of the protein binding.

1.3.1. Valproate Case 1: Protein Binding

- Valproate protein binding is influenced by albumin Cs which are ↓ with:
  http://www.ncbi.nlm.nih.gov/pubmed/17074939
  - female sex
  - elderly age
  - illnesses
- Valproate can be displaced from proteins by:
  - endogenous compounds:
    - hyperlipidemia
    - uremia or high creatinine Cs
    - high bilirubin
  - exogenous compounds: co-medications

1.3.1. Valproate Case 1: Protein Binding

- Drugs that can displace valproate (are other highly protein-bound drugs):
  - AEDs:
    - phenytoin
    - carbamazepine
  - NSAIDs, including:
    - fenoprofen
    - ibuprofen
    - mefanic acid
    - naproxen
    - tomeltin
  - Aspirin: important DDI with valproate

1.3.1. Valproate Case 1: Protein Binding

- Be very careful with a phenytoin-valproate combination:
  - Pharmacokinetics:
    - Phenytoin on valproate: ↓ total C (induction)
      ↑ free C (protein binding)

      Global effects on phenytoin: unclear
    - Valproate on phenytoin: ↑ total C (inhibition)
      ↑ free C (protein binding)

      Global effects on valproate: ↑ toxicity
  - Pharmacodynamics: poorly understood

1.3. Valproate Case 1: Protein Binding

- Aspirin DDI with valproate:
  - aspirin can inhibit the β-oxidation pathway:
    ↑ total valproate C.
  - aspirin can displace valproate from albumin:
    ↑ free valproate C.

1.3.2. Free Valproate Cs

1.3.2. Valproate Case 1: Free Valproate

- Fractions:
  - free valproate: active fraction
  - bound valproate: the inactive fraction

- Total valproate C
  may not reflect free valproate C well.
  Free valproate Cs are influenced by the Cs of:
  - total valproate,
  - plasma protein, and
  - other products binding to the proteins.

1.3.2. Valproate Case 1: Free Valproate

What do you mean by “free valproate is the active fraction?”

1.3.2. Valproate Case 1: Free Valproate

- Free valproate is the active fraction for:
  - pharmacodynamics:
    - efficacy, and
    - safety
  - pharmacokinetics:
    - inhibition of drug metabolism, and
    - induction of drug metabolism

1.3.2. Valproate Case 1: Free Valproate

- The total valproate and, more importantly, the bound valproate may be the important fraction for:
  - competing with other drugs for serum proteins.

1.3.2. Valproate Case 1: Free Valproate Cs

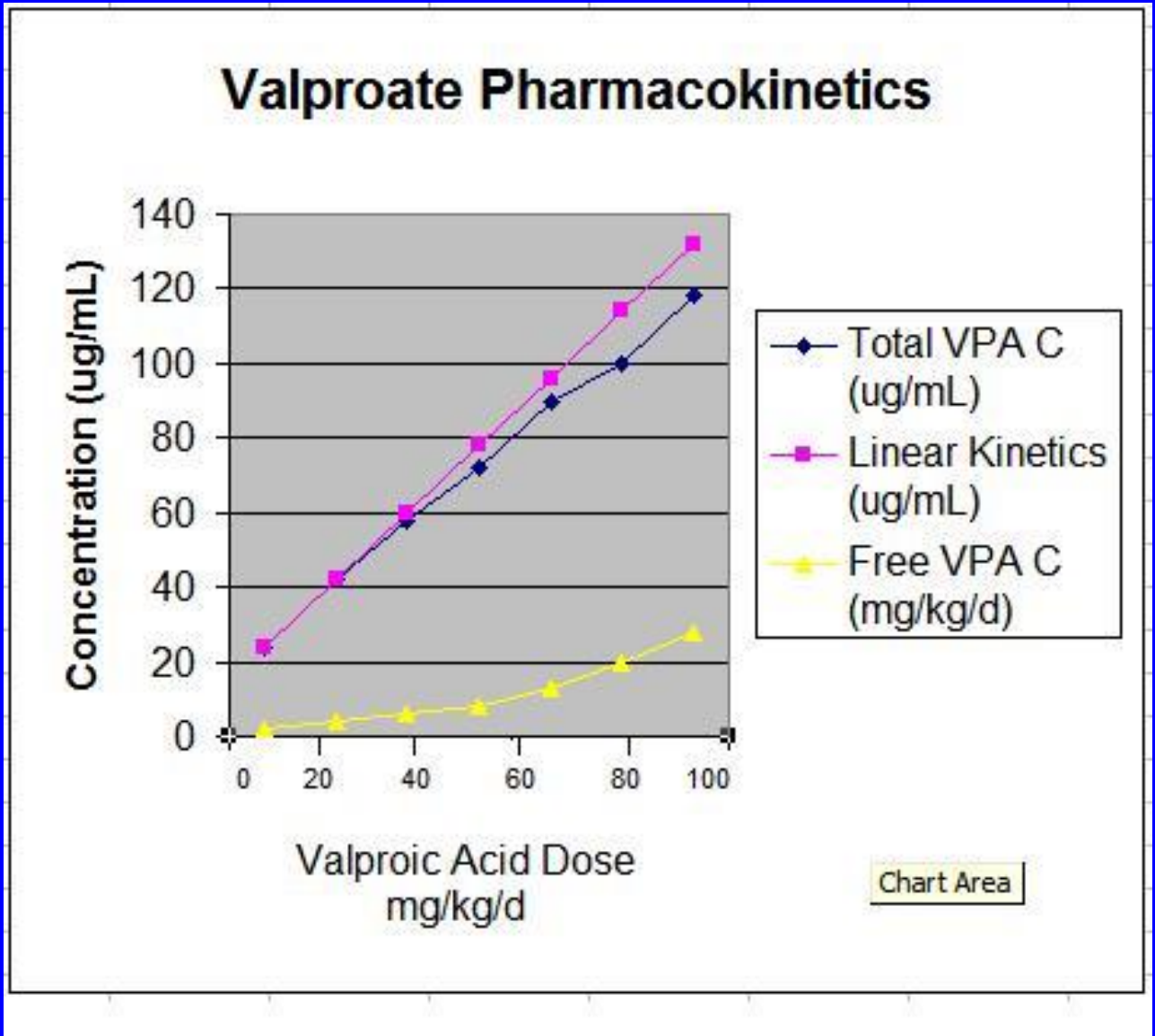
Day	VPA D mg/day	Total C μg/mL (50-125)	Free C μg/mL (4-12)	Toxicity
1	1000			
7	1000	112		
13	1000			Confused & dizzy
14	750			
17	750			Lethargic & incoherent
21	750	87		
22	500			
33	500	66		
47-53	500			Hand tremors
56	500	64	13.1	Hand tremors

1.3.2. Valproate Case 1: Free Valproate Cs

- Toxicity was present at:
  - low Ds (500 mg/day) and
  - low total valproate C: in the 60s µg/mL
  - but high free valproate C: 13.1 µg/mL (4-12 µg/mL is recommended)
- Pay attention to the next figure:
  - 3 curves:
    - black: total valproate C in reality
    - pink: ideal total valproate Cs if they follow a linear relationship with D
    - yellow: free valproate C in reality; There is a linear relationship with D from D range=50-100 mg/kg/d

1.3.2. Valproate Case 1: Free Valproate Cs (modified from textbook 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



1.3.2. Valproate Case 1: Free Valproate C

Can you estimate the free valproate C at day 7 using the day 56 free valproate C?

1.3.2. Valproate Case 1: Free Valproate C

Can you estimate the
free valproate C at day 7
using the
day 56 free valproate C?

Yes,
using linear kinetics.

1.3.2. Valproate Case 1: Beyond Total Cs

- We do not have the prior free valproate Cs:
  - day 7 valproate D =1000 mg/day;
    the D is twice that at day 56 (500 mg/day)
  - day 56 valproate C would have been twice as high: around 26.2 μg/mL (2 x 13.1 μg/mL)

1.3.2. Valproate Case 1: Free Valproate Cs

Day	VPA D mg/day	Total C μg/mL (50-125)	Free C (4-12)	Estimations
7	1000	112		26.2 (2 x 13.1)
56	500	64	13.1	Half D Close to half total C

1.3.2. Valproate Case 1: Free Valproate Cs

- Be careful about competition for protein binding: serum total C is the important value.
- Comparing risperidone and valproate units:
  - risperidone C: in ng/mL
  - valproate C: in μg/mL (1000 times higher)

- Risperidone protein binding may NOT be relevant for valproate protein binding. The Cs are much lower than valproate.

1.3.3. Aspirin’s Contribution

1.3.3. Valproate Case 1: Aspirin

- Very low aspirin D (81 mg/day) may contribute to this DDI and to valproate toxicity.
- Dr. de Leon has seen other valproate DDIs with this low aspirin D. See the presentation on Clozapine Case 5: High Doses.
- Other contributing factors:
  - mild hypoalbuminemia
  - polypharmacy

1.3.4. Other Contributing Factors

1.3.4. Valproate Case 1: Other Factors

- Mild hypoalbuminemia:
  - albumin C = 3.4 g/dl (recommended range is 3.5-5.0)
  - mild hypoalbuminemia may modestly ↑ free valproate C.

1.3.4. Valproate Case 1: Other Factors

- Polypharmacy:

  At first, the patient took 11 other medications.

  5 have high protein binding properties:
  - 99% for simvastatin (10 mg/day)
  - 92-99% for glipizide (10 mg/day)
  - 90-96% for bromocriptine (5 mg/day)
  - 77-90% for risperidone (2 mg/day)
  - 68% for hydrochlorothiazide (50 mg/day)

1.3.4. Valproate Case 1: Other Factors

- Polypharmacy:
  When the free valproate C was measured, the patient was still taking 3 medications with high protein binding:
  - 10 mg/day of simvastatin
  - 10 mg/day of glipizide
  - 5 mg/day of bromocriptine

1.4. Outcome

1.4. Outcome

1.4.1. Symptom Resolution

1.4.2. Final Explanation

1.4.1. Symptom Resolution

1.4.1. Valproate Case 1: Resolution

- Valproate was replaced with carbamazepine.
- This was associated with the disappearance of the symptoms.

1.4.2. Final Explanation

1.4.2. Valproate Case 1: Explanation

Might valproate intoxication explain this case?

1.4.2. Valproate Case 1: Explanation

Might valproate intoxication explain this case?

Probably, yes.

1.4.2. Valproate Case 1: Explanation

- Factors supporting valproate intoxication:
  - The signs were typical.
  - The signs disappeared after changing to carbamazepine.
  - Free valproate C was high: 13.1 µg/ml.
  - The aspirin-valproate DDI had been previously described.

1.4.2 Valproate Case 1: Explanation

- This case suggests that even very low aspirin D may contribute to ↑ free valproate Cs.
- This conclusion is limited by:
  - the case report design and
  - the lack of free valproate Cs during the highest valproate total Cs.

1.4.2. Valproate Case 1: Explanation

- Most importantly, remember, if:
  - unexpected neurological toxicity is associated with valproate treatment, and
  - total valproate Cs are normal,
  - you must measure free valproate Cs.

1.5. Valproate C/D Ratio

1.5. Valproate C/D Ratio

1.5.1. Calculating Patient's C/D Ratio
1.5.2. High Valproate C/D Ratio
1.5.3. Effect of Other Drugs on Valproate
1.5.4. Conclusion

1.5.1. Calculating Patient's C/D Ratio

1.5.1. Valproate Case 1: Patient's C/D Ratio

Remember, you calculate C/D Ratios by dividing drug serum C by D.

1.5.1. Valproate Case 1: Patient's C/D Ratio

- Dr. de Leon does not pay attention to units for C/D ratios. These ratios are practical tools for clinicians.
- Valproate C/D ratio values are very low (<0.2)
- Dr. de Leon recommends using values x 1000 C/D.

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

1.5.1. Valproate Case 1: Patient's C/D Ratio

Day	VPA D mg/day	Total C μg/mL	C/D ratio	1000 x CD ratio
1	1000			
7	1000	112	0.112 (112/1000)	112
13	1000			
14	750			
17	750			
21	750	87	0.116 (87/750)	116
22	500			
23	500	66	0.132 (66/500)	132
47-53	500			
56	500	64	0.128 (64/500)	128

1.5.1. Valproate Case 1: Patient's C/D Ratio

- In this patient:
  - the 1000 x C/D ratios: 112-132
- These are high values.
  Another way of describing this fact:
  This patient had:
  - therapeutic C>50μg/mL with
  - low valproate D=500 mg/day

1.5.2. High Valproate C/D Ratio

1.5.2. Valproate Case 1: High C/D Ratio

The patient had high valproate C/D ratios, which are a sign of poor metabolism.

1.5.2. Valproate Case 1: High C/D Ratio

How can you explain poor metabolism of a drug?

1.5.2. Valproate Case 1: High C/D Ratio

How can you explain poor metabolism of a drug?

By 1) genetic,
2) personal, or
3) environmental factors.

1.5.2. Valproate Case 1: High C/D Ratio

- Genetic factors:
  - valproate metabolism: complex
  - genetic variants influencing valproate D: poorly understood

Currently, clinicians only need to remember that genetic variations influence valproate D, but they are not ready for clinical use.

1.5.2. Valproate Case 1: High C/D Ratio

- Personal factors: http://www.ncbi.nlm.nih.gov/pubmed/24122696
  - renal impairment: not studied
    - renal elimination: limited (<5% of valproate is unmodified in urine)
    - measure free valproate C: ↓ albumin C and ↑ displacement by endogenous compounds
  - hepatic impairment: not well studied
    - used cautiously
    - measure free valproate C ↓ albumin C and ↑ displacement by endogenous compounds

1.5.2. Valproate Case 1: High C/D Ratio

- Environmental factors: Fundamentally, these are drugs.
  - Some ↓ valproate metabolism, causing high valproate C/D ratios.
  - Some ↑ valproate metabolism, causing low valproate C/D ratios.
  - The effects are complex in both directions.

1.5.3. Effect of Other Drugs on Valproate

1.5.3. Effect of Other Drugs on Valproate

1.5.3.1. ↓ Valproate Metabolism

1.5.3.2. ↑ Valproate Metabolism

1.5.3.3. Complex Metabolic Effects

1.5.3.1. Drugs ↓ Valproate Metabolism

1.5.3.1. Valproate Case 1: Drugs ↓ Valproate Metabolism

- Aspirin:
  - inhibits the β-oxidation pathway:
    ↑ total valproate C.
  - displaces valproate from albumin:
    ↑ free valproate C.
  - explains high valproate C/D ratio in this case.
- Felbamate:
  - inhibits the β-oxidation pathway.
- Fluoxetine:
  - a moderate inhibitor of CYP2C9;
    possibly, fluvoxamine produces similar effects.

1.5.3.2. Drugs ↑ Valproate Metabolism

1.5.3.2. Valproate Case 1: Drugs ↑ Valproate Metabolism

- 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 by UGT induction.
- Carbanapem antibiotics:
  - major ↑ in valproate metabolism
  - by mechanisms not well understood.

1.5.3.3. Drugs with Complex Effects

1.5.3.3. Drugs with Complex Effects

1.5.3.3.1. Valproate-Carbamazepine DDI
1.5.3.3.2. Valproate-Topiramate DDI
1.5.3.3.3. Valproate-Phenytoin DDI

1.5.3.3.1. Valproate-Carbamazepine DDI

1.5.3.3.1. Valproate Case 1: 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.

1.5.3.3.1. Valproate Case 1: 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)

1.5.3.3.1. Valproate Case 1: 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.

1.5.3.3.2. Valproate-Topiramate DDI

1.5.3.3.2. Valproate Case 1: Topiramate DDI

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

1.5.3.3.2. Valproate Case 1: 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.

1.5.3.3.2. Valproate Case 1: 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

1.5.3.3.3. Valproate-Phenytoin DDI

1.5.3.3.3. Valproate Case 1: Phenytoin DDI

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

1.5.3.3.3. Valproate Case 1: 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

1.5.4. High Valproate C/D Ratios: Conclusion

1.5.4. Valproate Case 1: Conclusion on High C/D Ratios

Aspirin
explains the patient's
high valproate C/D ratios,
which are a sign
of
poor metabolism.

Educational Objectives: Final

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 safety, one must consider
   - 2.1. Personal, environmental and genetic factors
   - 2.2. Pharmacodynamics and pharmacokinetics
3. Show familiarity with protein binding and valproate free concentrations.

Valproate Case 1 (Final)

Questions

- Please review the 10 questions on the pdf entitled "Questions on the Presentation Valproate Case 1 Pharmacokinetics".
- 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. B
4. A
5. D
6. D
7. D
8. A
9. A
10. A