

**Clozapine Case 5:
High Clozapine Doses
1-02-16**

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Alternative title:

**Do you get upset with
pharmacists?**

**Is it because they know
more pharmacology than
you?**

5. Clozapine Case 5: High Clozapine Doses

J Clin Psychopharmacology 33(6): 812-4, 2013.

by Riesselman A et al.

<http://www.ncbi.nlm.nih.gov/pubmed/24113673>

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 clozapine efficacy, one must consider:
 - 2.1. Personal, environmental and genetic factors.
 - 2.2. Pharmacodynamics and pharmacokinetics.
3. Summarize how to use clozapine levels in clinical practice.
4. Be aware that drug-drug interactions may be explained by combinations of several drugs.

Abbreviations

- AED: antiepileptic drug
- C: concentration
- C/D: concentration-to-dose ratio
- CI: confidence interval
- D: dose
- DDI: drug-drug interaction
- TDM: therapeutic drug monitoring
- UM: ultrarapid metabolizer
(subjects with high metabolic capacity)

Definition

■ Median:

- Wikipedia: “numerical value separating the higher half of a sample” <http://en.wikipedia.org/wiki/Median>
- Easier definition for physicians: 50th percentile.
Half the values are above and half are below.
It is a better average measure than the mean when you have only a few values or an asymmetric distribution.

Clozapine Case 5

5.0. Introduction:

Prior Case with High Doses

5.1. Case 5: Description

5.2. Case 5: Publication

5.3. Valproate and Clozapine

5.4. Other Changes

5.5. Final Conclusions

5.0. Introduction: Prior Case with High Doses

<http://www.ncbi.nlm.nih.gov/pubmed/9819075>

5.0. Clozapine Case 5: Prior Case

- In 1998, Bender and Eap (German and Swiss researchers) published a letter to the editor titled: “Very high cytochrome P4501A2 activity and nonresponse to clozapine.”

<http://www.ncbi.nlm.nih.gov/pubmed/9819075>

- They described 3 possible clozapine UMs, but presented clozapine Cs in only one.
- They thought he was a genetic UM, but the gene variant was not identified.

5.0. Clozapine Case 5: Prior Case

- A 21-yo ♂ smoker (20 cigarettes/day)
- Other medications:
 - lithium (600 mg/d)
 - haloperidol (20 mg/d) intermittently,
and
 - lorazepam (3 mg/d)
- Clozapine:
 - D: 600 mg/d
 - C < 100 ng/ml

5.0. Clozapine Case 5: Prior Case

How do you best determine his clozapine metabolism capacity?

5.0. Clozapine Case 5: Prior Case

How do you best determine his clozapine metabolism capacity?

Use his C/D ratio.

5.0. Clozapine Case 5: Prior Case

What is the
clozapine C/D ratio?

5.0. Clozapine Case 5: Prior Case

- In typical doses, clozapine appears to have a linear relationship between D and C, particularly within the same individual.
- Pharmacologists use a simple formula, the C/D ratio, to represent this relationship.

<http://www.ncbi.nlm.nih.gov/pubmed/15883149>

- The C/D ratio is a measure of
 - the ability to eliminate clozapine from the body (pharmacologists call this clozapine clearance).

5.0. Clozapine Case 5: Prior Case

What is his
clozapine C/D ratio?

5.0. Clozapine Case 5: Prior Case

What is his
clozapine C/D ratio?

C<100 and D=600

C/D<100/600<0.17.

5.0. Clozapine Case 5: Prior Case

Is a clozapine
C/D ratio < 0.17
normal?

5.0. Clozapine Case 5: Prior Case

Is a clozapine
C/D ratio < 0.17
normal?

No.

5.0. Clozapine C: C/D Ratio in the US

- The average US individual taking clozapine has a C/D ratio of 0.6-1.2.
<http://www.ncbi.nlm.nih.gov/pubmed/15883149>
- US ♀ non-smokers typically require 300 mg/d to reach a C \geq 350 ng/ml: C/D ratio of 1.2 (350/300).
- US ♂ smokers typically require 600 mg/d to reach a C \geq 350 ng/ml: C/D ratio of 0.6 (350/600).
- US ♀ smokers and ♂ non-smokers require 300-600 mg/d and C/D ratio between 0.6-1.2.

5.0. Clozapine C: C/D ratio in Asians

■ The C/D ratio in East Asians (Chinese and Koreans):

- may be higher.
- Dr. de Leon has no experience in treating them.
- A review of studies suggests C/D ratios are 2 times higher; C/D ranges: low 1s to high 2s

5.0. Clozapine Case 5: Prior Case

- During a prior hospitalization:
 - low clozapine C on D=900 mg/d under supervised intake
- Fluvoxamine (powerful CYP1A2 inhibitor) up to 100 mg/d:
 - ↑ clozapine C: 350 ng/ml
 - clozapine D: 500 mg/d
 - ↑ clozapine C/D ratio to 0.7

(vs 0.17)

5.0. Clozapine Case 5: Prior Case

- Fluvoxamine ↑ the C/D ratio from 0.17 to 0.7.
 - low C/D ratio: sign of rapid metabolism
 - high C/D ratio: sign of poor metabolism
 - Inhibitors such as fluvoxamine ↑ the C/D ratio.

5.0. Clozapine Case 5: Prior Case

- Smoking is an inducer of clozapine metabolism.
 - Inducers ↓ C/D ratio.
 - Nicotine is not an inducer.
 - Polycyclic aromatic hydrocarbons in smoke have inductive effects.

5.1. Description

5.1. Clozapine Case 5: Description

- In 2003, a psychiatrist working at a Kentucky state hospital contacted Dr. de Leon regarding a clozapine patient:
 - D=800 mg/d
 - but not responding
- Dr. de Leon recommended clozapine TDM.

5.1. Clozapine Case 5: Description

- 38-year-old African-American ♂ with schizoaffective disorder
- Smoker: 20 cigarettes/day (stable and controlled by staff).
- No caffeinated beverages on the unit.
- Clozapine TDM on D=800 mg/day:
 - clozapine C: 150 ng/ml
 - norclozapine C: 140 ng/ml
 - total C: 290 ng/ml

5.1. Clozapine Case 5: Description

What is his
clozapine C/D ratio?

5.1. Clozapine Case 5: Description

What is his
clozapine C/D ratio?

C=150 and D=800

C/D=150/800=0.19.

5.1. Clozapine Case 5: Description

Is a clozapine C/D
ratio=0.19 normal?

5.1. Clozapine Case 5: Description

Is a clozapine C/D
ratio=0.19 normal?

No.

**This clozapine C/D ratio is
similar to
Bender and Eap's patient.**

5.1. Clozapine Case 5: Description

What is his
total clozapine C/D ratio?

5.1. Clozapine Case 5: Description

What is his
total clozapine C/D ratio?

Total C=290 and D=800

Total C/D=290/800=0.36.

5.0. Clozapine Case 5: Prior Case

- Norclozapine is not active as an antipsychotic.
- Total C/D ratio is:
 - not helpful for efficacy.
 - helpful for pharmacologists, since it is a better measure of the ability to eliminate clozapine from the body (clozapine clearance).
 - a better measure if you are interested in safety (norclozapine is anti-muscarinic and contributes to constipation).

5.1. Clozapine Case 5: Description

What does a total
clozapine C/D ratio=0.36
indicate?

5.1. Clozapine Case 5: Description

What does a total
clozapine C/D ratio=0.36
indicate?

**Very high metabolic
activity.**

5.1. Clozapine Case 5: Description

What would you do to verify that the patient is a clozapine UM?

5.1. Clozapine Case 5: Description

What would you do to verify that the patient is a clozapine UM?

Repeat clozapine TDM.

5.1. Clozapine Case 5: Description

- The patient had a repeated TDM.
- Clozapine TDM using $D=1300$ mg/day:
 - Clozapine C: 310 ng/ml
 - Norclozapine C: 160 ng/ml
 - Total C: 290 ng/ml

5.1. Clozapine Case 5: Description

What is his
clozapine C/D ratio on
1300 mg/d?

5.1. Clozapine Case 5: Description

What is his
clozapine C/D ratio on
1300 mg/d?

C=310 and D=1300

$C/D=310/1300=0.24.$

5.1. Clozapine Case 5: Description

What is his total
clozapine C/D ratio on
1300 mg/d?

5.1. Clozapine Case 5: Description

What is his total
clozapine C/D ratio on
1300 mg/d?

Total C=470 and D=1300

Total C/D=470/1300=0.36.

5.1. Clozapine Case 5: Description

- Highest clozapine D that Dr. de Leon has ever seen.
- With clozapine D = 1300 mg/d the patient responded and was discharged after > 5 months.
- The patient appeared to be a clozapine UM similar to Bender and Eap's patient.

5.2. Publication

5.2. Clozapine Case 5: Publication

- In 2012, Dr. de Leon asked a pharmacist to review the chart to publish the case.
- Now for the rest of the presentation you are in Dr. de Leon's shoes.
- Pharmacists do not know C/D ratios. They can easily understand them if you clearly explain them.

5.2. Clozapine Case 5: Publication

You call the pharmacist.

You explain that you
have a person who
metabolizes clozapine
fast.

5.2. Clozapine Case 5: Publication

What is the first question
that the pharmacist will
ask you?

5.2. Clozapine Case 5: Publication

What is the first question that the pharmacist will ask you?

Was the patient taking any major inducer besides smoking?

5.2. Clozapine Case 5: Publication

The pharmacist asks you,
“What are the other
major clozapine
inducers?”

5.2. Clozapine Case 5: Publication

The pharmacist asks you,
“What are the other
major clozapine
inducers?”

Rifampin.

5.2. Clozapine Case 5: Publication

The pharmacist answers,
“The patient was not
taking rifampin.”

5.2. Clozapine Case 5: Publication

The pharmacist asks you:

“Are there other major clozapine inducers besides smoking and rifampin?”

5.2. Clozapine Case 5: Publication

The pharmacist asks you:

“Are there other major clozapine inducers besides smoking and rifampin?”

Yes,

the major AED inducers.

5.2. Clozapine Case 5: Publication

The pharmacist asks you,
“What are the major AED
inducers?”

**Carbamazepine,
phenytoin and
phenobarbital.**

5.2. Clozapine Case 5: Publication

The pharmacist tells you,
“The patient was
not taking
any of these AEDs,
but he was
on divalproex sodium.”

5.2. Clozapine Case 5: Publication

The pharmacist asks you,
“Is valproate a major
clozapine inducer?”

5.2. Clozapine Case 5: Publication

The pharmacist asks you,
“Is valproate a major
clozapine inducer?”

**According to the literature,
if anything,
valproate is an inhibitor.**

5.2. Clozapine Case 5: Publication

Then you remember a prior clozapine presentation in which Dr. de Leon described a study with a peculiar title, “Can valproic acid be an inducer of clozapine metabolism?”

<http://www.ncbi.nlm.nih.gov/pubmed/24764199>

5.3. Valproate and Clozapine

5.3. Clozapine Case 5: Valproate

- During the entire admission:
 - Enteric-coated divalproex sodium was given.
 - The D was always 1000 mg/d.
- He was taking a low but stable valproate D.

5.3. Clozapine Case 5: Valproate

Day	CLO Dose mg/d	CLO Level ng/ml	CLO C/D	Norclozapine ng/ml	Total C/D
48	800	150	0.19	140	0.36
87	900	100	0.11	170	0.30
108	900	79	0.09	160	0.27
115	900	130	0.14	170	0.33
125	1100	180	0.16	120	0.37
139	1300	310	0.24	160	0.36
147	1300	330	0.25	110	0.39
154	1300	510	0.39	210	0.55
162	1300	480	0.37	260	0.57

5.3. Clozapine Case 5: Valproate

Is there anything peculiar
about the total C/D
ratios?

5.3. Clozapine Case 5: Valproate

Is there anything peculiar
about the total C/D
ratios?

Yes.

5.3. Clozapine Case 5: Valproate

- Days 48-139:
 - Total C/D ratios range from 0.27-0.36.

5.3. Clozapine Case 5: Valproate

Day	CLO Dose mg/d	CLO Level ng/ml	CLO C/D	Norclozapine ng/ml	Total C/D
48	800	150	0.19	140	0.36
87	900	100	0.11	170	0.30
108	900	79	0.09	160	0.27
115	900	130	0.14	170	0.33
125	1100	180	0.16	120	0.37
139	1300	310	0.24	160	0.36

5.3. Clozapine Case 5: Valproate

- Days 154-162:
 - Total C/D ratios range from 0.55-0.57.

5.3. Clozapine Case 5: Valproate

Day	CLO Dose mg/d	CLO Level ng/ml	CLO C/D	Norclozapine ng/ml	Total C/D
154	1300	510	0.39	210	0.55
162	1300	480	0.37	260	0.57

5.3. Clozapine Case 5: Valproate

- Day 147: Total C/D ratio = 0.39
Middle value between
 - 0.27-0.36 (Day 48-139).
 - 0.55-0.57 (Day 154-162).

5.3. Clozapine Case 5: Valproate

You ask the pharmacist,
“Are you sure the
clozapine TDM values
are correct?”

5.3. Clozapine Case 5: Valproate

**You ask the pharmacist,
“Are you sure the
clozapine TDM values
are correct?”**

Yes, they are correct.

5.3. Clozapine Case 5: Valproate

You get annoyed and ask the pharmacist, “How do you explain the increase in the C/D ratio?”

5.3. Clozapine Case 5: Valproate

You get annoyed and ask the pharmacist, “How do you explain the increase in the C/D ratio?”

I have no explanation.

Moreover...

5.3. Clozapine Case 5: Valproate

You feel that
you are getting more annoyed
and decide never to call
a pharmacist again
to resolve
a pharmacological problem.

5.3. Clozapine Case 5: Valproate

You take three deep
breaths.

Then you ask...

5.3. Clozapine Case 5: Valproate

What do you mean by
“Moreover...”?

5.3. Clozapine Case 5: Valproate

What do you mean by
“Moreover...”?

**There is something
funny.**

5.3. Clozapine Case 5: Valproate

You ask,
“What is funny?”

5.3. Clozapine Case 5: Valproate

You ask,
“What is funny?”

There is
a second admission.

5.3. Clozapine Case 5: Valproate

- During the second admission:
 - No valproate for 6 months.
 - Surely, valproate's inductive effects are gone after 6 months.
 - Total C/D ratio=0.54, the same C/D ratio as at the end of the first admission.

5.3. Clozapine Case 5: Valproate

You take

three deep breaths.

Then,

you review all Cs and
classify them with colors.

5.3. Clozapine Case 5: Valproate

■ Colors:

- You leave in yellow: early C/D ratios: low
- You use pink: last C/D ratios: high
- You use red: 1 intermediate C/D ratio

5.3. Clozapine Case 5: Valproate

Day	CLO Dose mg/d	CLO Level ng/ml	CLO C/D	Norclozapine ng/ml	Total C/D
48	800	150	0.19	140	0.36
87	900	100	0.11	170	0.30
108	900	79	0.09	160	0.27
115	900	130	0.14	170	0.33
125	1100	180	0.16	120	0.37
139	1300	310	0.24	160	0.36
147	1300	330	0.25	110	0.39
154	1300	510	0.39	210	0.55
162	1300	480	0.37	260	0.57
SECOND ADMISSION NO VALPROATE FOR 6 MONTHS					
14	1300	410	0.32	290	0.54

5.3. Clozapine Case 5: Valproate

- Total C/D ratio in pink:
 - End of the first admission: 0.55-0.57.
 - Second admission: 0.54 with no valproate.

5.3. Clozapine Case 5: Valproate

You have it!!!

You are brilliant.

The pharmacist has made
a mistake.

5.3. Clozapine Case 5: Valproate

Valproate was discontinued at the end of the first admission.

5.3. Clozapine Case 5: Valproate

- Total C/D ratio in pink
 - End of the first admission: 0.55-0.57 because valproate was discontinued.
 - Second admission: 0.54 with no valproate for 6 months.
- Total C/D ratio: days 48-139 of the first admission:
 - Range of 0.27-0.36 because valproate was inducing clozapine metabolism.

5.3. Clozapine Case 5: Valproate

- On day 147: Total C/D ratio = 0.39 in red.
Middle value between
 - 0.27-0.36 (Days 48-139).
 - 0.55-0.57 (Days 154-162).

The inductive effects of valproate were starting to disappear on day 147.

5.3. Clozapine Case 5: Valproate

With your most ironic tone
you tell the pharmacist...

5.3. Clozapine Case 5: Valproate

**With your most ironic tone
you tell the pharmacist...**

You made a mistake.

**Valproate was
discontinued at the end
of the first admission.**

5.3. Clozapine Case 5: Valproate

The pharmacist
understands and
apologizes.

She will review the chart
again to double-check.

5.3. Clozapine Case 5: Valproate

Next day, the pharmacist
calls and says...

5.3. Clozapine Case 5: Valproate

Next day, the pharmacist
calls and says...

**Valproate was NOT
discontinued at the end
of the first admission.**

5.3. Clozapine Case 5: Valproate

You take
another deep breath and
review things again.
You review the Clozapine
Case 4 Presentation.

5.3. Clozapine Case 5: Valproate

As far you can tell from the prior presentation, if there are no medication changes, “sample issues” or caffeine/smoking can influence clozapine TDM. You tell the pharmacist.

5.3. Clozapine Case 5: Valproate

The pharmacist asks you,
“What do you mean by ‘sample
issues’ that can influence
clozapine TDM?”

5.3. Clozapine Case 5: Valproate

The pharmacist asks you,
“What do you mean by ‘sample
issues’ that can influence
clozapine TDM?”

You answer:

**“A different laboratory, or
lack of steady state, or
different hour of the day for
blood drawing.”**

5.3. Clozapine Case 5: Valproate

Then she asks,

“What changes in smoking/
caffeine can explain a ↓ in
clozapine metabolism seen at
the end of the first admission?”

5.3. Clozapine Case 5: Valproate

Then she asks,

“What changes in smoking/
caffeine can explain a ↓ in
clozapine metabolism seen at
the end of the first admission?”

You answer:

“↓ smoking or
↑ caffeine intake.”

5.3. Clozapine Case 5: Valproate

You ask the pharmacist to review the chart to address these issues.

5.3. Clozapine Case 5: Valproate

The pharmacist describes no changes in:

- 1) laboratory,
- 2) steady state condition,
- 3) hour of collection,
- 4) smoking, or
- 5) caffeine intake.

5.3. Clozapine Case 5: Valproate

Then she has the “guts” to
say “but”...

5.3. Clozapine Case 5: Valproate

This time you need to take
six deep breaths
before asking,
“What is the problem?”

5.3. Clozapine Case 5: Valproate

The pharmacist explains that the patient was taking other medications.

She asks for one day to review all the changes in these other medications.

5.3. Clozapine Case 5: Valproate

You have another day to review things.

5.3. Clozapine Case 5: Valproate

Next day, with a fresh brain you focus on the clozapine TDMS classified by “colors”.

5.3. Clozapine Case 5: Valproate

Day	CLO Dose mg/d	CLO Level ng/ml	CLO C/D	Norclozapine ng/ml	Total C/D
48	800	150	0.19	140	0.36
87	900	100	0.11	170	0.30
108	900	79	0.09	160	0.27
115	900	130	0.14	170	0.33
125	1100	180	0.16	120	0.37
139	1300	310	0.24	160	0.36
147	1300	330	0.25	110	0.39
154	1300	510	0.39	210	0.55
162	1300	480	0.37	260	0.57
SECOND ADMISSION NO VALPROATE FOR 6 MONTHS					
14	1300	410	0.32	290	0.54

5.3. Clozapine Case 5: Valproate

This time, you have it.

The answer is...

5.3. Clozapine Case 5: Valproate

This time, you have it.

The answer is...

**There is
a medication change
around day 147.**

5.4. Other Changes

5.4. Clozapine Case 5: Other Changes

You review medications with the pharmacist one by one and ask her for...

5.4. Clozapine Case 5: Other Changes

You review medications with the pharmacist one by one and ask her for...

changes

around day 147.

5.4. Clozapine Case 5: Other Changes

She starts the list of medications.

5.4. Clozapine Case 5: Other Changes

- Ipratropium/albuterol spray:
 - 2 puffs twice daily
 - No changes during first (or second) admission
- You conclude this drug is irrelevant.

5.4. Clozapine Case 5: Other Changes

- Atenolol:
 - 50 mg/d
 - Discontinued on day 86

- You conclude this drug is irrelevant.

5.4. Clozapine Case 5: Other Changes

- Gemfibrozil:
 - 1200 mg/d
 - Discontinued on day 121
- You conclude this drug is irrelevant.

5.4. Clozapine Case 5: Other Changes

- Olanzapine:
 - Before clozapine: 30 mg/d
 - On first clozapine TDM: 10 mg/d
 - Discontinued on day 50

- You conclude this drug is irrelevant.

5.4. Clozapine Case 5: Other Changes

- Enalapril:
 - 5 mg/d added on day 86
 - Continued during second admission
- You conclude this drug is irrelevant.

5.4. Clozapine Case 5: Other Changes

- Atarvostatin:
 - 10 mg/d added on day 85
 - Continued during second admission
- You conclude this drug is irrelevant.

5.4. Clozapine Case 5: Other Changes

- The last drug, aspirin:
 - 81 mg/d
 - Discontinued on day 140
 - Day 140 is close to the key day 147.
- You cannot believe it.
It has to be this small dose of aspirin.
You enter the aspirin information in the table with clozapine TDM.

5.4. Clozapine Case 5: Valproate

Day	CLO Dose mg/d	CLO Level ng/ml	CLO C/D	Norclozapine ng/ml	Tot C/D	Aspirin mg/d
48	800	150	0.19	140	0.36	81
87	900	100	0.11	170	0.30	81
108	900	79	0.09	160	0.27	81
115	900	130	0.14	170	0.33	81
125	1100	180	0.16	120	0.37	81
139	1300	310	0.24	160	0.36	81
147	1300	330	0.25	110	0.39	0 x 7 days
154	1300	510	0.39	210	0.55	0 x 14 days
162	1300	480	0.37	260	0.57	0 x 22 days
SECOND ADMISSION NO VALPROATE FOR 6 MONTHS						
14	1300	410	0.32	290	0.54	0

5.4. Clozapine Case 5: Other Changes

- Low total C/D ratio:
 - Days 48-139 of the first admission
 - Range=0.27-0.36
 - 1000 mg/d valproate + 81 mg/d aspirin
 - Clozapine metabolism was very fast.
- Higher total C/D ratio:
 - Days 154-162 of the first admission
 - Range=0.55-0.57
 - 1000 mg/d valproate + no aspirin
 - Second admission: 0.54
 - With no valproate for 6 months,
clozapine metabolism was slower.

5.4. Clozapine Case 5: Other Changes

- Total C/D ratio on day 147 of the first admission:
 - 0.39.
 - 1000 mg/d valproate + 0 mg/d aspirin
 - Aspirin is gone.
 - Effects on induction are beginning to ↓.

- Total C/D ratio on day 154 of the first admission:
 - 0.55.
 - 1000 mg/d valproate
 - Aspirin was discontinued 2 weeks prior.
 - Induction effects are gone.

5.4. Clozapine Case 5: Other Changes

- In this patient there was a further ↑ induction of clozapine metabolism with:
 - a low dose of valproate (1000 mg/d) + 81 mg/d aspirin.
- In this patient NO further clozapine induction with:
 - NO aspirin and a low dose of valproate (1000 mg/d), or
 - NO valproate.

5.4. Clozapine Case 5: Other Changes

Can aspirin induce
clozapine metabolism?

5.4. Clozapine Case 5: Other Changes

Can aspirin induce
clozapine metabolism?

No.

5.4. Clozapine Case 5: Other Changes

Is there a DDI between
aspirin and valproate?

5.4. Clozapine Case 5: Other Changes

Is there a DDI between aspirin and valproate?

Yes.

5.4. Clozapine Case 5: Other Changes

■ Aspirin DDI with valproate:

<http://www.ncbi.nlm.nih.gov/pubmed/17074939>

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

Free valproate is the active fraction.

- Aspirin contributed to valproate induction of clozapine metabolism by ↑ valproate's effects (adding aspirin = ↑ valproate D).

5.4. Clozapine Case 5: Other Changes

- Unfortunately, valproate TDM was not studied in this case.
Valproate Cs were not measured; more importantly, free valproate Cs were not measured.
- The proposed pharmacological mechanism
 - is possible,
 - but was not demonstrated.

5.5. Final Conclusions

5.5. Case 5: Final Conclusions

5.5.1. Two-Level DDI

5.5.2. Unusual Case?

5.5.3. Unusually Potent Induction

5.5.4. Dose-Related Induction

5.5.5. Low-Dose Aspirin

5.5.1. Two-Level DDI

5.5.1. Clozapine Case 5: Two-Level DDI

- This is a complex DDI:
 - Drug A interacts with Drug B which interacts with Drug C.
 - Aspirin inhibits valproate metabolism and protein binding which induces clozapine.
- Dr. de Leon does not previously remember finding a clinically relevant case with a DDI with two levels. He has probably missed many of these complex DDIs in the past.

5.5.2. Unusual Case

5.5.2. Clozapine Case 5: Unusual Case

Is this an unusual case?

5.5.2. Clozapine Case 5: Unusual Case

Is this an unusual case?

**The question is too broad
and
the literature is too limited
to answer this question.**

5.5.2. Clozapine Case 5: Unusual Case

- The next slides present some of the possible “unusual” features of this case:
 - potent inductive effects
 - inductive effects appear to be dose-dependent, and
 - involvement of low-dose aspirin.

5.5.3. Unusually Potent Induction

5.5.3. Clozapine Case 5: Potent Induction

Is this an unusually potent induction?

5.5.3. Clozapine Case 5: Potent Induction

Is this an unusually potent induction?

Let's estimate its size.

5.5.3. Clozapine Case 5: Potent Induction

- Total C/D ratio with no induction:
 - 3 values with a range: 0.54-0.57
 - Median value: 0.55
- Total C/D ratio during induction:
 - 6 values with a range: 0.27-0.36
 - Median value: 0.345
- This indicates a decrease of 37%
($0.37 = 0.55 - 0.345 / 0.55$).
- You search clozapine studies providing C decreases during induction.

5.5.3. Clozapine Case 5: Prior DDI Study

	↓Total C	95% CI
Phenobarbital	-28%	-42% to -11%
Valproate in smokers	-22%	-42% to 5%

Italian study (DDI studies using intra-subject design and/or parallel design or patients were studied for therapeutic drug monitoring [TDM])

<http://www.ncbi.nlm.nih.gov/pubmed/18484549>

To compare the patient's decrease in C (-37%) with this Italian study, you need to compare the 95% CIs. See Presentation "Introduction to Statistical Concepts".

5.5.3. Clozapine Case 5: Potent Induction

- This case showed a ↓ of 37% in total clozapine C
- Not significantly different from the Italian study, since 37% is within 95% CIs:

	95% CI
Phenobarbital	-42% to -11%
Valproate in smokers	-42% to 5%

- -37% is at the lower end of these CI ranges.

5.5.3. Clozapine Case 5: Potent Induction

- Valproate induction in this case appeared relatively potent and possibly:
 - Stronger than in average valproate patients (lower end of the CI)
 - At least similar to the strong induction usually seen in phenobarbital treatment

5.5.4. Dose-Related Induction

5.5.4. Clozapine Case 5: Dose-Related Induction

- In this patient, NO clozapine induction with:
 - a low dose of valproate (1000 mg/d)
- In this patient, clozapine induction with:
 - a low dose of valproate (1000 mg/d)
 - + 81 mg/d aspirin which may potentiate its effects by ↑ total and free valproate Cs.

5.5.4. Clozapine Case 5: Dose-Related Induction

- Valproate and other milder inducers may be inducers only in high doses.

<http://www.ncbi.nlm.nih.gov/pubmed/22332980>

See the presentation entitled

“Induction by Antiepileptic Drugs:
An Update for Clinicians”.

- Valproate high doses work through high free Cs.

The free serum valproate is what is active as an inducer.

5.5.4. Clozapine Case 5: Dose-Related Induction

- This case suggests the key element for valproate's induction is not dose but valproate free C. The main determinant of valproate's induction is not high dose but high free C. In a strict pharmacological sense, “dose-related” valproate induction should be called “free C-related” valproate induction.

5.5.5. Low-Dose Aspirin

5.5.5. Clozapine Case 5: Low-Dose Aspirin

- 81 mg/d is a low aspirin D.
- There is little data on the effects of aspirin dose on valproate DDI.

Dr. de Leon was not surprised.

A prior valproate toxicity case was explained by a DDI with 81 mg/d of aspirin. <http://www.ncbi.nlm.nih.gov/pubmed/19745660>

See the presentation entitled “Valproate Case 1”.

Questions

- Please review the 10 questions in the pdf document entitled “Questions on the Presentation - Clozapine Case 5: High Clozapine Doses”.
- 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 do not answer all the questions correctly, please review the PowerPoint presentation again to reinforce the pharmacological concepts.

Thank you

Answers

1. C

2. C

3. D

4. B

5. A

6. A

7. D

8. C

9. D

10. D