Clozapine Case 4: Perphenazine 1-02-16

Jose de Leon, MD

4. Clozapine Case 4

J Clin Psychiatry 1999;60:710

by Cooke C & de Leon J

http://www.ncbi.nlm.nih.gov/pubmed/10549694

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 safety, 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.

Abbreviations

- α: alpha, one of two types of adrenergic receptors
- ADR: adverse drug reaction
- C: concentration
- C/D: concentration-to-dose ratio
- CYP: cytochrome P450
- D: dose
- DDI: drug-drug Interaction
- FMO: flavin-containing monooxygenase
- M: muscarinic (two types of cholinergic receptors:
  - muscarinic, and
  - nicotinic)
- PM: poor metabolizer
- RCT: randomized controlled trial
- TDM: therapeutic drug monitoring
- UGT: uridine 5-diphosphate glucuronosyltransferase
- UM: ultrarapid metabolizer

Receptor Terminology

- **Allosteric Regulation:**
  The modification of the reactivity of ENZYMES by the binding of effectors to sites (ALLOSTERIC SITES) on the enzymes other than the substrate BINDING SITES

http://www.ncbi.nlm.nih.gov/mesh?term=allosteric%20regulation

Clozapine Case 4

4.0. Introduction

4.1. Clozapine Metabolism

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Clozapine Case 4

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4.0. Introduction

4.0. Case 4: Introduction

4.0.1. Description

4.0.2. Questions

4.0.1. Introduction: Description

4.0.1. Clozapine Case 4: Description

- C.C. Cooke, MD, was a resident who rotated for 1 month on Dr. de Leon's unit for treatment-refractory patients.
- She helped with the publication of this peculiar clozapine DDI during a 1-month clinical rotation.
- The patient asked to be on perphenazine. Dr. de Leon thought the patient was stable on haloperidol augmentation of clozapine but he agreed to comply with request to avoid non-compliance and proposed switching the patient from haloperidol to perphenazine.

4.0.1. Clozapine Case 4: Description

- 46-year-old Caucasian ♂ with schizoaffective disorder
- History of very serious violence toward female nurses when not compliant with medication
- Clozapine D ranged between 400-500 mg/day
- Taking other meds:
  - haloperidol: 15 mg/day for 6 months
  - valproic acid: 3000 mg/day for schizoaffective disorder and violence
  - benztropine: 9 mg/day (hypersalivation)
  - clonazepam: 1 mg/day (unknown indication; patient refused to discuss discontinuation).

4.0.2. Introduction: Questions

4.0.2. Clozapine Case 4: Questions

Do you need to ask any questions to be able to interpret clozapine C?

4.0.2. Clozapine Case 4: Questions

Do you need to ask any questions to be able to interpret clozapine C?

Yes, several questions are important.

4.0.2. Clozapine Case 4: Questions

Which questions?

4.0.2. Clozapine Case 4: Questions

First, “sample issues”,
that are important for all TDM Cs.
Were all Cs:
1) measured at the same lab,
2) Cs at steady state,
and 3) trough Cs?

4.0.2. Clozapine Case 4: Questions

First, “sample issues”,
that are important for all TDM Cs.
Were all Cs:
1) measured at the same lab,
2) Cs at steady state,
and 3) trough Cs?

Yes, all Cs were measured
1) at the same laboratory,
2) at least 1 week after clozapine (or any medication change), and
3) early in the morning (before meds).

4.0.2. Clozapine Case 4: Questions

Remember, for interpreting all TDMs
there are three “sample” issues
that are important:

1) different labs use different techniques that may provide different results.
Try to use the same lab for a patient’s Cs.

2) always draw Cs at steady state, and

3) Cs vary through the day.
Order trough Cs in the early morning
before any medication is given.

The concept of half-life is important and
is discussed in Clozapine Case 6: Half-Life.

4.0.2. Clozapine Case 4: Questions

Second, was the patient smoking?

4.0.2. Clozapine Case 4: Questions

Second, was the patient smoking?

Yes, he was a stable smoker of 10 cigarettes/day, which were controlled by staff. Smoking may cause a mild induction of clozapine metabolism.

4.0.2. Clozapine Case 4: Questions

Third, was he consuming any caffeine?

4.0.2. Clozapine Case 4: Questions

Third, was he consuming any caffeine?

No, he had no unit access to caffeinated beverages and could only leave the unit when escorted by staff. Caffeine can inhibit clozapine metabolism.

4.0.2. Clozapine Case 4: Questions

In summary, all Cs in this patient were measured in same lab, at steady state early morning, with stable levels of smoking and no access to caffeine.

4.0.2. Clozapine Case 4: Questions

Moreover, the patient was followed
for >400 days
(168 days before perphenazine and 263 after)
with >15 clozapine Cs.
It is easier
to interpret C variations
during perphenazine treatment
if you can compare Cs
before and after starting perphenazine.

4.1. Clozapine Metabolism

4.1. Clozapine Case 4: Clozapine Metabolism

4.1.1. Metabolic Enzymes

4.1.2. Genetic, Environmental and Personal Variables

4.1.1. Clozapine Metabolic Enzymes

4.1.1 Clozapine Case 4: Clozapine Metabolic Enzymes

4.1.1.1. Main Metabolic Enzyme

4.1.1.2. Main Metabolite

4.1.1.3. Metabolism in Detail

4.1.1.1. Main Clozapine Metabolic Enzyme

4.1.1.1.Clozapine Metabolism: CYP1A2.

- Remember: CYP1A2 is the main enzyme. It may account for 70% of clozapine metabolism.

  http://www.ncbi.nlm.nih.gov/pubmed/7893591

- CYP1A2 metabolizes clozapine to:
  - Norclozapine (also called desmethylclozapine).

4.1.1.2. Main Clozapine Metabolite

4.1.1.2. Clozapine Metabolite

- Norclozapine: no antipsychotic activity
  - Patented by a pharmaceutical company
  - Norclozapine placebo-controlled RCT for: ● antipsychotic efficacy or ● cognitive augmentation were conducted but never published.
- Norclozapine:
  - reflects clozapine metabolism, and
  - can contribute to ADRs, particularly to antimuscarinic ADRs.

4.1.1.2. Clozapine Metabolite

- Clozapine and norclozapine have high affinity for muscarinic receptors.
- At colon: M_3 receptors
  Clozapine treatment is frequently associated with constipation (a sign of M_3 blockade).
  A RCT indicated serum norclozapine Cs contributed to constipation http://www.ncbi.nlm.nih.gov/pubmed/12920408
- Clozapine frequently causes hypersalivation through two possible mechanisms:
  - muscarinic receptors (most important):
    - clozapine is a partial agonist at M_1 and M_3 .
    - norclozapine is an allosteric agonist of M_1.
  - α receptors: clozapine is an α_1 antagonist.

4.1.1.3. Clozapine Metabolism in Detail

4.1.1.3. Clozapine Metabolism in Detail

- Main metabolic pathway to norclozapine:
  - CYP1A2 is the most important enzyme,
  - CYP2C19 may have a greater role than previously thought. http://www.ncbi.nlm.nih.gov/pubmed/25200585
  - CYP2D6 and CYP3A4 may have minor roles.
- Second pathway to clozapine-N-oxide:
  - by: • CYP3A4 and
    • FMO
  - probably is a reversible pathway
- Glucuronidation by UGTs is probably a minor pathway.

4.1.2. Genetic, Environmental and Personal Variables

4.1.2. Genetic, Environmental and Personal Variables

4.1.2.1. Genetic Variables

4.1.2.2. Environmental Variables

4.1.2.3. Personal Variables

4.1.2.1. Genetic Variables

4.1.2.1. Clozapine Metabolism: Genetic Variables

- CYP1A2:
  - The literature does not provide a clear description of PMs and UMs. If they exist, they are rare (<1%).
- CYP2C19 PMs may have lower ability to metabolize clozapine.

4.1.2.2. Environmental Variables

4.1.2.2. Environmental Variables

- Inducers: ↑ metabolism & ↓ serum Cs.
- Inhibitors: ↓ metabolism & ↑ serum Cs.
- Correction factor: Multiply dose by this number to correct for the effect of the inducer or inhibitor.
  - Inducer: correction factor >1 (e.g., 2)
  - Inhibitor: correction factor <1 (e.g., 0.5)

4.1.2.2. Environmental Variables

4.1.2.2.1. Inducers

4.1.2.2.2. Inhibitors

4.1.2.2.3. Valproic Acid

4.1.2.2.1. Inducers

4.1.2.2.1. Inducers

- Rifampin: probably very powerful
- Potent antiepileptic drugs (correction factor 1.5-2 x):
  - carbamazepine (careful; associated with agranulocytosis)
  - phenobarbital
  - phenytoin
- Omeprazole: (correction factor 1.5 x)
  - others from the same family:
    - esomeprazole
    - lansoprazole
- Polycyclic aromatic hydrocarbons in smoke:
  - tobacco smoking: (correction factor 1.5 x)
  - cannabis smoking: may be the same
  - charbroiled food: unlikely to be relevant
  - toasted coffee: may be relevant in South Asians
- Cruciferous vegetables (broccoli & Brussels sprouts) are unlikely to be relevant.

4.1.2.2.2. Inhibitors

4.1.2.2.2. Inhibitors

4.1.2.2.2.1. Psychiatric Drugs

4.1.2.2.2.2. Non-psychiatric Drugs

4.1.2.2.2.1. Psychiatric Inhibitors

4.1.2.2.2.1. Psychiatric Inhibitors

- Fluvoxamine: CYP1A2 and CYP2C9 inhibition
  Very powerful: only use with TDM
  Correction factor down to 0.10-0.20
- Fluoxetine and paroxetine: mild inhibitors
  Rarely clinically relevant: correction factor: 0.75-0.80
- Sertraline may be relevant only in high doses:
  see Clozapine Case 3 Presentation.

4.1.2.2.2.2. Non-Psychiatric Inhibitors

4.1.2.2.2.2. Non-Psychiatric Inhibitors

- Ciprofloxacin: probably a powerful inhibitor
  - norfloxacin: also probably a CYP1A2 inhibitor
  - safe members from the family that are NOT inhibitors:
    - gatifloxacin
    - gemifloxacin
    - levofloxacin
    - moxifluxacin
    - trovafloxacin
- Oral contraceptives (estrogen) are clinically-relevant inhibitors.
- Amiodarone: probably a relevant inhibitor
- Be careful with erythromycin and clarithromycin (powerful CYP3A4 inhibitors): monitor with TDM.
- Caffeine: correction factor 0.5 x
  See Clozapine Case 1 presentation.

4.1.2.2.3. Valproic Acid

4.1.2.2.3. Valproic Acid

- Valproic acid can:
  - be a mild inhibitor of clozapine metabolism,
  - be a mild inducer of clozapine metabolism (possibly in smokers)

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

  - have major inductive effects (rare)
    - in sensitive patients
    - dose-related (better defined as related to the free serum valproic Cs).

See Clozapine Case 5 Presentation.

4.1.2.3. Personal Variables

4.1.2.3. Personal Variables

- Age: ↑ age ↓ renal excretion. Be careful in geriatric.
- Sex: ♀: relatively lower metabolism
  Partly explained by estrogens (CYP1A2 inhibitors)
  Contaminated by smoking (♂ tend to smoke more)
- Pregnancy: should ↓ metabolism but not studied (CYP1A2/CYP2C19 inhibitor)
- Severe inflammation/infection: ↓ metabolism
  See Clozapine Case 2 Presentation
- East Asians (Chinese, Japanese & Koreans):
  ↓ metabolism: □ lower CYP2C19 activity
  □ unclear if lower CYP1A2 activity
  See Clozapine Case 3 Presentation
- ↑ weight associated with ↓ mild Cs in TDM studies:
  Relevant: □ extreme obesity or
  □ dramatic weight changes in a patient

4.2. Baseline Clozapine TDM

4.2. Case 4: Baseline Clozapine TDM

4.2.1. First Clozapine TDM

4.2.2. All Baseline Clozapine TDM

4.2.1. First Clozapine TDM

4.2.1. Clozapine Case 4: First Clozapine TDM

- First TDM:
  - Clozapine D = 500 mg/day
  - Clozapine C = 653 ng/ml
  - Norclozapine C = 242 ng/ml

4.2.1. Clozapine Case 4: First Clozapine TDM

What was the clozapine C/D ratio in this first TDM?

4.2.1. Clozapine Case 4: First Clozapine TDM

What was the clozapine C/D ratio in this first TDM?

C/D=653/500=1.3.

4.2.1. Clozapine Case 4: First Clozapine TDM

Is a clozapine C/D ratio=1.3 normal in a US ♂ smoker?

4.2.1. Clozapine Case 4: First Clozapine TDM

Is a clozapine C/D ratio=1.3 normal in a US ♂ smoker?

Mildly abnormal in Dr. de Leon's experience.

4.2.1. Clozapine Case 4: First Clozapine TDM

- In US Caucasians, a C/D ratio:
  - >1.2 indicates poor metabolic capacity.
  - <0.6 indicates high metabolic capacity.
  - 0.6-1.2 is probably normal.
- This is influenced by smoking:
  - ♀ non-smokers: C/D ratios ≤1.2
  - ♂ smokers: C/D ratios ≥ 0.6
  - ♀ smokers and ♂ smokers: intermediate C/D ratios of 0/6-1.2

http://www.ncbi.nlm.nih.gov/pubmed/25200585

4.2.2. All Baseline Clozapine TDMs

4.2.2. All Baseline Clozapine TDMs

Day	Clo D	C (ng/ml)			C/D Ratio	
	mg/day	Clo	NorC	Total	Clo	Total
-168	500	653	242	895	1.3	1.8
-164	500	755	274	1029	1.5	2.1
-143	400	557	185	742	1.4	1.9
-136	400	704	204	908	1.8	2.3
-108	500	823	303	1126	1.7	2.3
-73	400	621	196	817	1.6	2.0
-45	450	613	201	814	1.4	1.8
-16	450	657	181	838	1.5	1.9

Clo: clozapine; NorC: norclozapine

4.2.2. All Baseline Clozapine TDMs

Summary of 8 TDMs

	Range	Mean
Clozapine D (mg/day)	400-500	450
Clozapine C/D	1.3-1.8	1.5
Total Clozapine C/D	1.8-2.3	2.0

4.2.2. All Baseline Clozapine TDMs

Is a clozapine C/D ratio=1.3-1.8 normal in a US ♂ smoker?

4.2.2. All Baseline Clozapine TDMs

Is a clozapine C/D ratio=1.3-1.8 normal in a US ♂ smoker?

Mildly abnormal in Dr. de Leon's experience.

4.2.2. All Baseline Clozapine TDMs

Why is the clozapine C/D ratio mildly elevated?

4.2.2. All Baseline Clozapine TDMs

Why is the clozapine C/D ratio mildly elevated?

Probably due to the co-medication.

4.2.2. All Baseline Clozapine TDMs

- Co-medications:
  - haloperidol: partly metabolized by CYP2D6
  - benztropine: possibly metabolized by CYP2D6 (delirium has been associated with co-prescription of CYP2D6 inhibitors)
  - clonazepam: partly metabolized by CYP3A4
  - valproic acid: may be a mild inducer (and possibly a competitive inhibitor)

4.3. Adding Perphenazine

4.3. Case 4: Adding Perphenazine

4.3.1. Clinical Outcome

4.3.2. Next Course of Action

4.3.3. Intervention

4.3.1. Perphenazine: Clinical Outcome

4.3.1. Clozapine Case 4: Perphenazine Outcome

- The patient has a history of:
  - severe violence due to delusions
  - noncompliance in taking meds
  - requests for irrational medication changes
- The patient:
  - reports feeling better on perphenazine (in the past)
  - wants to be switched from haloperidol to perphenazine

4.3.1. Clozapine Case 4: Perphenazine Outcome

- Medications (clozapine 450 mg/d):
  - taken off haloperidol
  - perphenazine D:↑ 24 to 48 mg/d
- Within the second week:
  - the patient complained of
    - knee buckling and
    - hypersalivation
  - psychosis worsened, and included threatening behavior

4.3.1. Clozapine Case 4: Perphenazine Outcome

What do neurologists call knee buckling?

4.3.1. Clozapine Case 4: Perphenazine Outcome

What do neurologists call knee buckling?

Myoclonus.

4.3.1. Clozapine Case 4: Perphenazine Outcome

The patient has myoclonus and hypersalivation. These 2 symptoms are suggestive of…

4.3.1. Clozapine Case 4: Perphenazine Outcome

The patient has myoclonus and hypersalivation. These 2 symptoms are suggestive of…

Clozapine intoxication.

4.3.1. Clozapine Case 4: Perphenazine Outcome

Worsening of psychosis indicates…

4.3.1. Clozapine Case 4: Perphenazine Outcome

Worsening of psychosis indicates…

It is hard to say (see next slide).

4.3.1. Clozapine Case 4: Perphenazine Outcome

- Worsening of psychosis can be a sign:
  1) that perphenazine was not as effective as haloperidol (patient was stable on haloperidol),

  and/or

  2) of a clozapine intoxication.

  In the experience of Dr. de Leon, clozapine intoxication:
  - can occasionally manifest as delirium
  - but does not manifest as a pure psychotic exacerbation without confusion.

4.3.1. Clozapine Case 4: Perphenazine Outcome

This is why it is important to make only ONE medication change at a time, particularly in complex patients.

4.3.1. Clozapine Case 4: Perphenazine Outcome

- Dr. de Leon thought adding a third antipsychotic was not a good idea. This is why he proposed stopping haloperidol before adding perphenazine.
- In retrospect, this complicated the interpretation.

4.3.2. Perphenazine: Next Course of Action

4.3.2. Clozapine Case 4: Perphenazine Next

How will you verify a clozapine intoxication?

4.3.2. Clozapine Case 4: Perphenazine Next

How will you verify a clozapine intoxication?

With clozapine TDM.

4.3.2. Clozapine Case 4: Perphenazine Next

- During the 11th day on perphenazine and 7 days after ↑ 48 mg/d:
  - clozapine D: 450 mg/day
  - clozapine C: 1451 ng/ml
  - norclozapine C: 484 ng/ml
  - total C: 1935 ng/ml

4.3.2. Clozapine Case 4: Perphenazine Next

Was the clozapine C=1461 ng/ml compatible with a clozapine intoxication?

4.3.2. Clozapine Case 4: Perphenazine Next

Was the clozapine C=1461 ng/ml compatible with a clozapine intoxication?

Yes, a C>1000 ng/ml is definitively too high.

The concept of clozapine C therapeutic range is discussed in a prior presentation (see Clozapine Case 1: The Relevance of CYP).

4.3.2. Clozapine Case 4: Perphenazine Next

What was the clozapine C/D ratio on perphenazine?

4.3.2. Clozapine Case 4: Perphenazine Next

What was the clozapine C/D ratio on perphenazine?

C/D=1451/450=3.2.

4.3.2. Clozapine Case 4: Perphenazine Next

What was the total clozapine C/D ratio on perphenazine?

4.3.2. Clozapine Case 4: Perphenazine Next

What was the total clozapine C/D ratio on perphenazine?

C/D=1935/450=4.3.

4.3.2. Clozapine Case 4: Perphenazine Next

Day	Clo D	C (ng/ml)			C/D Ratio	
	mg/day	Clo	NorC	Total	Clo	Total
-168	500	653	242	895	1.3	1.8
-164	500	755	274	1029	1.5	2.1
-143	400	557	185	742	1.4	1.9
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-73	400	621	196	817	1.6	2.0
-45	450	613	201	814	1.4	1.8
-16	450	657	181	838	1.5	1.9
11	450	1451	484	1935	3.2	4.3

Clo: clozapine; NorC: norclozapine

4.3.2. Clozapine Case 4: Perphenazine Next

Comparison TDM

	Before	Perphenazine
N	8	1
	Means	
Clozapine C/D	1.5	3.2
Total Clozapine C/D	2.0	4.3

Ratios are increased > 2 x.
This indicates that clozapine metabolism is decreased by half and is severely impaired.

4.4.3. Clozapine Case 4: Diagnosis

- 2 days later (day 13 on perphenazine) (after refusing 350 mg night dose from total of 450 mg/d):
  - clozapine C: 1162 ng/ml
  - norclozapine C: 469 ng/ml
  - total C: 1631 ng/ml
  - perphenazine C: 19 ng/ml

- These clozapine Cs were not in steady state but continued to be too high.

4.3.3. Perphenazine: Intervention

4.3.3. Clozapine Case 4: Intervention

Please remember we have two problems:

1) clozapine intoxication signs and
2) worsening of the psychosis.

4.3.3. Clozapine Case 4: Intervention

What will you do after seeing the TDM results to resolve these 2 issues?

4.3.3. Clozapine Case 4: Intervention

What will you do after seeing the TDM results to resolve these 2 issues?

Propose to the patient a switch back from perphenazine to haloperidol.

4.3.3. Clozapine Case 4: Intervention

- Perphenazine was discontinued.
- Haloperidol (15 mg/day) was restarted.
- 8 days later:
  - clozapine C: 693 ng/ml
  - norclozapine C: 222 ng/ml
  - total C: 915 ng/ml

4.3.3. Clozapine Case 4: Intervention

What was the clozapine C/D ratio 8 days after perphenazine discontinuation?

4.3.3. Clozapine Case 4: Intervention

What was the clozapine C/D ratio 8 days after perphenazine discontinuation?

C/D=693/450=1.5.

4.3.3. Clozapine Case 4: Intervention

What was the
total clozapine C/D ratio
8 days after perphenazine
discontinuation?

4.3.3. Clozapine Case 4: Intervention

What was the
total clozapine C/D ratio
8 days after perphenazine
discontinuation?

C/D=915/450=2.0.

4.3.3. Clozapine Case 4: Intervention

- Another 2 clozapine TDMs showed similar values.
  They are described in next slide.

4.3.2. Clozapine Case 4: Perphenazine Next

Day	Clo D	C (ng/ml)			C/D ratio	
	mg/day	Clo	NorC	Total	Clo	Total
-168	500	653	242	895	1.3	1.8
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-73	400	621	196	817	1.6	2.0
-45	450	613	201	814	1.4	1.8
-16	450	657	181	838	1.5	1.9
11	450	1451	484	1935	3.2	4.3
21	450	693	222	915	1.5	2.0
46	450	738	243	981	1.6	2.2
67	450	529	193	722	1.2	1.6

Clo: clozapine; NorC: norclozapine

4.3.3. Clozapine Case 4: Intervention

Comparison TDM

	Before	Perphenazine	After
N	8	1	3 .
	Mean		
Clozapine C/D	1.5	3.2	1.5
Total clozapine C/D	2.0	4.3	1.9

The C/D ratios return to baseline.

4.3.3. Clozapine Case 4: Intervention

- The change to haloperidol was associated with:
  - improvement of psychosis
  - disappearance of threatening behavior
  - no hypersalivation
  - no knee buckling
- The patient agreed to 150 mg haloperidol decanoate injection.
- Oral haloperidol was discontinued and haloperidol decanoate injections were started and given every 3 weeks.

4.4. Clozapine TDM Follow-Up

4.4. Clozapine TDM Follow-Up

4.4.1. Medication Changes

4.4.2. Clozapine TDM Follow-up

4.4.3. Interpretation

4.4.1. Follow-Up: Medication Changes

4.4.1. Case 4: Follow-Up Medication Changes

- The patient was followed-up for > 200 days:
  - He asked to be switched from benztropine (9 mg/day) to trihexyphenidyl (4 mg/day).
  - He agreed to continue haloperidol decanoate every 3 weeks (first 150 mg and then 200 mg).
  - He finally agreed to clonazepam discontinuation and
  - valproate D ↓ slightly to 2750 mg/day.
- Medication reduction was accomplished.

4.4.1. Case 4: Follow-Up Medication Changes

- Before perphenazine, clozapine D=450 mg/day had provided clozapine Cs in 600 ng/ml, which is clearly >350 ng/ml.
- Dr. de Leon tried ↓ clozapine D=350 mg/day, but Cs ranged in the low 300s ng/ml.
- He ↑ clozapine D back to 450 mg/day, which provided a clozapine C=433 ng/ml, > recommended 350 ng/ml lower limit.
- Pink values reflect medication reduction.

4.4.2. Follow-Up: Clozapine TDM

4.4.2. Case 4: Clozapine TDM Follow-Up

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-108	500	823	303	1126	1.7	2.3
-73	400	621	196	817	1.6	2.0
-45	450	613	201	814	1.4	1.8
-16	450	657	181	838	1.5	1.9
11	450	1451	484	1935	3.2	4.3
21	450	693	222	915	1.5	2.0
46	450	738	243	981	1.6	2.2
67	450	529	193	722	1.2	1.6
123	350	327	129	456	0.9	1.3
151	350	318	126	444	0.9	1.3
179	350	311	127	438	0.9	1.3
207	350	327	129	456	0.9	1.3
263	450	433	162	595	1.0	1.3

4.4.2. Case 4: Clozapine TDM Follow-Up

Comparison TDM

	Before	Perphenazine	After Med Reduction
N	8	1	5
		Means	
Clozapine C/D	1.5	3.2	0.9
Total clozapine C/D	2.0	4.3	1.2

After the medication reduction, the clozapine C/D ratio=0.9 (<1.2), which is within the normal US range.
The total clozapine C/D ratio=1.2 also looks normal.

4.4.3. Follow-Up: Interpretation

4.4.3. Case 4: Follow-Up Interpretation

Comparison TDM

	Before	Perphenazine	After Med Reduction
Clozapine Metabolism	Slightly ↓	Very ↓	Normal for US

4.4.3. Follow-Up: Interpretation

4.4.3.1. Before Perphenazine

4.4.3.2. On Perphenazine

4.3.3.3. After Perphenazine

4.3.3.4. Longitudinal Course of Clozapine Metabolism

4.4.3.1. Before Perphenazine: Interpretation

4.4.3.1. Case 4: Interpretation Before

How do you explain that clozapine C/D ratios were slightly ↓ before, very ↓on perphenazine, and normal after?

4.4.3.1. Case 4: Interpretation Before

- It is possible that the patient, despite being ♂ and a mild smoker, has average baseline metabolic capacity.
- Imagine that, before perphenazine, clozapine metabolism was already compromised by competitive inhibition of:
  - CYP2D6 from
    - benztropine, and
    - haloperidol
  - CYP3A4: clonazepam, and
  - possibly by an unknown mechanism: valproate

4.4.3.2. On Perphenazine: Interpretation

4.4.3.2. Case 4: Perphenazine Interpretation

What do we know about perphenazine metabolism?

4.4.3.2. Case 4: Perphenazine Interpretation

- In vivo perphenazine studies suggest:
  - the most important enzyme is CYP2D6

http://www.ncbi.nlm.nih.gov/pubmed/17429316

- In vitro study suggests other CYPs are also involved:
  - CYP1A2
  - CYP3A4
  - CYP2C19

http://www.ncbi.nlm.nih.gov/pubmed/11136295

- Population US study:
  - African-Americans: faster metabolism
  - Smokers: faster metabolism
    Proposed that metabolism is by CYP1A2.

http://www.ncbi.nlm.nih.gov/pubmed/19843655

4.4.3.2. Case 4: Perphenazine Interpretation

Is this relevant in this case?

4.4.3.2. Case 4: Perphenazine Interpretation

Is this relevant in this case?

Probably yes.
Perphenazine can be a competitive inhibitor of CYP2D6 and perhaps CYP1A2.

4.4.3.2. Case 4: Perphenazine Interpretation

- This is a patient with compromised clozapine metabolism.
- Perphenazine acted as a competitive inhibitor for clozapine metabolism, and saturated the system.
  The ability to metabolize clozapine was ↓ in half when compared to baseline.
- The concept of competitive inhibition is explained in the Clozapine Case 3 Presentation.

4.4.3.3. After Perphenazine: Interpretation

4.4.3.3. Case 4: Interpretation After

How do you explain that clozapine metabolism normalized in the end?

4.4.3.3. Case 4: Interpretation After

- Several medications were changed:
  - benztropine was discontinued (competitor for CYP2D6)
  - clonazepam was discontinued (competitor for CYP3A4)
  - haloperidol: from oral to decanoate. Haloperidol may compete for CYP2D6. It is not known whether this change (oral vs. decanoate) influences CYP2D6 competitive inhibition or not.

4.4.3.3. Case 4: Interpretation After

- With these medication changes:
  - The clozapine C/D ratio become normal. A clozapine C/D ratio=0.9, is in the middle of the US normal range=0.6-1.2.

4.4.3.4. Longitudinal Course of Clozapine Metabolism

4.4.3.4. Case 4: Longitudinal Course of Clozapine Metabolism

Day	Clo D	C (ng/ml)			C/D Ratio	
	mg/day	Clo	NorC	Total	Clo	Total
-168	500	653	242	895	1.3	1.8
-164	500	755	274	1029	1.5	2.1
-143	400	557	185	742	1.4	1.9
-136	400	704	204	908	1.8	2.3
-108	500	823	303	1126	1.7	2.3
-73	400	621	196	817	1.6	2.0
-45	450	613	201	814	1.4	1.8
-16	450	657	181	838	1.5	1.9
11	450	1451	484	1935	3.2	4.3
21	450	693	222	915	1.5	2.0
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123	350	327	129	456	0.9	1.3
151	350	318	126	444	0.9	1.3
179	350	311	127	438	0.9	1.3
207	350	327	129	456	0.9	1.3
263	450	433	162	595	1.0	1.3

4.4.3.4. Case 4: Longitudinal Course of Clozapine Metabolism

- Clozapine metabolism longitudinal course:
  - slightly ↓: competitive inhibition by multiple medications
  - very ↓: competitive inhibition by adding perphenazine to multiple medications
  - slightly ↓: competitive inhibition by multiple medications
  - normal: after stopping other medications.

Questions

- Please review the 10 questions in the pdf document entitled “Questions on the Presentation: Clozapine Case 4”.
- 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. D
2. D
3. C
4. D
5. A
6. B
7. D
8. A
9. D
10. B