Clozapine Case 2: Infection 12-18-15

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2. Clozapine Case 2

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http://www.ncbi.nlm.nih.gov/pubmed/14499324

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

- AGNP: (Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie). German TDM expert group
- C: concentration
- C/D: concentration-to-dose ratio
- CRF: corticotropin-releasing factor
- CRP: C-reactive protein
- D: dose
- EM: extensive metabolizer
- PM: poor metabolizer
- TDM: therapeutic drug monitoring
- URI: upper respiratory infection

Clozapine Case 2

2.0 Introduction

2.1 Tobacco Smoking

2.2 Low-Dose Olanzapine

2.3. Clozapine Trial

2.4. Olanzapine and Inflammation

2.5. Inflammation and CYPs

Clozapine Case 2

2.0 Introduction

2.1 Tobacco Smoking

- 2.1.1. Smoking Compounds
- 2.1.2. Pharmacokinetic Effects of 10 cigarettes/day
- 2.1.3. Pharmacodynamic Effects of 10 cigarettes/day

2.2 Low-Dose Olanzapine

- 2.2.0. Description
- 2.2.1. Therapeutic Window
- 2.2.2. Olanzapine Cs
- 2.2.3. Pharmacodynamics

2.3. Clozapine Trial

- 2.3.1. First Clozapine Cs
- 2.3.2. Clozapine Cs During Infection

2.4. Olanzapine and Inflammation

2.5. Inflammation and CYPs

- 2.5.1. Pharmacology
- 2.5.2. Clinical Relevance in Psychiatry

2.0. Introduction

2.0. Case 2: Introduction

http://www.ncbi.nlm.nih.gov/pubmed/14499324

- 34-year-old ♂ with schizophrenia; weight of 102 Kg (history of very severe violence)
- He smoked 10 cig/day.
- On low olanzapine doses (2.5-10 mg/day) for 2 years: stable, better than previously, but not ready for discharge.
- Twice previously clozapine was tried at another hospital (low WBC > 3000).
- After unsuccessful trials on all atypical antipsychotics, clozapine was tried again.

2.1. Tobacco Smoking

2.1. Tobacco Smoking

2.1.1. Smoking Compounds

2.1.2. Pharmacokinetic Effects of 10 cigarettes/day

2.1.3. Pharmacodynamic Effects of 10 cigarettes/day

2.1.1. Smoking Compounds

2.1.1. Case 2: Tobacco Compounds

What are the main pharmacological compounds that tobacco smoking delivers?

2.1.1. Case 2: Tobacco Compounds

What are the main pharmacological compounds that tobacco smoking delivers?

Nicotine and other alkaloids.

2.1.1. Case 2: Tobacco Compounds

What other pharmacological compounds does tobacco smoking deliver?

2.1.1. Case 2: Tobacco Compounds

What other pharmacological compounds does tobacco smoking deliver?

Smoke.

2.1.2. Pharmacokinetic Effects of 10 cigarettes/day

2.1.2. Clozapine Case 2: Pharmacokinetics of 10 cig/d

- Low “dose” of cigarettes for schizophrenia patient (under “controlled smoking” on his unit)
- Several enzymes metabolize nicotine:
  - CYP2A6 is the major enzyme.
  - Other CYPs and glucuronidation.

http://www.ncbi.nlm.nih.gov/pubmed/20554984

- Cotinine is the major metabolite.

2.1.2. Clozapine Case 2: Pharmacokinetics of 10 cig/d

- Low “dose” of cigarettes
  but clinically relevant.
- Tobacco smoke (polycyclic
  aromatic hydrocarbons)
  is an inducer of:
  - CYP1A2
  - Some glucuronidation enzymes

2.1.3.Pharmacodynamic Effects of 10 cigarettes/day

2.1.3. Clozapine Case 2: Pharmacodynamics of 10 cig/d

- Nicotine is an agonist of nicotine receptors.
- Cholinergic receptors:
  - nicotine receptors
  - muscarinic receptors

2.1.3. Clozapine Case 2: Pharmacodynamics of 10 cig/d

- A nicotine receptor has 5 subunits.
- Brain expresses:
  - 9 α subunits (α_2 through α_{10}) and
  - 3 β subunits (β_2 through β_4).
- The most abundant receptors are:
  - $\alpha_4\beta_2$ (most important for nicotine addiction),
  - $\alpha_3\beta_4$ (most important for cardiovascular),
  - and $\alpha 7$, homomeric (role in learning and sensory gating).

2.1.3. Clozapine Case 2: Pharmacodynamics of 10 cig/d

- Nicotine releases:
  - dopamine
  - glutamate
  - GABA

  Important for nicotine dependence.
- Nicotine releases CRF:

  May be important for nicotine withdrawal.

2.1.3. Clozapine Case 2: Pharmacodynamics of 10 cig/d

- Smoke inhibits: MAO-A, and MAO-B.
- This inhibition may ↓dopamine metabolism and contribute to nicotine addiction.
- The MAO inhibition appears to be caused by condensation products of acetaldehyde.

2.2. Low-Dose Olanzapine

2.2. Low-Dose Olanzapine

2.2.0. Description
2.2.1. Therapeutic Window
2.2.2. Olanzapine Cs
2.2.3. Pharmacodynamics

2.2.0. Low-Dose Olanzapine: Description

2.2.0. Case 2: Low-Dose Olanzapine

- Olanzapine initiation:
  - 5 mg/day (2.5 mg twice a day) was started.
  - Two weeks later the patient showed mild improvement from formal thought disturbance.
  - Quetiapine was discontinued.

2.2.0. Case 2: Low-Dose Olanzapine

- Olanzapine stabilization:
  - The patient showed definite improvement in formal thought disturbance and orientation.
  - Olanzapine C: 5 ng/ml
    (probably appropriate for low dose)
  - The tremor continued, so benztropine was ↑ from 3 to 4 mg/day with no effects.

2.2.0. Case 2: Low-Dose Olanzapine

- Olanzapine stabilization:
  - Due to improvement, a progressive attempt was made to transfer the patient from a low stimuli unit for violent patients to a locked treatment-refractory unit.
  - Despite his improvement, the patient could not tolerate over-stimulation.
  - The patient continued to have great difficulty being around young women.

2.2.0. Case 2: Low-Dose Olanzapine

- Olanzapine stabilization (other meds):
  - Valproate: 5250 mg/day for seizures.
  - Propranolol: 80 mg/day for akathisia.
  - Gemfibrozil: 1200 mg/day for hyperlipidemia.
  - Benztropine: 4 mg/day for tremor.

2.2.0. Case 2: Low-Dose Olanzapine

- Olanzapine stabilization:
  Very sensitive to akathisia:
  - Present in spite of propranolol (and valproate and benztropine)
  - With low Cs of antipsychotics: quetiapine or olanzapine

2.2.0. Case 2: Low-Dose Olanzapine

What can we say from the pharmacological point of view about a patient kept on low olanzapine doses (2.5-10 mg/day)?

2.2.0. Case 2: Low-Dose Olanzapine

What can we say from the pharmacological point of view about a patient kept on low olanzapine doses (2.5-10 mg/day)?

Little.

2.2.0. Case 2: Low-Dose Olanzapine

- Olanzapine is a wide-therapeutic-range drug.
- This means that pharmacology sets few constraints on the prescriber's actions.
- Little can be said about this low dose until we are sure the prescriber knows what he/she is doing.

2.2.1. Olanzapine: Therapeutic Window

2.2.1. Olanzapine Therapeutic Window

How can Dr. de Leon demonstrate to you that olanzapine is in fact a wide-therapeutic-window drug?

2.2.1. Olanzapine Therapeutic Window

How can Dr. de Leon demonstrate to you that olanzapine is in fact a wide-therapeutic-window drug?

By looking at its AGNP therapeutic reference range (20-80 ng/ml).

http://www.ncbi.nlm.nih.gov/pubmed/22053351

2.2.1. Olanzapine: Therapeutic Window

What is the therapeutic window/index for olanzapine?

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What is the therapeutic window/index for olanzapine?

80/20=4

2.2.1. Olanzapine: Therapeutic Window

What does a therapeutic window of 4 mean?

2.2.1. Olanzapine: Therapeutic Window

What does a therapeutic window of 4 mean?

It indicates a wide therapeutic window (since it is >3).

2.2.2. Low-Dose Olanzapine: Cs

2.2.2. Case 2: Olanzapine Cs

How can we comment on the Cs of this olanzapine treatment?

2.2.2. Case 2: Olanzapine Cs

How can we comment on the Cs of this olanzapine treatment?

By calculating the C/D ratio.

2.2.2. Case 2: Olanzapine Cs

- Olanzapine low D provides low C.
  - D: 2.5 mg/day
  - C: 5 ng/ml.

2.2.2. Case 2: Olanzapine Cs

What is his olanzapine C/D?

2.2.2. Case 2: Olanzapine Cs

What is his olanzapine C/D?

C/D=2 (5/2.5).

2.2.2. Case 2: Olanzapine Cs

- Before starting clozapine:
  - D: 10 mg/day
  - C: 18 ng/ml.

2.2.2. Case 2: Olanzapine Cs

What is his second olanzapine C/D?

2.2.2. Case 2: Olanzapine Cs

What is his second olanzapine C/D?

C/D=1.8 (18/10).

2.2.2. Case 2: Olanzapine Cs

- After 300 mg/day of clozapine:
  - D: 10 mg/day
  - C: 19 ng/ml.

2.2.2. Case 2: Olanzapine Cs

What is his third olanzapine C/D?

2.2.2. Case 2: Olanzapine Cs

What is his third olanzapine C/D?

C/D=1.9 (19/10).

2.2.2. Case 2: Olanzapine Cs

What is the olanzapine C/D range?

2.2.2. Case 2: Olanzapine Cs

What is the olanzapine C/D range?

C/D=1.8 to 2.0

C/D was consistently around 2.

2.2.2. Case 2: Olanzapine Cs

Is an OLA C/D=2 normal?

2.2.2. Case 2: Olanzapine Cs

Is an OLA C/D=2 normal?

It has not been well studied.

2.2.2. Case 2: Olanzapine Cs

- Limited olanzapine C/D ratio data suggest:
  - Smokers: C/D around 1.6.
  - Non-smokers: C/D around 2.5.

http://www.ncbi.nlm.nih.gov/pubmed/19084370

2.2.3. Low-Dose Olanzapine Pharmacodynamics

1.2.2. Case 2: Olanzapine Pharmacodynamics

What can we say from a pharmacodynamic point of view about this olanzapine treatment?

1.2.2. Case 2: Olanzapine Pharmacodynamics

What can we say from a pharmacodynamic point of view about this olanzapine treatment?

The patients was very sensitive to akathisia that was present with low Cs.

2.3. Clozapine Trial

2.3. Clozapine Trial

2.3.1. First Clozapine Cs
2.3.2. Clozapine Cs During Infection

2.3.1. First Clozapine Cs

2.3.1. Case 2: First Clozapine Cs

- Clozapine was added to:
  - Olanzapine: 10 mg/day.
  - Valproate: 5250 mg/day for seizures.
  - Propranolol: 80 mg/day for akathisia.
  - Gemfibrozil: 1200mg/day for hyperlipidemia.
  - Benztropine: 4 mg/day for tremor.

2.3.1. Case 2: First Clozapine Cs

- Clozapine:
  - D: 300 mg/day
  - Clozapine C: 195 ng/ml.
  - Norclozapine C: 120 ng/ml.

2.3.1. Case 2: First Clozapine Cs

What is his clozapine C/D?

2.3.1. Case 2: First Clozapine Cs

What is his clozapine C/D?

C/D=0.7 (195/300).

2.3.1. Case 2: First Clozapine Cs

What is his total clozapine C/D?

2.3.1. Case 2: First Clozapine Cs

What is his total clozapine C/D?

C/D=1.1 (315/300).

2.3.1. Case 2: First Clozapine Cs

Week	CLO D mg/day	CLO C ng/ml	CLO[1] C/D ratio	NOR C ng/ml	Total ng/ml	Total C/D[2] ratio
4	300	195	0.7	120	315	1.1

CLO: clozapine; NOR: norclozapine.

[1]Clozapine C/D ratio = CLO C/CLO D.

[2]Total clozapine C/D ratio = CLO C+NOR C/CLO D.

2.3.1. Case 2: First C/D Ratio

Is a CLO C/D=0.7 normal?

2.3.1. Case 2: First C/D Ratio

Is a CLO C/D=0.7 normal?

Yes.

2.3.1. Case 2: First C/D Ratio

- In the USA:
  - A C/D ratio >1.2 indicates poor metabolic capacity.
  - A C/D ratio <0.6 indicates high metabolic capacity.
  - The C/D ratio usually ranges from 0.6-1.2.

http://www.ncbi.nlm.nih.gov/pubmed/16040229

2.3.1. Case 2: First C/D Ratio

- 0.7 is toward the low range of 0.6-1.2 (toward rapid metabolism).
- He is a male smoker. Both male gender and smoking are associated with:
  - ↑ clozapine metabolism and
  - ↓ C/D ratio.

2.3.1. Case 2: First C/D Ratio

- Other CYP1A2 drugs taken by the patient may ↓ clozapine metabolism by competitive inhibition:
  - olanzapine
  - propranolol
- Valproate can be a mild:
  - inhibitor, or
  - inducer.

2.3.1. Case 2: First C/D Ratio

After reviewing all the data, is a CLO C/D=0.7 normal?

2.3.1. Case 2: First C/D Ratio

After reviewing all the data, is a CLO C/D=0.7 normal?

Yes, it is a normal C/D.

2.3.2. Clozapine C/D Ratio During Infection

2.3.2. Case 2: Infection C/D Ratio

- The patient is taking 600 mg/day.
- During the weekend, he was:
  - Sedated
  - Falling on the floor (knee buckling)
- URI: He had not taken an antibiotic before Dr. de Leon arrived at the unit early Monday morning.

2.3.2. Case 2: Infection C/D Ratio

The patient displayed sleepiness and falling on the floor.

Is that relevant?

2.3.2. Case 2: Infection C/D Ratio

The patient displayed sleepiness and falling on the floor.

Is that relevant?

Yes.

2.3.2. Case 2: Infection C/D Ratio

Why?

2.3.2. Case 2: Infection C/D Ratio

Why?

These are signs of clozapine intoxication.

2.3.2. Case 2: Infection C/D Ratio

After questioning nurses, Dr de Leon was sure patient had “knee bucling”

What do neurologists call knee buckling?

2.3.2. Case 2: Infection C/D Ratio

After questioning nurses, Dr de Leon was sure patient had “knee bucling”

What do neurologists call knee buckling?

Myoclonus.

2.3.2. Case 2: Infection C/D Ratio

How can you be sure this is a clozapine intoxication?

2.3.2. Case 2: Infection C/D Ratio

How can you be sure this is a clozapine intoxication?

Draw a blood level (TDM). It will be unavailable for several days.

2.3.2. Case 2: Infection C/D Ratio

You do not have access to clozapine Cs.

What do you do next?

2.3.2. Case 2: Infection C/D Ratio

You do not have access to clozapine Cs.
What do you do next?

↓ the clozapine D.

2.3.2. Case 2: Infection C/D Ratio

The clozapine
D was ↓ to 400 mg/day
and
the signs of intoxication
decreased.

2.3.2. Case 2: Infection C/D Ratio

- A nasal drainage culture:
  + Streptococcus Group C.
- Clozapine C upon arrival:
  - D: 600 mg/day
  - C: 1245 ng/ml
  - Norclozapine C: 472 ng/ml.

2.3.2. Case 2: Infection C/D Ratio

What is this clozapine C/D?

2.3.2. Case 2: Infection C/D Ratio

What is this clozapine C/D?

2.1 (1245/600).

2.3.2. Case 2: Infection C/D Ratio

What is this total clozapine C/D?

2.3.2. Case 2: Infection C/D Ratio

What is this total clozapine C/D?

2.9 (1717/600).

2.3.2. Case 2: Infection C/D Ratio

Week	CLO D mg/day	CLO C ng/ml	CLO[1] C/D ratio	NOR C ng/ml	Total ng/ml	Total C/D[2] ratio
4	300	195	0.7	120	315	1.1
8 Infection	600	1245	2.1	472	1717	2.9

CLO: clozapine; NOR: norclozapine.

[1]Clozapine C/D ratio = CLO C/CLO D.

[2]Total clozapine C/D ratio = CLO C+NOR C/CLO D.

2.3.2. Case 2: Infection C/D Ratio

The CLO C/D went
from 0.7 (before)
to 2.1 (after the infection).

2.3.2. Case 2: Infection C/D Ratio

The total CLO C/D went from 1.1 (before) to 2.9 (after the infection).

2.3.2. Case 2: Infection C/D Ratio

The C/D increased (and the total C/D even more). This is a sign of… ?

2.3.2. Case 2: Infection C/D Ratio

The C/D increased (and the total C/D even more). This is a sign of… ?

↓ in clozapine metabolism

2.3.2. Case 2: Infection C/D Ratio

Week	CLO D mg/day	CLO C ng/ml	CLO[1] C/D ratio	NOR C ng/ml	Total ng/ml	Total C/D[2] ratio
4	300	195	0.7	120	315	1.1
8 Infection	600	1245	2.1	472	1717	2.9
9	400	352	0.9	154	506	1.3
10	400	277	0.7	152	429	1.1
12	600	436	0.7	283	719	1.2
14	700	545	0.8	316	861	1.2
16	700	471	0.7	285	756	1.1
17	800	540	0.7	314	854	1.1
18	800	793	1.0	472	1265	1.6
22	800	697	0.9	370	1067	1.3
26	800	659	0.8	354	1013	1.3
31	800	564	0.7	206	770	1.0
38	800	755	0.9	344	1099	1.4
40	700	599	0.9	305	904	1.3
44	700	434	0.6	263	697	1.0
46	600	477	0.8	260	737	1.2
48	700	590	0.8	301	891	1.3

CLO: clozapine; NOR: norclozapine.

[1]Clozapine C/D ratio = CLO C/CLO D.

[2]Total clozapine C/D ratio = CLO C+NOR C/CLO D.

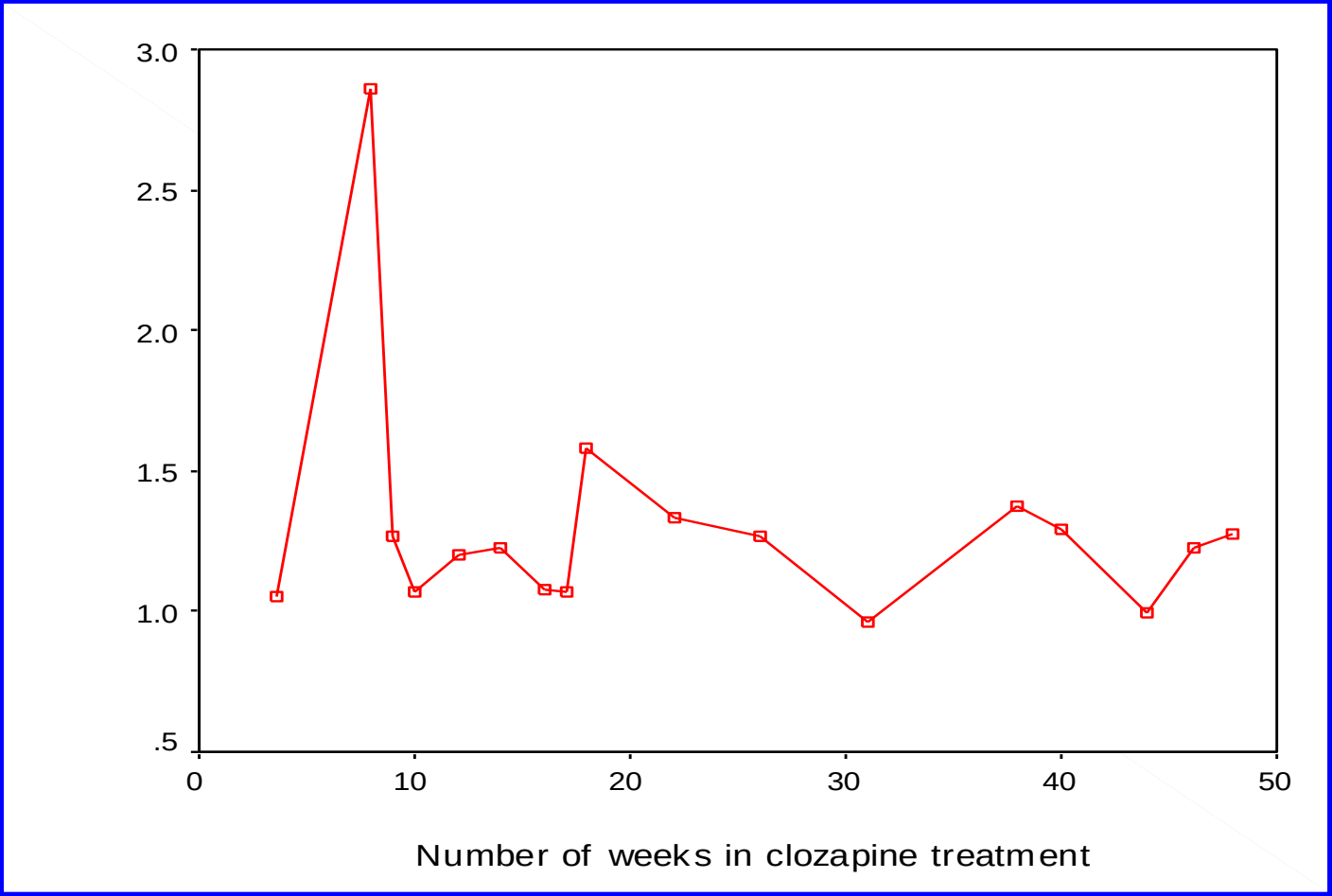
2.3.2. Case 2: Infection C/D Ratio

- TDM before and after infection:
  - Clozapine C/D = 0.6-0.9
  - Total C/D = 1.0-1.6
- TDM during infection:
  - Clozapine C/D = 2.1
  - Total C/D = 2.9

2.3.2. Case 2: Infection C/D Ratio

Focus on the total C/D, which dramatically increased with the Streptococcus Group C infection.

2.3.2. Case 2: Infection C/D Ratio



2.3.2. Case 2: Infection C/D Ratio

The prior figure indicates that total C/D increased during the infection (it approximately doubled).

2.3.2. Case 2: Infection C/D Ratio

Doubling of the total total clozapine C/D during the infection indicates a ↓ in clozapine metabolism by half.

2.3.2. Case 2: Infection C/D Ratio

- Obviously, the ↓ in clozapine metabolism can only be explained by a temporal (environmental) abnormality: the infection.

2.3.2. Case 2: Infection C/D Ratio

- The literature had shown that theophylline C increases
  - in children with URI, and
  - in adults with fever and pneumonia.

  The dose needs to be cut in half.
- Cytokines inhibit CYP1A2, which metabolizes theophylline.

2.3.2. Case 2: Infection C/D Ratio

- More recent literature describes ↓ clozapine metabolism during:
  - pneumonias,
  - severe URI with fever,
  - pyelonephritis, and
  - appendicitis.
  - Severe inflammations:
    - lamotrigine-induced rash
- CRP has been used as a marker.

2.4. Olanzapine and Inflammation

2.4. Olanzapine and Inflammation

Week	Olanzapine D mg/day	Olanzapine C ng/ml	Olanzpine[1] C/D ratio ng/ml	Clozapine D
Before CLO	2.5	5	2	0
Before CLO	10	18	1.8	0
4	10	19	1.9	300
8 Infection	10	32	3.2	600

[1]Olanzapine C/D ratio = Olanzapine C/Olanzapine D.

2.4. Olanzapine and Inflammation

- Olanzapine metabolism also ↓:
  Olanzapine C/D ratio was:
  - around 2 before infection
  - ↑ to 3.2 during infection
- Olanzapine: metabolized by CYP1A2
- Effects of infection on metabolism:
  - olanzapine: less important (wide-therapeutic-window drug)
  - clozapine: very important (narrow-therapeutic-window drug)

2.5. Inflammation and CYPs

2.5. Inflammation and CYPs

2.5.1. Pharmacology

2.5.2. Clinical Relevance in Psychiatry

2.5.1. Inflammation and CYPs: Pharmacology

2.5.1. Inflammations and CYPs: Pharmacology

- Shah & Smith,2015 http://www.ncbi.nlm.nih.gov/pubmed/25519488 in a pharmacology review describe:
  ↑ cytokines in inflammation can inhibit several metabolism enzymes, including:
  - CYP1A2, and
  - CYP3A4.
- One form of phenoconversion is when:
  an EM (normal metabolizer) becomes a PM.
- Co-prescribing an inhibitor was the typical case of conversion from an EM to PM.
  Inflammation (and severe infections) can be another cause of phenoconversion to a PM.

2.5.2. Inflammation and CYPs: Clinical Relevance in Psychiatry

2.5.2 Inflammation and CYPs: Psychiatry

2.5.2.1. CYP1A2 Psychiatric Drugs
2.5.2.2. CYP3A4 Psychiatric Drugs

2.5.2.1. Inflammation and CYPs: CYP1A2 Psychiatric Drugs

2.5.2.1. Inflammations and CYP1A2 Psychiatric Drugs

- Inflammation and infection can definitively inhibit metabolism of clozapine and olanzapine.
- Other psychiatric drugs partly dependent on CYP1A2 for their metabolism are:
  - asenapine, and
  - duloxetine

  Be careful if any of your patients are taking any of these drugs. They could become intoxicated during severe infections or severe inflammations.
- During severe inflammation/infections consider
  - measuring TDM (if available), and/or
  - cut the dose in half (0.5 dose correction) if any signs of toxicity appear.

2.5.2.2. Inflammation and CYPs: CYP3A4 Psychiatric Drugs

2.5.2.2. Inflammations and CYP3A4 Psychiatric Drugs

- Recent studies http://www.ncbi.nlm.nih.gov/pubmed/26449925 http://www.ncbi.nlm.nih.gov/pubmed/26032842 suggest inflammation can inhibit metabolism of psychiatric drugs metabolized by CYP3A4:
  - risperidone, and
  - quetiapine.
- If these are verified, it would have major clinical relevance related to multiple psychiatric drugs.
- The next slide provides a comprehensive list of CYP3A4 psychiatric drugs. Whenever a severe inflammation/infection occurs, be alert to toxicity due to ↓ in their metabolism.

2.5.2.2. Inflammations and CYP3A4 Psychiatric Drugs

CYP3A4	CYP2D6/CYP3A4	CYP2C19/CYP3A4
ANTIDEPRESSANTS		
reboxetine		
trazadone		
vilazadone		
BENZODIAZEPINES		
alprazolam		clobazam
midazolam		diazepam
triazolam		
MOOD STABILIZERS		
carbamazepine		
SECOND-GENERATION ANTIPSYCHOTICS		
cariprazine	aripiprazole	
lurasidone	brexpiprazole	
quetiapine	iloperidone	
	risperidone	

Theoretical presentations on pharmacokinetics provide more details.

Questions

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