Clozapine Case 1
The Relevance of CYP
12-18-15

Jose de Leon, MD

1. Clozapine Case 1

J Clin Psychiatry 1996;57:175-176

http://www.ncbi.nlm.nih.gov/pubmed/8601555

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. Realize 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.

Educational Objectives

This presentation has considerable data on clinical pharmacology:

1. Repeated practice and review of your patients' drugs is the only way of learning and remembering pharmacological facts.
2. Psychiatry textbooks tend to present a lot of pharmacodynamic data, but frequently we do not know the clinical relevance of this data.
3. Dr. de Leon gives more relevance to pharmacokinetic data than most psychiatric textbooks.
4. Please pay attention to the red font, which indicates important pharmacological data to remember.

Abbreviations

- Receptors:
  - α: alpha & β: beta
    (two types of adrenergic receptors: α and β)
  - H: histamine
  - M: muscarinic (two types of cholinergic receptors:
    muscarinic and nicotinic)
- Pharmacokinetics basic concepts:
  - C: concentration
  - D: dose
  - C/D: concentration-to-dose ratio
- Pharmacokinetics by pharmacologists:
  - They use therapeutic drug monitoring (TDM) to measure serum/plasma Cs or levels.
  - The German TDM expert group is called AGNP: (Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie).

Statistical Abbreviations for slide 73

- CI: confidence interval
- OR: odds ratio
- RCT: randomized clinical trial

The presentation “Introduction to Statistical Concepts Needed for Clinical Pharmacology” explains how to interpret ORs and CIs.

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

Relevance of This Case for Dr. de Leon

- In 1994, Dr. de Leon was supervising an NIH-funded double-blind clozapine study in Philadelphia.
  http://www.ncbi.nlm.nih.gov/pubmed/10553738
  - In theory, he was supposed to be an expert in clozapine clinical pharmacology.
  - Actually, he was ignorant of clozapine metabolism, and completely unaware of scientific developments in pharmacokinetics.
- He attended an international scientific meeting.
  (Collegium Internationale Neuro-Psychopharmacologicum [CINP])
  - Two researchers from the Karolinksa Institute (Sweden) presented a poster on clozapine metabolism.

Relevance of This Case for Dr. de Leon

- Dr. de Leon invited them to lecture. They presented a new concept: clozapine is metabolized by CYP1A2. http://www.ncbi.nlm.nih.gov/pubmed/7893591
- A few months later, a psychiatry fellow working on the clozapine study, Dr. White, called Dr. de Leon and asked his opinion about this case.
- This case convinced Dr. de Leon that:
  - rather than being an expert on clozapine, he was ignorant of how to properly use it.
  - "CYP" knowledge is very important in treating patients.
- In 1995, he moved to the University of Kentucky, and one of the main reasons he selected that position was the possibility of developing a collaboration with a pharmacologist with CYP expertise.

Clozapine Case 1

1.0. Introduction
1.1. Fluoxetine

1.2 Diazepam

1.3. Hypersalivation
1.4. Intoxication

1.5. Interpreting Clozapine Cs
1.6. Interpreting the Patient's C/D Ratio
1.7. Case Interpretation
1.8. Other

Clozapine Case 1

1.0. Introduction
1.1. Fluoxetine
- 1.1.1 Sedation
- 1.1.2. Pharmacokinetics
- 1.1.3. Pharmacodynamics

1.2 Diazepam
- 1.2.1. Sedation
- 1.2.2. Pharmacokinetics
- 1.2.3. Pharmacodynamics

1.3. Hypersalivation
1.4. Intoxication
- 1.4.1. Pharmacokinetics
- 1.4.2. Pharmacodynamics

1.5. Interpreting Clozapine Cs
1.6. Interpreting the Patient's C/D Ratio
1.7. Case Interpretation
1.8. Other

1.0. Introduction

1.0.Clozapine Case 1: Introduction

http://www.ncbi.nlm.nih.gov/pubmed/8601555

- 31-year-old African-American female
  - Non-smoker
  - Diagnosis of schizoaffective disorder
  - Same medication for 5 months' duration
    - Fluoxetine 30 mg/d
    - Diazepam 8 mg/d
    - Clozapine 550 mg/d
  - Chief complaint:
    - Increased sedation,
    - hypersalivation, and
    - inability to work (cognitive impairment).

1.0.Clozapine Case 1: Introduction

Increased sedation and cognitive impairment can indicate

1.0.Clozapine Case 1: Introduction

Increased sedation
and cognitive impairment
can indicate

Drug intoxication

1.1. Fluoxetine

1.1. Clozapine Case 1: Fluoxetine

Can 30 mg/day of fluoxetine cause drug intoxication presenting with sedation?

1.1. Clozapine Case 1: Fluoxetine

Can 30 mg/day of fluoxetine cause drug intoxication presenting with sedation?

Let's review fluoxetine's

1) sedation profile,

2) pharmacokinetics, and

3) pharmacodynamics.

1.1.1. Fluoxetine Sedation

1.1.1. Clozapine Case 1: Fluoxetine Sedation

- Typically, SSRIs can cause
  - agitation and
  - anxiety.
- They can also cause fatigue.

http://www.amazon.com/Handbook-Psychiatric-Therapy-Hyman Arana/dp/0781774861/ref=sr_1_1?ie=UTF8&s=books&qid=1278707314&sr=1-1

- According to fluoxetine's package insert, somnolence occurs in >10% (5-17%).

http://www.amazon.com/Drug-Information-Handbook-Clinically-Professionals/dp/1591953421/ref=sr_1_1?s=books&ie=UTF8&qid=1449934433&sr=1-1&keywords=drug+information+handbook

1.1.2. Fluoxetine Pharmacokinetics

1.1.2. Clozapine Case 1: Fluoxetine Pharmacokinetics

What can you say about fluoxetine 30 mg/day pharmacokinetics?

1.1.2. Clozapine Case 1: Fluoxetine Pharmacokinetics

- Typical fluoxetine doses: 20-40 mg/day.
  http://www.amazon.com/Handbook-Psychiatric-Therapy-Hyman Arana/dp/0781774861/ref=sr_1_1?ie=UTF8&s=books&qid=1278707314&sr=1-1
- Fluoxetine is metabolized by CYPs:
  - CYP2D6 is the major enzyme.
  - Others are
    - CYP2C9,
    - CYP2C19, and
    - CYP3A4.

  http://www.ncbi.nlm.nih.gov/pubmed/25196459
- Norfluoxetine is the main metabolite.

1.1.2. Clozapine Case 1: Fluoxetine Pharmacokinetics

- Fluoxetine (and norfluoxetine) are drug metabolism inhibitors:
  - Potent: CYP2D6
  - Moderate: CYP2C9
  - Weak to moderate:
    - CYP2C19 and
    - CYP3A4

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

1.1.3. Fluoxetine Pharmacodynamics

1.1.3. Clozapine Case 1: Fluoxetine Pharmacodynamics

What can you say about fluoxetine 30 mg/day pharmacodynamics?

1.1.3. Clozapine Case 1: Fluoxetine Pharmacodynamics

- Antidepressants (and antipsychotics) cause sedation by means of H_1 antagonism.

http://www.ncbi.nlm.nih.gov/pubmed/24494611

- Fluoxetine has very low affinity for H_1 receptors.

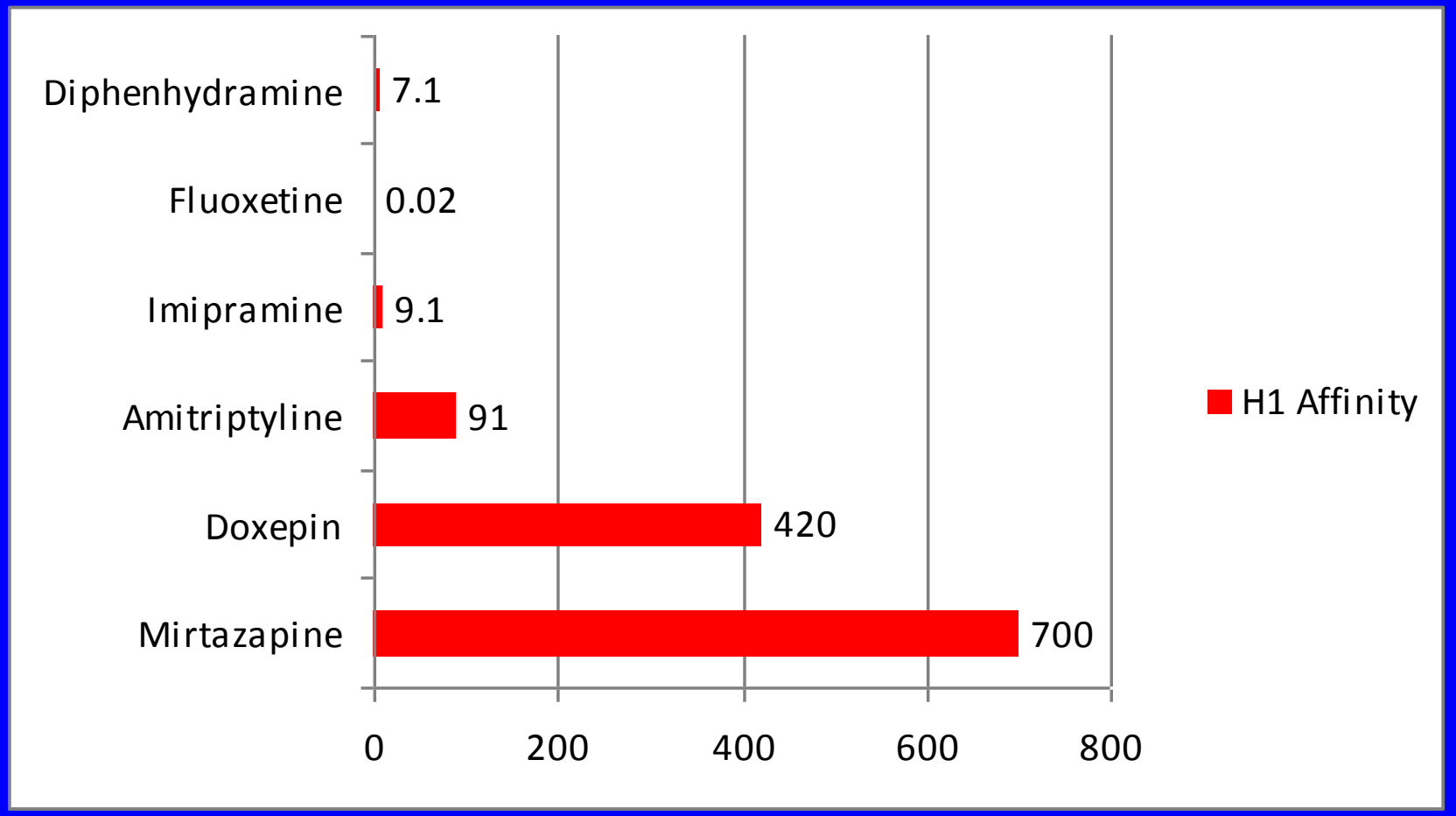
http://www.ncbi.nlm.nih.gov/pubmed/14552650

1.1.3. Clozapine Case 1: Fluoxetine Pharmacodynamics

- Affinity is typically expressed as the equilibrium dissociation constant.
- To extrapolate in the real world, remember:
  - It is measured in molars (correct by molecular weight to change to mg).
  - Dosages vary across antidepressants:
    - some in 100s mg/d,
    - others in 10s mg/d.
- In this article: http://www.ncbi.nlm.nih.gov/pubmed/14552650
  - The figure represents the inverse of affinity (high value indicates high affinity).
  - Multiply by a factor of 10^{-7}.
  - Diphenhydramine: probe for H_1 antagonism.

1.1.3. Clozapine Case 1: Fluoxetine Pharmacodynamics

http://www.ncbi.nlm.nih.gov/pubmed/14552650 Information taken from that article to design this figure



1.1. Clozapine Case 1: Fluoxetine

What is your conclusion?
Did 30 mg/day of fluoxetine cause the sedation?

1.1. Clozapine Case 1: Fluoxetine

What is your conclusion?
Did 30 mg/day of fluoxetine cause the sedation?

Not likely:

1) fluoxetine is not sedating and

2) the dose was not changed.

1.2. Diazepam

1.2. Clozapine Case 1: Diazepam

Can 8 mg/day of diazepam cause drug intoxication presenting with sedation?

Let's review diazepam's

1) sedation profile,

2) pharmacokinetics, and

3) pharmacodynamics.

1.2.1. Diazepam Sedation

1.2.1. Clozapine Case 1: Diazepam Sedation

- Sedation is a very common manifestation of diazepam intoxication.

1.2.2. Diazepam Pharmacokinetics

1.2.1. Clozapine Case 1: Diazepam Pharmacokinetics

What can you say about diazepam 8 mg/day pharmacokinetics?

1.2.1. Clozapine Case 1: Diazepam Pharmacokinetics

- Diazepam doses vary widely around the world.
- 8 mg/day is relatively low for US patients.
- Diazepam is metabolized by:
  - CYP2C19: high affinity.
  - CYP3A4: low affinity (It may be more important in high doses).

http://www.ncbi.nlm.nih.gov/pubmed/16384813

1.2.1. Clozapine Case 1: Diazepam Pharmacokinetics

What do you know about genetic influences on diazepam metabolism?

1.2.1. Clozapine Case 1: Diazepam Pharmacokinetics

- CYP2C19: polymorphic (PM/UM)
- CYP2C19 PMs:
  - East Asians: 10-25%
  - Caucasians and African-Americans: <5%

  More prone to diazepam sedation. http://www.ncbi.nlm.nih.gov/pubmed/16384813
- CYP2C19 UMs. http://www.ncbi.nlm.nih.gov/pubmed/19059065
  - Described in Sweden: 3%

1.2.1. Clozapine Case 1: Diazepam Pharmacokinetics

What do you know about environmental influences on diazepam metabolism?

1.2.1. Clozapine Case 1: Diazepam Pharmacokinetics

- Fluoxetine (and norfluoxetine) inhibit diazepam metabolism. Fluoxetine is a:
  - mild to moderate CYP2C19 inhibitor, and
  - mild to moderate CYP3A4 inhibitor.

1.2.3. Diazepam Pharmacodynamics

1.2.3. Clozapine Case 1: Diazepam Pharmacodynamics

What can you say about diazepam 8 mg/day pharmacodynamics?

1.2.3. Clozapine Case 1: Diazepam Pharmacodynamics

- Diazepam is an allosteric modulator of GABA-A receptors.
  http://www.ncbi.nlm.nih.gov/pubmed/18457867
- It increases GABA affinity.
- GABA is the most important inhibitor neurotransmitter.

1.2. Clozapine Case 1: Diazepam

What is your conclusion?
Did 8 mg/day of diazepam cause the sedation?

1.2. Clozapine Case 1: Diazepam

What is your conclusion?
Did 8 mg/day of diazepam cause the sedation?

It is unclear.

Two arguments in favor:

1) diazepam is sedating,

2) diazepam D was low, but an inhibitor (fluoxetine) was present.

One argument against it: 1) diazepam D was not changed for months.

1.3. Hypersalivation

1.3.Clozapine Case 1: Hypersalivation

The patient complained of hypersalivation, in addition to sleepiness and cognitive impairment.

Is that relevant?

1.3.Clozapine Case 1: Hypersalivation

The patient complained of hypersalivation, in addition to sleepiness and cognitive impairment.

Is that relevant?

Yes

1.3.Clozapine Case 1: Hypersalivation

- Hypersalivation:
  - does not usually occur in fluoxetine intoxication,
  - can occur in diazepam intoxication (by interfering with swallowing),
  - is a typical sign of clozapine intoxication.

1.4. Clozapine Intoxication

1.4. Clozapine Intoxication

1.4.1.Clozapine Intoxication: Pharmacokinetics

1.4.2.Clozapine Intoxication: Pharmacodynamics

1.4. Clozapine Case 1: Clozapine Intoxication

How do you verify a clozapine intoxication?

1.4. Clozapine Case 1: Clozapine Intoxication

How do you verify a clozapine intoxication?

Measure serum clozapine Cs (levels or TDM).

1.4.1. Clozapine Intoxication: Pharmacokinetics

1.4.1.Clozapine Intoxication: Pharmacokinetics

1.4.1.1. Therapeutic Reference Range

1.4.1.2. Therapeutic Window

1.4.1.3. Patient's C

1.4.1. Clozapine Case 1: Intoxication Pharmacokinetics

- Two concepts are needed:
  - therapeutic reference range (AGNP definition)
  - therapeutic window/index (calculated by Dr. de Leon with AGNP data)

These concepts are described in the presentation titled: “Pharmacokinetics of Oral Second Generation Antipsychotics”

1.4.1.1. Therapeutic Reference Range

1.4.1.1. Therapeutic Reference Range

- Therapeutic Reference Range = range of medication C:
  - a lower limit below which a drug-induced therapeutic response is relatively unlikely to occur and
  - an upper limit above which tolerability decreases or above which it is relatively unlikely that therapeutic improvement may still be enhanced.
- Clozapine: 350-600 ng/mL

1.4.1.2. Therapeutic Window

1.4.1.2. Therapeutic Window

- To find the therapeutic window or index:
  Divide upper limit by lower limit.

- Dr. de Leon classifies a drug's therapeutic window as:
  - narrow ≤ 3, or
  - wide > 3.

1.4.1.2. Therapeutic Window

What is the therapeutic window/index for clozapine?

1.4.1.2. Therapeutic Window

What is the therapeutic window/index for clozapine?

600/350=1.7

1.4.1.2. Therapeutic Window

- Clozapine has a narrow therapeutic window. It is a drug prone to cause intoxications.
- Dr. de Leon's practice:
  - C > 600 ng/ml:
    First: review for dose-related symptoms:
    - sedation,
    - hypersalivation,
    - constipation, or
    - seizures (or myclonus, see Case 2)

    Second: consider ↓ D
  - C > 1000 ng/ml: ↓ D in absence of symptoms. Recommended by Simpson (Dr. de Leon's mentor http://www.ncbi.nlm.nih.gov/pubmed/412427)

1.4.1.3. Patient's Cs

1.4.1.3. Clozapine Case 1: Patient's Cs

- Patient's plasma Cs:
  - Clozapine 1500 ng/ml
  - Norclozapine 630 ng/ml

1.4.1.3. Clozapine Case 1: Patient's Cs

What comment can you make about these concentrations?

1.4.1.3. Clozapine Case 1: Patient's Cs

What comment can you make about these concentrations?

They are compatible with intoxication.

1.4.2. Clozapine Intoxication: Pharmacodynamics

1.4.2.Clozapine Intoxication: Pharmacodynamics

1.4.2.1. Sedation Pharmacodynamics

1.4.2.2. Hypersalivation Pharmacodynamics

1.4.2.1. Clozapine Sedation: Pharmacodynamics

1.4.2.1. Clozapine Case 1: Sedation Pharmacodynamics

- RCT Meta-analysis: clozapine is very sedating:

Leucht et al., 2013: http://www.ncbi.nlm.nih.gov/pubmed/23810019

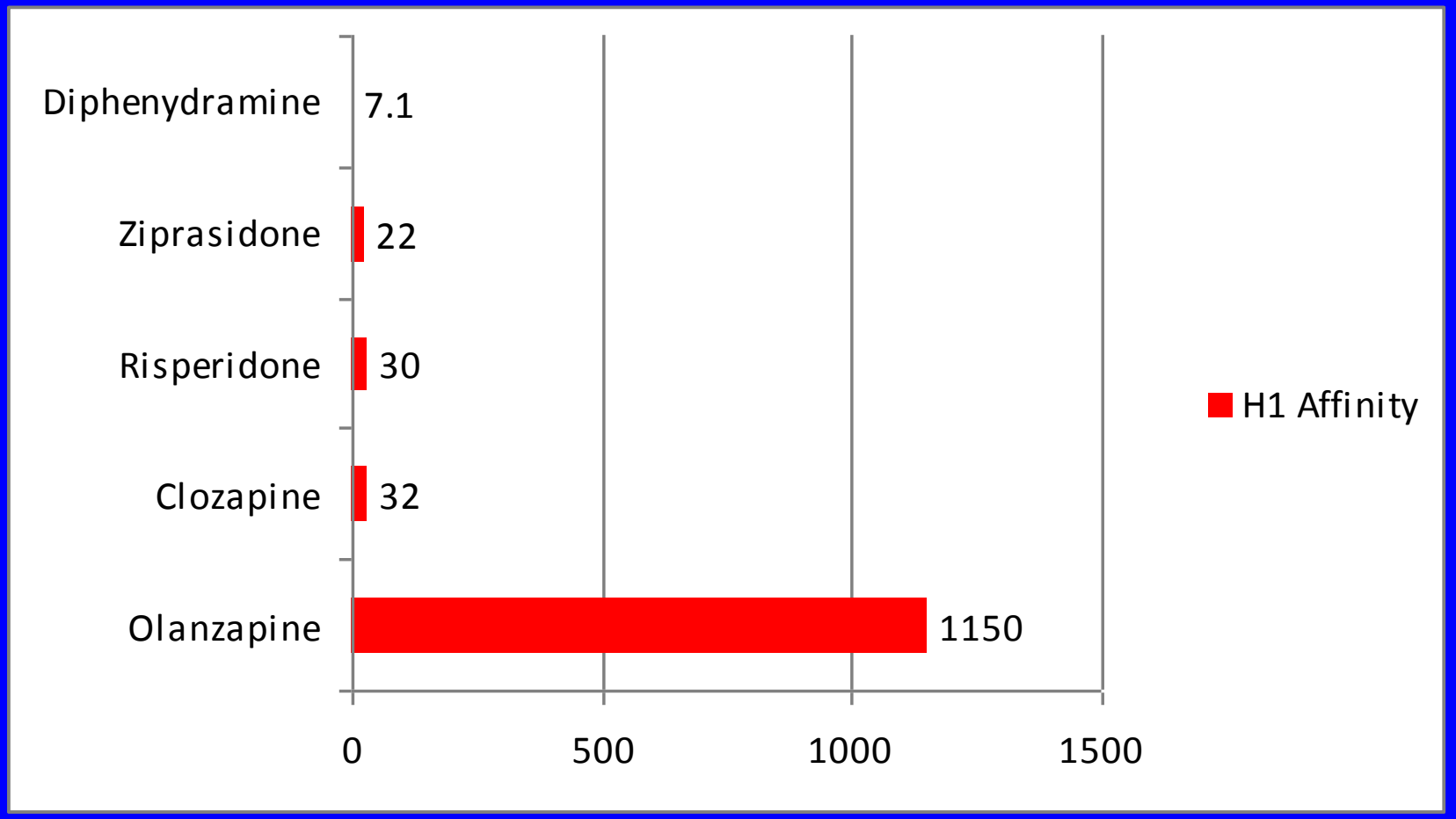
	ORs in order (95% CI) (drug versus placebo)
clozapine	8.82 (4.72 to 15.1)
ziprasidone	3.80 (2.58 to 5.42)
quetiapine	3.76 (2.68 to 5.19)
olanzapine	3.34 (2.46 to 4.50)
asenapine	3.28 (1.37 to 6.69)
haloperidol	2.76 (2.04 to 3.66)
risperidone	2.45 (1.76 to 3.35)
lurasidone	2.45 (1.31 to 4.24)
aripiprazole	1.84 (1.05 to 3.05)
iloperidone	1.71 (0.63 to 3.77); no different from placebo
paliperidone	1.40 (0.85 to 2.19); no different from placebo
amisulpride	1.42 (0.72 to 2.51); no different from placebo

1.4.2.1. Clozapine Case 1: Sedation Pharmacodynamics

- Clozapine has high affinity for H_1 receptors.
  http://www.ncbi.nlm.nih.gov/pubmed/24494611
- Sedation is probably explained by H_1 antagonism.

1.4.2.1. Clozapine Case 1: Sedation Pharmacodynamics

http://www.ncbi.nlm.nih.gov/pubmed/10340682 Information is taken from that article to design this figure.



1.4.2.2. Clozapine Hypersalivation: Pharmacodynamics

1.4.2.2. Clozapine Case 1: Hypersalivation Pharmacodynamics

- Clozapine has high affinity for M_1-M_5 receptors.
- Clozapine typically causes constipation (muscarinic antagonist).
  Norclozapine may contribute.
  It does not produce dry mouth (antagonism).
- 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 a $\alpha_1$antagonist.

1.5. Interpreting Clozapine Cs

1.5. Interpreting Clozapine Cs

- Pharmacokinetic concepts are going to be used to interpret the patient's Cs.
- Since the 1990s pharmacologists have used the concept of C/D ratio in articles.

http://www.ncbi.nlm.nih.gov/pubmed/7974626

It has not been describe in textbooks.

- Dr. de Leon has published on it:
  - a clozapine guideline

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

  - a CYP article: http://uknowledge.uky.edu/psychiatry_facpub/27/

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

1.5. Interpreting Clozapine Cs

- The best way of understanding the use of C/D ratio is reviewing other cases from this psychopharmacology course and practicing with your patients.
- Dr. de Leon started using C/D ratios in clozapine patients. You may want to start practicing with them.

1.5. Clozapine Case 1: Interpreting Clozapine Cs

1.5.1. Norclozapine C

1.5.2. Narrow Therapeutic Window

1.5.3. Normal Variations

1.5.4. C/D Ratio

1.5.5. Total C/D Ratio

1.5.1. Norclozapine C

1.5.1. Norclozapine C

- Norclozapine (or desmethylclozapine):
  - primary metabolite by demethylation
  - in vitro studies: binds to brain receptors
  - not marketed,
    but it was studied as a possible antipsychotic
  - also metabolized by CYP1A2
- Norclozapine C:
  - Norclozapine does not contribute to therapeutic activity.
  - It may contribute to clozapine's antimuscarinic effects.

http://www.ncbi.nlm.nih.gov/pubmed/12920408

  - Norclozapine Cs + clozapine Cs reflect metabolism better than only clozapine Cs.

1.5.2. Narrow Therapeutic Window

1.5.2. Narrow Therapeutic Window

- Remember:
  - therapeutic reference range = 350-600 ng/ml
  - therapeutic window = 1.7 (600/350)

  Clozapine is a narrow therapeutic window drug.

1.5.3. Normal Variations

1.5.3. Clozapine C: Normal Variations

- Unexperienced clinicians tend to overinterpret small clozapine Cs
- Expect some day-to-day variations.
- Confounding factors of clozapine Cs that you can control:
  - timing of collection
  - dose and schedule
  - drug interactions (including smoking)
- Confounding factors you cannot control:
  - laboratory
  - technique (different methods)
  - natural variations

1.5.3. Clozapine C: Normal Variations

- Dr. de Leon thinks that only a change by a factor of 2 is clinically meaningful.

http://www.ncbi.nlm.nih.gov/pubmed/14762234

- Translating the theory to an example:
  - A patient with clozapine C = 500 ng/ml;
    - relevant change: Cs >1000, or < 250 ng/ml
    - irrelevant change: Cs: 250-1000 ng/ml
  - A change from 500 ng/ml to 400 ng/ml is not clinically meaningful.

1.5.4. C/D Ratio

1.5.4. Clozapine C/D Ratio

- In typical Ds, clozapine has a linear relationship between D and C.
  - In a group
  - More importantly, in the same individual. The individual has a constant C/D ratio, as long as you do not change metabolism, by adding an inducer or inhibitor.
- Pharmacologists use this simple formula, the C/D ratio, to represent the ability to clear a drug from the body.

1.5.4. Clozapine C/D ratio

- Plasma clozapine Cs exceeding 350 ng/ml are described as therapeutic, with most US individuals requiring a D of 300-600 mg/d to reach these levels.

- To reach a C of 350 ng/ml:
  - Requires 300 mg/d: C/D of 1.2 (350/300)
  - Requires 600 mg/d: C/D of 0.6 (350/600)

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

1.5.4. Clozapine C/D ratio

- Therefore, the average US individual taking clozapine has a C/D of 0.6-1.2.
- Average US ♀ non-smokers require 300 mg/d to reach a C ≥ 350 ng/ml: C/D of 1.2 (350/300).
- Average US ♂ smokers require 600 mg/d to reach a C ≥ 350 ng/ml: C/D of 0.6 (350/600).
- Average US ♀ smokers and ♂ non-smokers require 300-600 mg/d and have C/Ds between 0.6-1.2.

1.6.4. Clozapine C: C/D Ratio

- Adding an inhibitor: ↑ C/D ratio.
- Adding an inducer ↓ C/D ratio.
- In a US patient, a C/D ratio
  - >1.2: poor metabolic capacity
  - <0.6: high metabolic capacity
- Normal C/D ratio = 0.6-1.2; this probably applies to most people. East Asians: C/D ratios = 0.3-0.6

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

1.5.6. Total C/D Ratio

1.5.6. Total C/D Ratio

- Total C = Clozapine C + Norclozapine C
- Not relevant for efficacy.
  Norclozapine is not an antipsychotic.
- Relevant for:
  - safety
  - studying clozapine metabolism:
    - effects of inducers and
    - effects of inhibitors

  Norclozapine is also metabolized by CYP1A2.

1.6. Interpreting the Patient's C/D Ratio

1.6. Interpreting the Patient's C/D Ratio

- Clozapine Case 1 introduces the C/D ratio as a new concept.
- The C/D ratio will be used and reinforced in other 5 clozapine cases and cases using other drugs.
- You will better understand the concept after reviewing other cases.
- Pharmacists and psychiatry residents with mathematical skills tend to easily grasp the C/D ratios.

1.6. Interpreting the Patient's C/D Ratio

Clo D	Cs (ng/ml)			C/D ratios	
mg/day	Clo	Nor	Total	Clo	Total
550	1500	630	2130	2.7[1]	3.9[2]

[1]1500/550=2.7

[2]2130/550=3.9

1.6. Clozapine Case 1: C/D Ratio Interpretation

What comment can you make about a clozapine C/D=2.7?

1.6. Clozapine Case 1: C/D Ratio Interpretation

What comment can you make about a clozapine C/D=2.7?

It is too high (USA range: 0.6-1.2).

1.6. Clozapine Case 1: C/D Ratio Interpretation

An abnormally high clozapine C/D is indicative of…

1.6. Clozapine Case 1: C/D Ratio Interpretation

An abnormally high clozapine C/D is indicative of…

Poor clozapine metabolism.

1.7. Case Interpretation

1.7. Case Interpretation

What type of factors
can explain
poor clozapine metabolism?

1.7. Case Interpretation

What type of factors can explain poor clozapine metabolism?

Genetic, environmental and personal factors.

1.7. Clozapine Case 1: Case Interpretation

- Genetics:
  - Clozapine intoxication was not present prior.
  - It cannot be genetic.
- Environment:
  - Fluoxetine is a mild inhibitor of clozapine metabolism but its effects should have started before (no D change for 5 months).
  - No changes in medications or smoking
- Personal factors:
  - Renal elimination has small influences in clozapine Cs but no changes in renal function.

1.7. Clozapine Case 1: Case Interpretation

- The patient denied any changes in health/medication.
- Medication compliance was verified by the patient's mother who supervised the medication every morning.

1.7. Clozapine Case 1: Case Interpretation

Is there any other factor that can explain a decrease in clozapine metabolism?

1.7. Clozapine Case 1: Case Interpretation

- After being specifically asked about changes in caffeine intake, the patient acknowledged a massive ↑ in caffeine intake.
- She reported a caffeine intake:
  - a 200-mg caffeine tablet/day to "wake herself up"
  - drinking one liter of tea per day
- We estimated caffeine intake:
  - 200 mg + 300 mg = 500 mg/day

    caffeine content in tea: 5 oz. cup = 45 mg;

    6.6 cups = 1 liter; 1 liter of tea = 300 mg of caffeine.
- Non-smoker: 2-3 times higher caffeine Cs than smokers with the same caffeine D. Smoking induces CYP1A2. http://www.ncbi.nlm.nih.gov/pubmed/12551740

1.8. Other: Caffeine

1.8. Clozapine Case 1: Caffeine

- Caffeine is metabolized mainly by CYP1A2.
- CYP1A2 may account for 70% of clozapine metabolism.

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

1.9. Clozapine Case 1: Caffeine

- One week after discontinuing caffeine intake:
  - Serum levels with the same dosages:
    - Clozapine C: 630 ng/ml
    - Norclozapine C: 330 ng/ml
  - No sedation

1.8. Clozapine Case 1: Caffeine

Clo D	Cs (ng/ml)			C/D ratios		
mg/day	Clo	Nor	Total	Clo	Total	Caffeine
550	1500	630	2130	2.7	3.9	Yes
550	630	330	960	1.1[1]	1.7[2]	No .

[1]630/550 = 1.1

[2]960/550 = 1.7

1.8. Clozapine Case 1: Caffeine

What comment can you make about a clozapine C/D =1.1?

1.8. Clozapine Case 1: Caffeine

What comment can you make about a clozapine C/D =1.1?

It is normal (USA range: 0.6-1.2).

1.8. Clozapine Case 1: Caffeine

She is in
the upper range of
normality.
Why?

1.8. Clozapine Case 1: Caffeine

She is in
the upper range of
normality.
Why?
She is
a non-smoking ♀.

Questions

- Please review the 10 questions in the Word document entitled “Questions on the Presentation: Clozapine Case 1”.
- 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. A
7. C
8. B
9. C
10. D