Quetiapine Case 2 Therapeutic Drug Monitoring 1-27-16

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2. Quetiapine Case
Therapeutic Drug Monitoring
(unpublished)

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 quetiapine safety, one must consider:
    - 2.1. Personal, environmental and genetic factors.
    - 2.2. Pharmacodynamics and pharmacokinetics.
3. Be familiar with the use of quetiapine levels in clinical practice.

Abbreviations

- AED: anti-epileptic drug
- AP: antipsychotic
- C: concentration
- C/D: concentration dose ratio
- CYP: cytochrome P450
- D: dose
- DDI: drug-drug interaction
- TCA: tricyclic antidepressant
- TDM: therapeutic drug monitoring
- UM: ultrarapid metabolizer

Quetiapine Case 2

2.0. Case Description

2.1. Quetiapine Pharmacokinetics

2.2. Quetiapine C/D Ratios

2.3. Quetiapine Case TDM

2.4. Interpretation of Case

2.5. Conclusions

Quetiapine Case 2

2.0. Case Description

2.1. Quetiapine Pharmacokinetics

- 2.1.1. Metabolism
- 2.1.2. DDI
- 2.1.3. TDM

2.2. Quetiapine C/D Ratios

- 2.2.1. Concept of C/D Ratio
- 2.2.2. C/D Ratios from Therapeutic Range Data
- 2.2.3. C/D Ratios from Data Available in 1999

2.3. Quetiapine Case TDM

- 2.3.1. First TDM Results
- 2.3.2. TDM After Medication Change
- 2.3.3. TDM During Follow-up

2.4. Interpretation of Case

2.5. Conclusions

- 2.5.1. Complexity of Quetiapine TDM
- 2.5.2. Do Not Combine Quetiapine and Potent Inducers
- 2.5.3. Unusual Cases Require Thinking about Pharmacokinetic and Pharmacodynamic Mechanisms

2.0. Quetiapine Case 2: Case Description

2.0. Case Description

The patient was followed for > 4 years

AP treatment was first quetiapine,

second olanzapine and

third clozapine.

He arrived with 4 AEDs but was switched to only valproate, co-prescribed with APs.

<u>The same patient is used in several presentations:</u>

Quetiapine Case 2: Therapeutic Drug Monitoring

Quetiapine Case 3: Akathisia

Clozapine Case 2: Infection

Valproate Case 3: Formulation

2.0. Quetiapine Case 2: Case Description

- 31-year-old Caucasian ♂
- Diagnosis of schizophrenia:
  - very disorganized and psychotic
  - extensive history of violence
- Treatment for seizures:
  - arrived with 4 AEDs
- Treatment for hyperlipidemia: gemfibrozil 12 mg/day
- Treatment with propranolol 80 mg/day
  - probably for hypertension
  - There were no signs of hypertension, but it became obvious that propranolol was needed for akathisia.

2.0. Quetiapine Case 2: Case Description

- Quetiapine D:
  - the patient was taking 700 mg/day.
  - this D is very close to the US maximum recommended D: 750 mg/day.
- The patient continued to be
  - psychotic and
  - extremely disorganized.

2.0. Quetiapine Case 2: Case Description

How do you know
this quetiapine D is enough?

2.0. Quetiapine Case 2: Case Description

How do you know
this quetiapine D is enough?

Focus first on pharmacokinetics and secondly on pharmacodynamics.

2.0. Quetiapine Case 2: Case Description

In questioning whether a D is adequate, why do you focus on pharmacokinetics first?

2.0. Quetiapine Case 2: Case Description

In questioning whether a D is adequate, why do you focus on pharmacokinetics first?

First, pharmacokinetics facilitates pharmacodynamics, and secondly, it is easier to study.

2.0. Quetiapine Case 2: Case Description

What do you mean by the statement, “Pharmacokinetics facilitates pharmacodynamics”?

2.0. Quetiapine Case 2: Case Description

What do you mean by the statement, “Pharmacokinetics facilitates pharmacodynamics”?

If you do not have enough C at the site of action, a drug will not be efficacious.

2.0. Quetiapine Case 2: Case Description

What do you mean by the statement that pharmacokinetics is easier to study?

2.0. Quetiapine Case 2: Case Description

What do you mean by the statement that pharmacokinetics is easier to study?

You can study the patient's pharmacokinetics with TDM.

You cannot study the patient's pharmacodynamics (it requires brain imaging).

2.0. Quetiapine Case 2: Case Description

- If you did not know how to answer the prior questions, you need to review these prior presentations.
  - "Introduction to Clinical Pharmacology" describes pharmacokinetics & pharmacodynamics.
  - "Pharmacodynamics of Second-Generation Antipsychotics" emphasizes that pharmacokinetics facilitates pharmacodynamics.
  - "Pharmacokinetics of Oral Second-Generation Antipsychotics" provides a summary of quetiapine pharmacokinetics.
- This presentation focuses on quetiapine TDM and pharmacokinetics, so we are going to review that topic first.

2.1. Quetiapine Pharmacokinetics

2.1. Quetiapine Case 2: Quetiapine Pharmacokinetics

What do you know about quetiapine pharmacokinetics?

2.1. Quetiapine Pharmacokinetics

2.1.1. Metabolism

2.1.2. DDIs

2.1.3. TDM

2.1.1. Quetiapine Metabolism

2.1.1. Quetiapine Case 2: Quetiapine Metabolism

What do you know about quetiapine metabolism?

2.1.1. Quetiapine Case 2: Quetiapine Metabolism

- Quetiapine:
  - is mainly metabolized by CYP3A.
  - has a metabolic profile similar to:
    - cariprazine, and
    - lurasidone.

2.1.2. Quetiapine DDIs

2.1.2. Quetiapine Case 2: Quetiapine DDIs

What do you know about quetiapine DDIs?

2.1.2. Quetiapine Case 2: Quetiapine DDIs

- Effects of other drugs on quetiapine:
  - CYP3A inhibitors: ↓ metabolism
  - CYP3A inducers: ↑ metabolism
- Effects of quetiapine on other drugs:
  - not an inducer
  - not a major inhibitor, but competitive inhibition is possible.

2.1.2. Quetiapine DDIs

2.1.2.1. Effects of Inducers on Quetiapine
2.1.2.2. Effects of Inhibitors on Quetiapine
2.1.2.3. Effects of Other Drugs on Quetiapine

2.1.2.1. Effects of Inducers on Quetiapine (similar effects for cariprazine and lurasidone)

2.1.2.1. Quetiapine Case 2: Effects of Inducers on Quetiapine

DDI	Corr F	Action
Rifampicin[1]		Avoid
AED potent inducers[2]		Avoid
AED mild inducers[3]		Avoid[4]
Other mild inducers[5]		Avoid[4]

[1]Very potent inducer

[2]Carbamazepine, phenytoin and phenobarbital. Correction factor is too high for clinical practice (>5)

[3]High-dose topiramate (≥400 mg/d) and oxcarbazepine (≥1200 mg/d) may be mild inducers. Others are clobazam, eslicarbazepine, felbamate and rufinamide.

[4]It is better to avoid use, but do not combine unless you are familiar with quetiapine TDM.

[5]St. John's wort or some corticosteroids (e.g., dexamethasone or prednisone)

2.1.2.1. Quetiapine Case 2: Effects of Inducers on Quetiapine

- Main messages from Dr. de Leon:
  - Quetiapine is very sensitive to induction.
  - Do not combine with potent CYP3A inducers.
    Dr. de Leon has seen too many cases of this combination with lack of antipsychotic efficacy.
    (2 or 3 antipsychotics were prescribed)

2.1.2.1. Quetiapine Case 2: Effects of Inducers on Quetiapine

- Mild CYP3A4 inducers are problematic:
  - Dr. de Leon has always recommended avoiding them in quetiapine patients.
  - If you want to prescribe them, you need to become an expert in quetiapine TDM (review this presentation several times).
  - A recently published case supports the hypothesis that adding oxcarbazepine may eliminate quetiapine efficacy.

http://www.ncbi.nlm.nih.gov/pubmed/26469302

2.1.2.2. Effects of Inhibitors on Quetiapine (similar effects for cariprazine and lurasidone)

2.1.2.2. Quetiapine Case 2: Effects of Inhibitors on Quetiapine

DDI	Corr F	Action
Ketoconazole		Avoid[1]
Erythromycin (& clarithromycin)		Avoid[1]
Grapefruit juice		Avoid[1]
Diltiazem		Avoid[1]
Fluoxetine/fluvoxamine[2]		Not studied
Inflammation[3]		Be careful

[1]All of these are powerful CYP3A4 inhibitors. It is better to avoid them.

[2]Fluoxetine and fluvoxamine are mild/moderate CYP3A4 inhibitors. Be careful, as they are not well studied.

[3]Any systemic inflammation or any serious infection including pneumonias, upper respiratory infections with fever, or appendicitis.

2.1.2.2. Quetiapine Case 2: Effects of Inhibitors on Quetiapine

- Main messages from Dr. de Leon:
  - Quetiapine is too sensitive to use potent CYP3A4 inhibitors; avoid them, although quetiapine is a relatively safe drug.
  - Be very careful during serious infections or inflammations; they can ↑ quetiapine C and cause toxicity. http://www.ncbi.nlm.nih.gov/pubmed/26032842

2.1.2.3. Effects of Other Drugs on Quetiapine (specific to quetiapine; does not apply to cariprazine and lurasidone)

2.1.2.3. Quetiapine Case 2: Effects of Other Drugs on Quetiapine

- Limited TDM studies indicate:
  - Lamotrigine may be a mild inducer.
  - Valproate may be a mild inhibitor.

  In most cases, this should not be clinically relevant since quetiapine is a wide therapeutic window drug.
- The limited available data suggests that clinicians can ignore the effects of these 2 drugs on quetiapine.

2.1.3. Quetiapine TDM

2.1.3. Quetiapine Case 2: Quetiapine TDM

- Therapeutic reference range: 100-500 ng/mL

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

- Wide therapeutic index/window: 5 (500/100=5)
  This means that quetiapine DDIs with inhibitors are not likely to be clinically relevant.

2.2. Quetiapine C/D Ratios
(unpublished and
not available in other places)

2.2. Quetiapine C/D Ratios

- The concept of C/D ratio has been described in prior presentations.

  (See the presentation “Clozapine Case 1: The Relevance of CYP.”)

- No information has been published on how to use quetiapine C/D ratios to interpret quetiapine TDM.
- This section will use available published information to set the basis for using quetiapine C/D ratios in clinical practice.

2.2. Quetiapine C/D Ratios

2.2.1. The Concept of C/D Ratio
2.2.2. C/D Ratios from Therapeutic Range Data
2.2.3. C/D Ratios from Data Available in 1999

2.2.1. The Concept of C/D Ratio

2.2.1. The Concept of C/D Ratio

- In typical Ds, quetiapine 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 its 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.

2.2.1. The Concept of C/D Ratio

- Adding an inhibitor: ↑ C/D ratio.
- Adding an inducer: ↓ C/D ratio.

2.2.2. Calculating C/D Ratios from Therapeutic Range Data

2.2.2. Quetiapine Case 2: Therapeutic Range & C/D Ratio

- You can estimate average C/D ratios using:
  - C from the therapeutic reference range: 100-500 ng/mL
  - D (average dose) from prescribing information:
    D In adults with schizophrenia: 150-750 mg/day:
    mean is 450 (150+750/2=900/2)

http://dailymed.nlm.nih.gov/dailymed/search.cfm?labeltype=all&query=QUETIAPINE+FUMARATE&pagesize=20&page=1

2.2.2. Quetiapine Case 2: Therapeutic Range & C/D Ratio

How do you calculate average C/D ratios?

2.2.2. Quetiapine Case 2: Therapeutic Range & C/D Ratio

How do you calculate average C/D ratios?

Divide

500 by 450 (500/450=1.1)

and

150 by 450 (150/450=0.3).

2.2.2. Quetiapine Case 2: Therapeutic Range & C/D Ratio

Typical
average C/D ratios
based on
therapeutic reference range
and
average recommended Ds
are between 0.3-1.1

2.2.3. C/D Ratios from Data Available in 1999

2.2.3. Quetiapine Case 2: C/D Ratio from Data in 1999

- In 1999 when the patient was treated, there was little quetiapine TDM published data.
- Dr. de Leon asked the company, which provided unpublished data from a multicenter study.

2.2.3. Quetiapine C/D Ratio in 1999

2.2.3.1. Cs from the Multicenter Study
2.2.3.2. Estimating C/D Ratios

2.2.3.1. Quetiapine C/D Ratios: Multicenter Data

2.2.3.1. Quetiapine Case 2: Multicenter Data

Dose	Trough Levels	Peak (1-1.5 hrs)
mg/day	ng/ml	ng/ml
75	13.9	
150	27.8	
225		277♂ (286 ♀)
300	43.9	
450		625 ♂ (572♀)
600	91.1	
750	93.7	778 ♂ (879♀)

2.2.3.1. Quetiapine Case 2: Multicenter Data

- These TDM results have not been systematically published.
- Trough data briefly described

Arvanitis LA, Miller BG. Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. The Seroquel Trial 13 Study Group. Biol Psychiatry. 1997 Aug 15;42(4):233-46. PubMed PMID: 9270900. http://www.ncbi.nlm.nih.gov/pubmed/9270900

- Peak data briefly described

Gunasekara NS, Spencer CM. Quetiapine . A review of its use in schizophrenia. CNS Drugs. 1998;9(4):325-40.

2.2.3.1. Quetiapine Case 2: Multicenter Data

Can you comment on this data?

2.2.3.1. Quetiapine Case 2: Multicenter Data

- Cs fluctuate considerably during the day.
- Peaks = roughly 10 x troughs.

2.2.3.1. Quetiapine Case 2: Multicenter Data

Why are peaks so high compared to troughs?

2.2.3.1. Quetiapine Case 2: Multicenter Data

Why are peaks so high compared to troughs?

It is due to quetiapine's short half-life.

2.2.3.1. Quetiapine Case 2: Multicenter Data

What is the clinical relevance?

2.2.3.1. Quetiapine Case 2: Multicenter Data

What is the clinical relevance?

It is difficult to interpret quetiapine TDM.

2.2.3.1. Quetiapine Case 2: Multicenter Data

- Quetiapine TDM is influenced by:
  - D administration (twice or three times a day)
  - time to the last D

2.2.3.2. Estimating Quetiapine C/D Ratios

2.2.3.2. Quetiapine Case 2: Estimating C/D Ratios

Can you estimate the quetiapine C/D ratio using this study?

2.2.3.2. Quetiapine Case 2: Estimating C/D Ratios

Can you estimate the quetiapine C/D ratio using this study?

Yes.

2.2.3.2. Quetiapine Case 2: Estimating C/D Ratios

Dose mg/day	Trough C ng/ml	C/D Ratio
75	13.9	0.19
150	27.8	0.19
300	43.9	0.15
600	91.1	0.15
750	93.7	0.13

2.2.3.2. Quetiapine Case 2: Estimating C/D Ratios

- C/D ratio in this study: 0.12-0.15 (from troughs).
- Dr. de Leon has little experience with clinical quetiapine TDM and no research experience.
- You should not trust data from only one study.

2.2.3.2. Quetiapine Case 2: Estimating C/D Ratios

Dose mg/day	Peak C ng/ml	C/D Ratio
225	277♂	1.2
	286 ♀	1.3
450	625 ♂	1.4
	572♀	1.3
750	778 ♂	1.0
	879♀	1.2

2.2.3.2. Quetiapine Case 2: Estimating C/D Ratios

- C/D ratios in the multicenter study:
  - 0.12 - 0.15 from trough Cs
  - 1.0 - 1.4 from peak Cs
- Average C/D ratios from therapeutic range (TDM studies) and average D:
  - 0.3-1.1

2.2.3.2. Quetiapine Case 2: Estimating C/D Ratios

- Summary of quetiapine TDM:
  - quetiapine has a very short half-life, with peak Cs = 10 x trough Cs.
- TDM interpretation is complicated:
  - variations in administration (2 versus 3 times/day) and
  - time to last drug intake may have relevant effects on trough Cs.
- Quetiapine C/D ratio interpretation is complicated:
  - Be sure they are trough Cs.

2.3. Quetiapine Case TDM

2.3. Quetiapine Case TDM

2.3.1. First TDM Results
2.3.2. TDM After Medication Change
2.3.3. TDM During Follow-Up

2.3.1. First TDM Results

2.3.1. Quetiapine Case 2: First TDM Results

Dose mg/day	Trough C ng/ml	C/D Ratio
Found		
700	<10[1]	<0.01
Expected (Company Study)		
75	13.9	0.19
750	93.7	0.12

[1]Result was below the detection limit of 10 ng/ml

2.3.1. Quetiapine Case 2: First TDM Results

- If the study data is correct:
  - C/D ratio =
    >10 times lower than expected.
    (<0.01 found vs. 0.12 expected).
- C <10 corresponds to D <75 mg/d.
  The patient is taking D=700 mg/d.
- A quetiapine C <10 ng/ml and quetiapine D <75 mg/d are probably subtherapeutic.

2.3.1. Quetiapine Case 2: First TDM Results

What should you ask first?

2.3.1. Quetiapine Case 2: First TDM Results

What should you ask first?

Is he taking his quetiapine?

2.3.1. Quetiapine Case 2: First TDM Results

- Yes:
  - the patient resides in a small locked unit for acutely violent patients.
  - it has a high staff/patient ratio.
  - he was very cooperative with medication intake.

2.3.1. Quetiapine Case 2: First TDM Results

What is your next question?

2.3.1. Quetiapine Case 2: First TDM Results

What is your next question?

What other medications is he taking?

2.3.1. Quetiapine Case 2: First TDM Results

- Gemfibrozil
- Propranolol
- AEDs:
  - Phenytoin
  - Valproic acid
  - Diazepam

2.3.1. Quetiapine Case 2: First TDM Results

What would you do next?

2.3.1. Quetiapine Case 2: First TDM Results

What would you do next?

Discontinue phenytoin.

2.3.1. Quetiapine Case 2: First TDM Results

Why?

2.3.1. Quetiapine Case 2: First TDM Results

Why?

Phenytoin is a major CYP3A4 inducer.

2.3.1. Quetiapine Case 2: First TDM Results

- Potent inducers:
  - CYPs:
    - Massive effects: CYP2B6, CYP3A4
    - Moderate effects: CYP1A2, CYP2A6
    - Mild effects: CYP2C (CYP2C8, CYP2C9 and CYP2C19)
  - UGTs: several

- More potent than carbamazepine

2.3.1. Quetiapine Case 2: First TDM Results

- Correction factors (described if ≥1.5):
  - 5 x: lurasidone, quetiapine
  - 3 x: haloperidol, paliperidone
  - 2-3 x: olanzapine
  - 2 x: aripiprazole, carbamazepine, iloperidone, lamotrigine, mirtazapine, risperidone, TCAs, topiramate
  - 1.5-2 x: clozapine
  - 1.5 x: felbamate

2.3.2. Quetiapine Case 2: TDM Results After a Medication Change

(Months After Phenytoin Discontinuation)

2.3.2. Quetiapine Case 2: TDM Results After Change

Dose mg/day	Trough C ng/ml	C/D Ratio
Found		
700	13	<0.01
Expected (company study)		
75	13.9	0.19
750	93.7	0.12

2.3.2. Quetiapine Case 2: TDM Results After Change

- If the study data is correct:
  - C/D ratio =
    10 times lower than expected.
    (0.01 found vs. 0.12 expected).
  - C =13 corresponds to D <75 mg/d. The patient is taking D =700 mg/d.
- Quetiapine C is detectable but very low.

2.3.2. Quetiapine Case 2: TDM Results After Change

- A resting and postural tremor became obvious.
- His mother reported that the patient always had tremors with APs.

2.3.2. Quetiapine Case 2: TDM Results After Change

- More worrisome, after an extra quetiapine D for agitation:
  - worsening of tremor
  - unusual gait (mother described hip surgery in childhood)
  - possible objective signs of akathisia (too disorganized to report a subjective component)

2.3.2. Quetiapine Case 2: TDM Results After Change

- Due to this unusual situation and the lack of published data on quetiapine TDM, Dr. de Leon drew a peak quetiapine level.
- Dr. de Leon rarely uses peak levels, but the company provided peak quetiapine levels.

2.3.2. Quetiapine Case 2: TDM Results After Change

Dose mg/day	Peak C ng/ml	C/D ratio
Found		
700 (200/500)[1]		
200 extra	240[2]	0.27[3]
Expected (Company Study)		
225	277[4]	1.2
750 (3 x 250)[5]	778[4]	1.0

[1]Taking 200 mg in the AM and 500 at night
[2]1 hour after 200 mg extra dose
[3]240/900=0.27
[4]1-1.5 hours after last dose
[5]Taking three 250 mg doses

2.3.2. Quetiapine Case 2: TDM Results After Change

- If the study data is correct:
  - C/D ratio =
    >3 times lower than expected.
    (0.27 found vs. 1.0 expected).
  - C =240 corresponds to
    D <225 mg/d
    The patient is taking D = 900 mg/d.

2.3.2. Quetiapine Case 2: TDM Results After Change

- The extra Ds of quetiapine for agitation were discontinued:
  - Gait abnormality and akathisia disappeared.
- Going from undetectable to detectable Cs made the patient susceptible to ADRs.

2.3.2. Quetiapine Case 2: TDM Results After Change

- Benztropine 3 mg/day was added. It did not control the tremor. Three years later, Dr. de Leon finally concluded that the tremor was relatively independent of APs.

2.3.3. TDM Results During Follow-Up

2.3.3. Quetiapine Case 2: TDM Results During Follow-Up

- During the next few months, the D was 700 mg/d of quetiapine until it was discontinued.
- Several trough TDMs:
  The lowest and highest are described to provide a C/D range.

2.3.3. Quetiapine Case 2: TDM Results During Follow-Up

Dose mg/day	Trough C ng/ml	C/D Ratio
Lowest found		
700	18	0.02
Expected (Company Study)		
75	13.9	0.19
150	27.8	0.19
750	93.7	0.12

2.3.3. Quetiapine Case 2: TDM Results During Follow-Up

- Using the patient's lowest TDM and assuming the company study data is correct:
  - C/D ratio =
    6 times lower than expected
    (0.02 found vs. 0.12 expected)
  - C =18 corresponds to
    D =75-150 mg/d.
    The patient's D =700 mg/d.

2.3.3. Quetiapine Case 2: TDM Results During Follow-Up

Dose mg/day	Trough C ng/ml	C/D Ratio
Highest Found		
700	38	0.05
Expected (Company Study)		
150	27.8	0.19
300	43.9	0.15
750	93.7	0.12

2.3.3. Quetiapine Case 2: TDM Results During Follow-Up

- Using the patient's highest TDM and assuming the company study data is correct:
  - C/D ratio =
    2 times lower than expected.
    (0.05 found vs. 0.12 expected).
  - C =38 corresponds to
    D =150-300 mg/d.
    The patient's D =700 mg/d.

2.4. Interpretation of the Case

2.4. Case 2 Quetiapine: Interpretation

Is there any unusual pharmacokinetic issue?

2.4. Case 2 Quetiapine: Interpretation

Is there any unusual pharmacokinetic issue?

Yes.

2.4. Case 2 Quetiapine: Interpretation

- Repeated C/D ratios: too low
  - On phenytoin: >10 times lower than expected (<0.01 found vs. 0.12 expected)
  - After phenytoin:
    - Trough: 10 times lower than expected (0.01 found vs. 0.12 expected)
    - Peak: >3 times lower than expected (0.27 found vs. 1.0 expected)
  - Follow-up trough:
    - Lowest: 6 times lower than expected (0.02 found vs. 0.12 expected)
    - Highest: 2 times lower than expected. (0.05 found vs. 0.12 expected)

2.4. Case 2 Quetiapine: Interpretation

- Repeated C/D ratios that are too low after stopping phenytoin are compatible with quetiapine UM status.
  There are no similar published cases and no CYP3A4 UMs.

2.4. Case 2 Quetiapine: Interpretation

- A discharge summary from several years before indicated that the patient needed high doses of carbamazepine (1500-2000 mg/day) to reach therapeutic levels.

2.4. Case 2 Quetiapine: Interpretation

- Dr. de Leon cannot find any published cases requiring such high carbamazepine doses.
- The Drug Information Handbook on adult recommended doses:
  - Usual: 800-1200 mg/d.
  - Maximum: 1600 mg/d.
  - Some patients require up to 1600-2400 mg/d.

http://www.amazon.com/Drug-Information-Handbook-Comprehensive-Professionals/dp/1591953073/ref=sr_1_1?s=books&ie=UTF8&qid=1350489676&sr=1-1&keywords=drug+information+handbook+2012-2013

2.4. Case 2 Quetiapine: Interpretation

How is carbamazepine metabolized?

2.4. Case 2 Quetiapine: Interpretation

How is carbamazepine metabolized?

By CYP3A4.

2.4. Case 2 Quetiapine: Interpretation

- The patient was taking 30 mg/day of diazepam for seizures upon arrival (1 of 4 AEDs).
- Dr. de Leon measured diazepam TDM, and Cs were undetected.
- Another presentation will be developed in the future to describe diazepam TDM in this patient.

2.4. Case 2 Quetiapine: Interpretation

How is diazepam metabolized?

2.4. Case 2 Quetiapine: Interpretation

How is diazepam metabolized?

By CYP2C19 and CYP3A4.

2.4. Case 2 Quetiapine: Interpretation

- Diazepam TDM was compatible with CYP3A4 UM status.
- A prior report on carbamazepine D and TDM indicated metabolism compatible with CYP3A4 UM status.
- Quetiapine TDM indicated the patient is a quetiapine UM and this is compatible with CYP3A4 UM status.

2.4. Case 2 Quetiapine: Interpretation

- Although there were no published cases, Dr. de Leon assumed that the patient was a CYP3A4 UM.
- Dr. de Leon selected an AP in which CYP3A4 had no relevant role.

2.4. Case 2 Quetiapine: Interpretation

- At that time the only other second-generation APs available were:
  - clozapine (the patient had had low WBC twice),
  - olanzapine (his mother did not remember its prior use), and
  - risperidone.
- Dr. de Leon selected olanzapine which the patient metabolized normally.

2.4. Case 2 Quetiapine: Interpretation

Is there any unusual pharmacodynamic issue?

2.4. Case 2 Quetiapine: Interpretation

Is there any unusual pharmacodynamic issue?

Yes, once quetiapine Cs were low but detectable. The patient had akathisia.

2.4. Case 2 Quetiapine: Interpretation

- See the presentation “Quetiapine Case 3: Akathisia”. It focuses on pharmacodynamic issues.

2.5. Conclusions

2.5. Case 2 Quetiapine: Conclusions

What are your conclusions in this case?

2.5. Case 2 Quetiapine: Conclusions

- Dr. de Leon has reached 3 conclusions:
  - the complexity of interpreting quetiapine TDM.
  - do not combine quetiapine with potent inducers.
  - unusual pharmacological cases need “unusual thinking.” You need to use “mechanistic thinking”.

2.5. Conclusions

2.5.1. The Complexity of Quetiapine TDM
2.5.2. Do Not Combine Quetiapine and Potent Inducers
2.5.3. Unusual Cases Require Thinking about Pharmacokinetic and Pharmacodynamic Mechanisms

2.5.1. Complexity of Quetiapine TDM

2.5.1. Quetiapine Case 2: Conclusion about TDM

- About quetiapine TDM:
  - It is difficult to interpret.
  - It is not a good idea to use it unless you thoroughly understand quetiapine pharmacokinetics.
- If you use quetiapine TDM:
  - Repeat TDM in the same patient.
  - Take into account the huge variation in normality.

2.5.2. Do Not Combine Quetiapine and Potent Inducers

2.5.2. Quetiapine Case 2: Conclusion about Inducers

- Do not combine quetiapine with potent CYP3A4 inducers:
  - rifampin
  - AED inducers:
    - carbamazepine,
    - phenytoin, or
    - phenobarbital.
- Do not combine potent inducers with other APs mainly dependent on CYP3A4:
  - cariprazine, or
  - lurasidone.

2.5.3. Unusual Cases Require Thinking about Pharmacokinetic and Pharmacodynamic Mechanisms

2.5.3. Quetiapine Case 2: Conclusion about Unusual Cases

- About unusual patients:
  - Dr. de Leon's expertise is in difficult patients.
  - This is the patient who has taught Dr. de Leon the most during his last 20 years of dealing with difficult patients.
  - Dr. de Leon is still learning from him. http://www.ncbi.nlm.nih.gov/pubmed/26000191

2.5.3. Quetiapine Case 2: Conclusion about Unusual Cases

- Follow-up presentations on the same patient:
  - Quetiapine Case 3: focused on Akathisia
  - Clozapine Case 2: focused on Infection Effects on Clozapine TDM
  - Valproate Case 3: focused on the Effects of Different Formulations of Valproate TDM

2.5.3. Quetiapine Case 2: Conclusion about Unusual Cases

- You will rarely find these patients, but you will find them.
- Try always to remember that with each psychiatric drug, you will occasionally find patients needing:
  - very high Ds, or
  - very low Ds.

2.4. Quetiapine Case 2: Conclusions

- Dr. de Leon's experience with clinicians in these cases:
  - Most do not think clearly.
  - Few know they need to get a consult.
- If you want to treat these cases:
  - Think first about pharmacokinetics.
  - Secondly, think about pharmacodynamics.

Questions

- Please review the 10 questions in the pdf entitled "Questions on the Presentation Quetiapine Case 2: Therapeutic Drug Monitoring".
- 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. C
3. C
4. C
5. A
6. C
7. D
8. D
9. A
10. A