

Pharmacist Interactive Clinical Case Series (PICCS): Drug Induced Diseases

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1

Outline and Approach to Case

- Must be opened in “slideshow” for hyperlinks to work
- Read the case and the scenarios in the case
- Answer questions and make drug recommendations
 - Click on forward hyperlinks (Red Boxes) to follow through case based on your responses
 - Click on home hyperlink (Blue House Icon) to go back to the last correct step in the series

2

Case 1 Set Up

- Laquisha Torres is a 36 year old African American-Latina Fully Transitioned Transgendered Woman.
- CC: Lethargy and mild dizziness with exercise.
- HPI: Four days of continuous but slightly increasing lethargy and more recently, physical activity results in mild dizziness.
- PMH: Hypertension X 4 yrs, Toenail Fungal Infection X3 weeks
- Current Meds: CBD 600mg for anxiety, Terbinafine Topical, Itraconazole 200mg twice daily, Verapamil (Verelan SR) 200mg daily, Estradiol 5mg daily Maintenance Regimen.
- Physical Exam: No rales or bruits, slight ankle edema, height 5'8", weight 64kg, HR 49bpm, BP 118/80mmHg
- Labs: Na+ 137mEq/L, K+ 3.8mEq/L
- A 12-lead ECG is ordered

[SELECT RED BOX]

3

ECG 1

What is the P-P length in sec and the R-R length in sec (blue lines)?



- PP = 0.52s; RR = 1.44s
- PP = 1.44s; RR = 0.52s
- PP = 0.73s; RR = 0.73s

[SELECT ONE RED BOX]

4

PP = 0.52s; RR = 1.44s

- This is correct.
- The PP interval is 13 small boxes or 0.52s because [13 boxes X 0.04 s/box = 0.52s]
 - 60/PP interval is the number of depolarizations per minute (dpm) [60/0.52 = 115 dpm]
- The RR interval is 36 small boxes or 1.44s because [36 X 0.04 = 1.44s]
 - 60/RR interval is the ventricular rate (and in most cases the pulse rate) [60/1.44 = 41.7 bpm]

[SELECT RED BOX]

5

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[Click on Blue Box to go Back]



6

$PP = 0.73s; RR = 0.73s$


- This is not correct. It should be apparent that the PP Interval and RR intervals are not equal lengths.

[Click on Blue Box to go Back] 

7

ECG 2

What is the Rhythm?



25mm/sec 10mm/mV © Jason Winter 2016 - © ECG Educator


- Torsade de Pointes
- Third Degree AV Block
- Type-1 Second Degree AV Block

[SELECT ONE RED BOX]

8

Torsade de Pointes

- This is incorrect. TdP is a polymorphic ventricular tachycardia with wide QRS complexes and the amplitude (height) of the QRS complexes get progressively bigger and then smaller in a repeating pattern.

[Click on Blue Box to go Back] 

9

Third Degree AV Block


- This is correct. The RRs are evenly spaced with a rate of 40-45 depolarizations per minute and the p-waves are evenly spaced but with a completely different rate and no apparent connection (coordination) between the the Ps and the Rs.

[SELECT RED BOX]

10

Type-1 Second Degree AV Block

- This is not correct. Please try again.


[Click on Blue Box to go Back] 

11

Acute Treatment

The patient is given 0.5mg of atropine IV and the rhythm now looks like this:

What is the Rhythm?



25mm/sec 10mm/mV

- Torsade de Pointes
- Type-1 Second Degree AV Block
- Third Degree AV Block

[SELECT ONE RED BOX]

12

Torsade de Pointes

- This is not correct. Keep trying it though, it could be right later in the case...

[Click on Blue Box to go Back]



13

Type-1 Second Degree AV Block

- This is correct. The PR interval starts out normal and then gets longer and longer over the next two cardiac cycles but then the atrial wave (P-wave) does not transfer into the ventricles (no QRS complex).

[SELECT RED BOX]



14

Third Degree AV Block

- This is incorrect. Third degree AV block has no association between the atria and ventricles, that is not the case here. Look more closely at the pattern and apply the heart block poem.

[Click on Blue Box to go Back]



15

Cardiology Clinic

Ms. Torres is diagnosed as having heart block and responded well to the addition of an additional 0.5mg atropine IV. The patient is now back in sinus rhythm with a heart rate of 80bpm but with a PR interval of 265ms (severe first degree AV block). Which medication should be held at this time?

- Itraconazole
- Verapamil
- CBD

[SELECT ONE RED BOX]

16

Itraconazole

- Good guess, but no. Since the patient was stable on verapamil for a long time without issue, the most likely rationale is that itraconazole blocked CYP3A4 raising verapamil's concentrations and precipitating heart block.

[Click on Blue Box to go Back]



17

Verapamil

- Good job! Yes, verapamil is the most likely drug induced cause of the heart block. While the patient was treated for a long time with verapamil without issue, recently the patient received itaconazole for toenail fungus. The interaction through CYP3A4 raised verapamil's concentration.

[SELECT RED BOX]



18

CBD

- This is incorrect. CBD could have drug interactions but this is more likely through CYP2D6 than CYP3A4 where verapamil is metabolized. Just for the record, kava is much better studied as a chronic antianxiety drug.

[Click on Blue Box to go Back]



19

After Awhile

After 3 days of holding verapamil, the PR interval is now 186 ms, which is normal. Ms Torres's blood pressure is 155/89mmHg and she therapy for her hypertension. What would you recommend?

- Restart verapamil at ½ the dose
- Use terbinafine alone (stop itraconazole) and restart full dose verapamil
- Switch to hydrochlorothiazide 50mg once daily

[SELECT ONE RED BOX]

20

Restart Verapamil at ½ Dose

- This is a reasonable approach. On an exam, I would give you credit for this viable option. It does raise complexity though as the verapamil dose might have to be tweaked up and down a little to get the right response and then the itraconazole will only be used for several months and then therapy would need to be readjusted.

[Click on Blue Box to go Back]



21

Stop Itraconazole

- This is a reasonable choice but not my favorite. The patient is on combination therapy and this likely indicated refractory toenail fungus. If so, it is unlikely that a single topical drug would be sufficient.

[Click on Blue Box to go Back]



22

Switch to Hydrochlorothiazide

- This is correct. Hydrochlorothiazide is as effective as verapamil for reducing cardiac events in African American patients and similarly reduces the blood pressure as well. Since many more months of itraconazole therapy is needed, it is best to move on from verapamil at this time.

[SELECT RED BOX]




23

Fast Forward

- Laquisha Torres is now 66 years old.
- CC: Passing out while jogging and then when sitting at home reading.
- HPI: Over the past two days patient has had two syncopal episodes, one while jogging and another while sitting at home reading. Started to feel a warm sensation and then just passed out.
- PMH: Atrial fibrillation X 7 weeks, now well controlled. Hypertension.
- Meds: Dofetilide 250mcg twice daily (7 weeks ago), Atenolol 100mg daily, hydrochlorothiazide 50mg daily, Estradiol 5mg, Megestrol 40mg twice daily (started 4 days ago).
- Labs: Na⁺ 136mEq/L, K⁺ 3.2mEq/L, CrCl 68mL/min
- ECG: See next slide...

24

ECG-3



What is the PR, QT, RR, and QTc intervals?

- PR = 0.12s, QT = 0.44s, RR = 0.76s, QTc = 0.504s
- PR = 0.20s, QT = 0.44s, RR = 0.57s, QTc = 0.480s

25

PR = 0.12s, QT = 0.44s, RR = 0.76s, QTc = 0.504s

- This is correct. PR = 3 boxes X 0.04s = 0.12s; QT = 11 boxes X 0.04 = 0.44s; RR = 19 boxes X 0.04s = 0.76s.
- QTc interval = $QT/(RR)^{1/2} = 0.44/(0.76)^{1/2} = 0.44/0.872 = 505s$.


Not relevant to this case, but the QTc interval calculation is not as accurate if the heart rate is too far below 60 bpm.

[SELECT RED BOX]

26

PR = 0.20s, QT = 0.44s, RR = 0.57s, QTc = 0.480s

- This is incorrect. Please try again with PR = 3 boxes, QT = 11 boxes, and RR = 19 boxes.

[Click on Blue Box to go Back] 

27

Diagnosis

- This patient has a markedly elevated QTc interval with a HR of 76 bpm. What is the most likely explanation of her syncopal episodes?


- Absence seizures
- Torsade de Pointes
- Type-2, 2nd degree heart block

[SELECT ONE RED BOX]

28

Absence Seizures

- While this is a cause of syncope in some people, it is not as likely as another cause given the case.

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29

Torsade de Points

- This is correct! The QTc interval prolongation > 500ms is a big risk factor for the development of Torsade de Pointes, which can cause syncope. The episodes come and go so it was not picked up at the time the ECG was taken.

[SELECT RED BOX]

30

Type-2, 2nd Degree Heart Block

- This is incorrect. There is no loss of a P-wave to make it into the ventricles in this ECG, the big issue lies in the QTc interval.

[Click on Blue Box to go Back]



31

What is To Blame?

- Given the patient's drug therapy, which drug is most likely to cause QTc interval prolongation?

- Estradiol
- Dofetilide
- Dofetilide + Megestrol

[SELECT ONE RED BOX]

32

Estradiol

- This is incorrect.

[Click on Blue Box to go Back]



33

Dofetilide

- This is incorrect. While dofetilide is the drug that has the greatest capacity to cause QTc interval prolongation, she was on it for more than 5 half lives. If severe QTc interval prolongation doesn't occur when you hit steady state, it is less likely to newly occur. However, if you add a drug that blocks metabolism of dofetilide, innately promotes QTc interval prolongation, reduces its renal clearance, causes hypokalemia or hypomagnesemia, or dramatically reduces the heart rate; you could get more advanced QTc interval prolongation and Torsade de Pointes.

[Click on Blue Box to go Back]



34

Dofetilide + Megestrol

- This is correct. Megestrol can support Transgendered woman's transition and maintenance but it is a cation tubular secretion inhibitor. It is contraindicated with dofetilide and is a strong precaution with procainamide for that same reason.

[SELECT RED BOX]



35

Treatment Options

- Dofetilide is halted and intravenous magnesium 1g over 10 minutes and then 1g an hour for 8 hours given to the patient as prophylaxis against Torsade de Points and to decrease the QTc interval. The QTc interval at the end is 470ms and the next day is 425ms. What should be done now?

- Discontinue megestrol and restart dofetilide
- Switch dofetilide to propafenone
- Switch dofetilide to amiodarone

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36

Discontinue Megestrol and Restart Dofetilide

- While this is a reasonable choice, the patient might really desire the anti-adrenergic effects the drug provides. If there was not another good option for the atrial fibrillation, it would not be a bad choice.

[Click on Blue Box to go Back]



37

Switch to Propafenone

- This is the best choice. Propafenone is similarly effective to prevent recurrences of atrial fibrillation as dofetilide. It is not contraindicated with megestrol. If this patient had structural heart disease (left ventricular hypertrophy, myocardial infarction, or heart failure), propafenone would be contraindicated.

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38

Amiodarone

- While amiodarone has a lower risk of Torsade de Pointes and better efficacy for preventing AF recurrence than other Class III antiarrhythmic agents, it has a lot of adverse effects include some that can be fatal, like pulmonary fibrosis. Since the issue can be easily handled by switching to another agent like propafenone, that should be tried first. If Torsade de Pointes occurs on two or more antiarrhythmic agents or if they are ineffective, amiodarone would be an excellent choice. Like dofetilide, amiodarone is an excellent choice if the patient has both heart failure and AF.

[Click on Blue Box to go Back]



39