Disclosures:

- Dr. White has received no funding from any company that makes any of the drugs covered in this presentation and is not an individual stock owner for any of the companies either. He does not have any financial or nonfinancial conflicts of interest germane to this presentation. In addition, he will be discussing drug adverse events which are aligned with those already denoted in the drugs package inserts, albeit in much greater depth. He will not be talking about investigational drugs or the off-label use of drugs.

Objectives

At the conclusion of this lecture the successful learner will be able to:

- Identify heart block
- Differentiate between 1st, type-1 2nd, type-2 2nd, and 3rd degree AV block
- Describe the drugs and dietary supplements that can cause heart block and what to do if drug induced heart block occurs acutely and chronically
- Identify QTc interval prolongation and describe how much of an elevation dramatically enhances the risk of Torsade de Pointes
- Describe drugs and dietary supplements that may prolong QTc interval and interventions for acute Torsade de Pointes or chronic QTc interval prolongation
- Apply knowledge to a patient relevant case

This entire lecture is based on the following book chapter:
Normal Durations: Each Small Block = 40ms

- PR Interval = 8 blocks:
  - 8 blocks X 0.04 sec/block = 0.36sec
  - 0.36 sec = 360 ms

- Normal PR interval <200ms

- First degree AV block PR-200ms
- Severe PR prolongation >240ms

White CM, Song J, Kales J. Cardiac Arrhythmias, Chapter 20.

Notes:

- PR interval is fixed duration but >200ms, no lost QRS complexes
- PR progressively lengthens until a QRS complex is dropped, then pattern repeats
- No progressive lengthening in PR but still missing a QRS
- Green is consistent distance, blue is consistent distance but no relationship between the P and QRS complexes

Drugs That Induce Heart Block: (Red Box = Gotta Know)

<table>
<thead>
<tr>
<th>Beta-Blockers: Metoprolol, Propranolol, Atenolol, etc</th>
<th>Anti-Arrhythmics</th>
<th>Psychoactive</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-Blockers: Metoprolol, Propranolol, Atenolol, etc</td>
<td>Class Ia: Quinidine, Procainamide</td>
<td>Opioids</td>
<td>Propofol</td>
</tr>
<tr>
<td>Class Ib: Lidocaine, Mexiletine</td>
<td></td>
<td>Denepazol</td>
<td>Succinylcholine</td>
</tr>
<tr>
<td>Class III: Amiodarone, Dronedarone, Sotalol</td>
<td></td>
<td>Phenothiazines: Chlorpromazine, etc</td>
<td>Cannabis</td>
</tr>
<tr>
<td>Phenytoin</td>
<td></td>
<td>Propafenone</td>
<td></td>
</tr>
</tbody>
</table>

What Do You Do After Heart Block?

- Once heart block resolves (PR < 200ms, symptoms resolved):
  - Is drug really needed, are there equally good alternatives?
    - Yes: use alternative
    - [IF THE ANSWER IS NO]...
      - If due to gross overdose - is risk of new overdose low?
        - Yes: restart; No: Stop
      - If due to inappropriate dose for age, renal function, hepatic function
        - Can a lower dose or drug in same class with different clearance pathway be used?
          - Yes: restart; No: Stop
      - If due to drug interaction - can interaction be avoided?
        - Yes: restart one of the offending agents; No: use lower doses and monitor more closely

Pharmacokinetic/Dynamic Drug Interactions

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Elimination Pathway</th>
<th>Some Inhibitors</th>
<th>Pharmacodynamic Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol, Propranolol, Carvedilol</td>
<td>CYP206</td>
<td>Quinidine, theophylline, SSRIs (fluoxetine, paroxetine, sertraline), duloxetine, bupropion, CYP3A4 inhibitors, amiodarone, dronedarone</td>
<td>All other PR interval prolonging drugs</td>
</tr>
<tr>
<td>Atenolol, Nadolol</td>
<td>Renal</td>
<td>Renal Dysfunction</td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td>CYP3A4</td>
<td>Ketorolac, iraconazole, HMG CoA reductase inhibitors, cyclosporin, grapefruit juice, erythromycin, clarithromycin, nefazodone, amiodarone, dronedarone</td>
<td></td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Multiple CYP's</td>
<td>Quinidine (due to kinetic and dynamic)</td>
<td></td>
</tr>
</tbody>
</table>
| Digoxin | P-Glycoprotein | Quinidine, amiodarone, trecinamide, propafenone, verapamil | [For digoxin, drugs that lower potassium (loop diuretics, thiazide diuretics) increase risk of digoxin toxicity including heart block]
Calculating QTc Interval on Resting ECG: Everything MUST BE in Seconds not MS

- Calculate QT interval in sec
- Calculate RR interval in sec
- Apply formula:
  \[ QTc = \frac{QT}{\sqrt{RR}} \]

Torsade de Pointes (TdP)

- A polymorphic ventricular tachycardia
- Can be caused by R-on-T phenomenon (depolarization in vulnerable repolarization state)


Torsade de Pointes

- Polymorphic Ventricular Tachycardia
- Caused by QTc interval prolongation >500ms (0.5 sec)
- OR increased >60 ms from baseline
- Caution with Class Ia or III agents if baseline QTc interval is >440ms
- Caution with non-AAs agents that prolong QTc interval (antipsychotics, fluoroquinolones, macrolides, select opioids [methadone, kratom, oliceridine, loperamide]) if baseline QTc interval >470ms
- Female gender has higher QTc interval than men (13 msec higher)
- Hypokalemia, hypomagnesemia increases QTc interval
- Class IA and III agents except amiodarone have greater QTc interval prolongation when heart rate slower (reverse use dependence)

Acute Treatment of TdP

- Hemodynamically stable:
  - IV magnesium is drug of choice (2g bolus then 1g/hour for 18 hours)
  - Lidocaine is second line therapy (see lidocaine)
- Hemodynamically unstable (unconscious, can’t mentate, causing myocardial ischemia)
  - Electrically shock right away

What Do You Do After TdP or Severe QTc Interval Prolongation?

- Once QTc interval resolves (<440ms or less than 30ms increase from baseline, symptoms resolved):
  - Is drug really needed, are there equally good alternatives?
    - Yes - use alternative
    - No: use antiarrhythmic
      - If the answer is no...
        - If due to gross overdose - is risk of new overdose low?
          - Yes - restart; No - Stop
        - If due to inappropriate dose for age, renal function, hepatic function
          - Can a lower dose or drug in same class with different clearance pathway be used?
            - Yes - restart; No - Stop
        - If due to drug interaction - can interaction be avoided?
          - Yes - restart one of the offending agents; No - use lower doses and monitor more closely

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<tr>
<td>Quinidine</td>
<td>CYP3A4</td>
<td>Ketoconazole, triazoles, HIV protease inhibitors, cyclosporin, grapefruit juice, erythromycin, clarithromycin, nefazodone</td>
<td>All other QT-Prolonging drugs in column A - macrolides, antipsychotics, tricyclic antidepressants, fluoroquinolones, methadone, kratom, loperamide (mega-dose)</td>
</tr>
<tr>
<td>Procainamide</td>
<td>Cation tubular secretion inhibitors</td>
<td>Ketoconazole, megestrol, cinetidine, hydrochlorothiazide, prochlorperazine, trimethoprim</td>
<td></td>
</tr>
<tr>
<td>Sotalol</td>
<td>Renal</td>
<td>Renal dysfunction</td>
<td></td>
</tr>
<tr>
<td>dofetilide</td>
<td>Cation tubular secretion inhibitors</td>
<td>Ketoconazole, megestrol, cinetidine, hydrochlorothiazide, prochlorperazine, trimethoprim</td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>CYP3A4 (minor)</td>
<td>Ketoconazole, triazoles, HIV protease inhibitors, cyclosporin, grapefruit juice, erythromycin, clarithromycin, nefazodone</td>
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<tr>
<td>Dronedarone</td>
<td>CYP3A4 (minor)</td>
<td>Ketoconazole, triazoles, HIV protease inhibitors, cyclosporin, grapefruit juice, erythromycin, clarithromycin, nefazodone</td>
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Conclusions

• Pharmacists need to use proper dosing and avoid drug interactions that can increase the risk of drug-induced disease
• Pharmacists need to look specifically for evidence of drug induced disease
  • Catch them early before severe toxicity results
• Pharmacists need to identify potential acute treatments and suggest whether and how to restart the drugs after the acute issues have passed