COVID-19: Implications for Pharmacists: Round 2, What’s New?

Objectives

- Describe the relationship between NSAIDs and COVID-19
- Summarize the cardiovascular implications of hydroxychloroquine use
- Review the role of azithromycin in treatment of COVID-19
- List the actions the Colorado Pharmacists Society has taken during the COVID-19 crisis.

Questions to be answered...

1. How big of a problem is QT prolongation with hydroxychloroquine?
2. Does azithromycin offer additional benefit when combined with an antimalarial?
3. Should we tell people to only use acetaminophen if they a fever suspected to be COVID-19?
4. How do you respond to a patient asking if they should stop their ACE/ARB?
5. What is CPS doing to address the COVID-19 crisis on behalf of pharmacists?

Hydroxychloroquine & Cardiac Conduction

- Hydroxychloroquine similar to quinine (class Ia antiarrhythmic)

Pharmacology implications
- Inhibition of sodium channels
- Inhibition of potassium (hERG) channels
- Hypokalemia from intracellular shifting can contribute to dysrhythmias
Ideal data

- QTc data before and after hydroxychloroquine 200 mg, 400 mg, and 600 mg
- Healthy patients
- Patients with cardiovascular diseases
- Patients taking additional QT prolonging medications – especially azithromycin

Long QT and Hydroxychloroquine; A Poorly Recognized Problem In Rheumatology Patients

- 2013 American College of Rheumatology abstract
- N=19, 16 female, 3 male
- CV history: hypertension (n=7), obesity (n=5), ischemic heart disease (n=4), deep vein thromboses (n=3) and cerebrovascular accidents (n=3)
- Dose: 200 mg (n=4), 400 mg (n=15) per day

<table>
<thead>
<tr>
<th>Baseline, mean (range)</th>
<th>6 mo after HCQ, mean (range)</th>
</tr>
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<tbody>
<tr>
<td>QTc, msec</td>
<td>424 (377-554)</td>
</tr>
<tr>
<td>Long QTc, n</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>449 (387-620)</td>
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</tbody>
</table>

Assessment of the Relationship Between Dose, Drugs, and QTc

- Descriptive data from cohort of patients with lupus
- ECGs on admission and six hours later
- QTc interval determined using Bazett’s formula

<table>
<thead>
<tr>
<th>Normal QTc, n=103</th>
<th>Prolonged QTc, 47</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 34 ± 84</td>
<td>36 ± 54</td>
</tr>
<tr>
<td>Hydroxychloroquine, n (%)</td>
<td>60 (58)</td>
</tr>
<tr>
<td>Mean HCQ dose, msec</td>
<td>283</td>
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</tbody>
</table>

Tisdale Risk Score for Drug-Induced QT

<table>
<thead>
<tr>
<th>Points</th>
<th>Risk Factors</th>
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<tbody>
<tr>
<td>1</td>
<td>Age ≥68 years, female sex, loop diuretic</td>
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<tr>
<td>2</td>
<td>Serum K+ ≤3.5 mEq/L, admission QTc ≥450 msec, acute myocardial infarction</td>
</tr>
<tr>
<td>3</td>
<td>≥2 QTc-prolonging drugs, sepsis, heart failure, one QTc-prolonging drug</td>
</tr>
<tr>
<td>21</td>
<td>Maximum Risk Score</td>
</tr>
</tbody>
</table>

Risk level points: Low risk ≤ 6, Moderate risk 7-10, High risk ≥ 11

Suggested contraindications: Baseline QTc > 500 msec, or Tisdale risk ≥ 11 without ECG monitoring

Hydroxychloroquine Cardiology Summary

- Prolongs QT similar to class I antiarrhythmic
- QT prolongation is dose related
- Small cohort showed mean QTc increase of 25 msec
  - Doses of 200 and 400 mg daily

Consider
- Continuous ECG monitoring for patients with baseline QT of > 500 msec or Tisdale score ≥ 11
- Hydroxychloroquine in multiple doses instead of daily dosing

Guidance: ACC COVID-19 Mayo COVID-19 QTc

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Gautret P, et al. #1, Open label trial

- HCQ, n=14
- HCQ + azith, n=6
- Controls, n=16 (outside hospital)

- N=6 HCQ lost to follow-up
  - 1 died
  - 3 transferred to ICU


Contagion Live article: COVID-19 Treatment: Updates March 19-24, 2020

- Erin McCreary, PharmD, BCIDP
- Jason Pogue, PharmD, BCIDP


Gautret P, et al. #2,

Treatment
- HCQ 200 mg PO TID x 10 days + azith 500 mg, 250 mg daily x 5 total days
- PLUS ceftriaxone 1 g daily if PNA or moderate-severe illness
- ECG at baseline and 2 days after treatment
- Treatment dc’d if QTc > 500 msec (Bazett’s formula)
- Concurrent QT prolonging medications discontinued

Outcome
- Symptom onset to treatment = 5 days
- Treatment started on day 0 = 49, 1 = 26
- Favorable outcome (discharged) = 65/80 (81%)
- Transferred to ICU = 3/80 (4%), 2 improved, 1 died
- NO QT DATA REPORTED

***Not yet peer reviewed***

Day 0 to 1: 10 pts are negative?!? (10 of 49)
Day 1 to 2: only 6 pts more
Day 3 – 5 pts have left the study (supposed to have 6 days of follow-up to be included)
Lacking viral load data
Control data

***Not yet peer reviewed***

Chen et al. HCQ RCT

- Chen et al. RCT, Wuhan, China, mild illness, otherwise healthy
- HCQ 200 mg BID x 5 days vs. standard of care

<table>
<thead>
<tr>
<th></th>
<th>HCQ, n=31</th>
<th>Control, n=31</th>
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</thead>
<tbody>
<tr>
<td>Age, years ± SD</td>
<td>44 ± 16</td>
<td>45 ± 15</td>
</tr>
<tr>
<td>Adverse effects, n (%)</td>
<td>2 (7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Clinical improvement, n (%)</td>
<td>25 (81)</td>
<td>17 (55)</td>
</tr>
<tr>
<td>Exacerbation, n (%)</td>
<td>2 (7)</td>
<td>9 (29)</td>
</tr>
<tr>
<td>Progressed to severe, n (%)</td>
<td>0 (0)</td>
<td>4 (13)</td>
</tr>
</tbody>
</table>

https://www.medrxiv.org/content/10.1101/2020.03.22.20040758v1

Questions to be answered...

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5. What is CPS doing to address the COVID-19 crisis on behalf of pharmacists?

Why all the concern?

- March 14, 2020:
  - French health officials suggested adverse events with NSAID use in patients with COVID-19; recommended acetaminophen instead

- March 18, 2020:
  - The European Medicines Agency response:
    - Currently “no scientific evidence” that NSAIDs, such as ibuprofen, could worsen coronavirus disease
    - When starting treatment for fever or pain in COVID-19, patients and healthcare professionals should consider all available treatment options including paracetamol and NSAIDs


FDA advises patients on use of non-steroidal anti-inflammatory drugs (NSAIDs) for COVID-19

- What is CPS doing to address the COVID-19 crisis on behalf of pharmacists?

- Hypertension, diabetes, CVD identified as common comorbidities in COVID-19
- SARS-CoV-2 binds to ACE2
- ACE2 increases in diabetes patients treated with ACEi or ARB
- ACE2 expression increased by ibuprofen and may facilitate COVID-19
Questions to be answered...

1. How big of a problem is QT prolongation with hydroxychloroquine?
2. Does azithromycin offer additional benefit when combined with an antimalarial?
3. Should we tell people to only use acetaminophen if they a fever suspected to be COVID-19?
4. How do you respond to a patient asking if they should stop their ACEi/ARB?
5. What is CPS doing to address the COVID-19 crisis on behalf of people with hypertension?

Random Facts and Confusion

- ACEI or ARB therapy can upregulate ACE2 expression in animal models.
- ACEI or ARB therapy might increase SARS-CoV-2 attachment and COVID-19.
- Observational data show that COVID-19 patients with CVD risk factors have worse outcomes.

FDA Advisory:

- Not aware of scientific evidence connecting NSAID use with worsening COVID-19 symptoms.
- NSAID label already warns that “the pharmacological activity of NSAIDs in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections”.
- Other options such as acetaminophen are reasonable to use, patients should consult a healthcare professional.
- Use typical NSAID precautions (e.g., nephrotoxicity, bleeding), nothing different just because of COVID-19.

Expert Opinions: ACEi/ARB and COVID-19

<table>
<thead>
<tr>
<th>Society</th>
<th>Update</th>
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<tbody>
<tr>
<td>Acute Society of Hypertension</td>
<td>March 10, 2020</td>
</tr>
<tr>
<td>American Society of Cardiology Council on Hypertension</td>
<td>March 11, 2020</td>
</tr>
<tr>
<td>American Cardiovascular Society</td>
<td>March 15, 2020</td>
</tr>
<tr>
<td>American Heart Association</td>
<td>March 16, 2020</td>
</tr>
<tr>
<td>American Society of Hypertension</td>
<td>March 16, 2020</td>
</tr>
<tr>
<td>American College of Physicians</td>
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<td>European Society of Cardiology Council on Hypertension</td>
<td>March 19, 2020</td>
</tr>
<tr>
<td>International Society of Hypertension</td>
<td>March 20, 2020</td>
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<tr>
<td>Renal Association, United Kingdom</td>
<td>March 20, 2020</td>
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<tr>
<td>Renal Association/European Dialysis and Transplant Association</td>
<td>March 20, 2020</td>
</tr>
<tr>
<td>American Heart Association/American College of Cardiology</td>
<td>May 18, 2020</td>
</tr>
<tr>
<td>Korean Society of Hypertension</td>
<td>March 20, 2020</td>
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</table>

All either recommend or strongly encourage continuing ACEi or ARB therapy.

Bottom Line: ACEi/ARB and COVID-19

- ACE2 is the functional receptor to SARS-CoV-2.
- Preclinical studies suggest ACEi/ARB therapy may increase ACE2 expression.
- Insufficient data to determine if findings translate to humans.
- Clinical trials are under way to further assess risks.
- Abrupt withdrawal of ACEi/ARB therapy in high CV risk patients may result in instability and adverse outcomes.
- Continue ACEi or ARB therapy in otherwise stable patients.

Random Facts and Confusion

- Retrospective review of elderly COVID-19 patients: significantly decreased risk of severe infection with ARB therapy.
- Small study from China showed ACEi or ARB not associated with increased morbidity and mortality.

No quality clinical data demonstrating beneficial or adverse outcomes among COVID-19 patients using an ACEi or ARB.
Questions to be answered…

1. How do you respond to a patient asking if they should stop their ACE/ARB?
2. How big of a problem is QT prolongation with hydroxychloroquine?
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What is CPS doing?

- Many asks granted from the governor’s office
  - Remote practice without prior authorization
  - Delayed technician certification deadline
  - Allowing pharmacists and techs in other states to temporarily practice in CO to meet staffing needs if necessary
  - Waiving all signature requirements (granted by b CMS)

- Requesting broader authority for pharmacists
  - Treatment of mild ailments
  - Therapeutic substitution for drug shortages
  - Working with hospital groups to try to ensure access to sedative medications for ventilated patients
  - Representing the pharmacy profession in larger healthcare discussions
  - Assisting the Department of Public Health (CDPHE)

What about PPE?

- Collecting and sharing information about best practices
- Facemasks prioritized for:
  - Essential surgeries/procedures
  - Close contact with a potentially infectious patient
- PPE should be used for immunizations
  - Influenza and pneumococcal vaccines strongly recommended due to increased risk of secondary infections

Community Pharmacy Best Practices

- eRx’s only
- No patient signatures (CMS has waived Part D plan signatures)
- Staff handling money/credit cards should wear gloves
- Process as credit vs. debit transactions to avoid PIN pad use
- Clean credit card machine keypads between customers
- Physical barriers (plexiglass or clear plastic)
- Drive-thru, delivery, or curb-side pick up whenever possible

We need to hear from you

- We can only advocate for issues we are made aware of
- Our avenues – other professional associations (local and national), CDPHE, legislators, governor’s office, etc.
- Call or email
  - Emily Zadvorny, Executive Director (emily.zadvorny@cuanschutz.edu; 303-818-9045)
  - Gina Moore, President (gina.moore@cuanschutz.edu; 720-939-6586)
**Favorite COVID-19 Resources**

- Society of Infectious Diseases Pharmacists
  - [https://www.sidp.org/](https://www.sidp.org/)
  - YouTube channel
- ASHP
  - Continuously updated “Assessment of Evidence for COVID-19-Related Treatments”
- Contagion Live
  - [https://www.contagionlive.com/](https://www.contagionlive.com/)
- COVID-19 and ACE2 and Hypertension

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**Questions:** sop.continuingeducation@cuanschutz.edu

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