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

Meghan Jeffres, PharmD, Gina Moore, PharmD, MBA, Joseph Saseen, PharmD
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.
Disclaimer

New data is created and distributed hourly. It is very possible that information presented today will already be outdated by the end of this webinar.

Slides last updated 4/1/2020
Questions to be answered…

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2. Does azithromycin offer additional benefit when combined with an antimalarial?
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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 cerebral vascular accidents (n=3)
- Dose: 200 mg (n=4), 400 mg (n=15) per day

<table>
<thead>
<tr>
<th></th>
<th>Baseline, mean (range)</th>
<th>6 mo after HCQ, mean (range)</th>
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<tbody>
<tr>
<td>QTC, msec</td>
<td>424 (377-584)</td>
<td>449 (387-620)</td>
</tr>
<tr>
<td>Long QTC, n</td>
<td>4</td>
<td>8</td>
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</table>

https://acrabstracts.org/abstract/long qt and hydroxychloroquine a poorly recognised problem in rheumatology patients/
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></th>
<th>Normal QTc, n=103</th>
<th>Prolonged QTc, 47</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>34 ± 84</td>
<td>36 ± 54</td>
</tr>
<tr>
<td>Hydroxychloroquine, n (%)</td>
<td>60 (58)</td>
<td>39 (83)</td>
</tr>
<tr>
<td>Mean HCQ dose, msec</td>
<td>283</td>
<td>333</td>
</tr>
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## 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>
</tr>
<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>
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### 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

***Not yet peer reviewed***

Gautret P, et al. #2,

- Symptom onset to treatment = 5 days
- Treatment started on day 0 = 49, 1 = 26

**Outcome**
- Favorable outcome (discharged) = 65/80 (81%)
- Transferred to ICU = 3/80 (4%), 2 improved, 1 died

**NO QT DATA REPORTED**
Gautret P, et al. #2,

- 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

Andrew Morris @ASPphysician · Mar 28
So in our totally useless followup study, mostly very low-risk pts (92%)—of whom only 14% had a fever—were coerced into experimental treatment in our hospital with HCQ/azithromycin. Thankfully, their virus cleared so I can keep pushing this non-evidence. mediterranee-infection.com/content/upl...

Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: an observational study

Running title: Hydroxychloroquine-Azithromycin and COVID-19

Philippe Gautret1,2,*, Jean-Christophe Lagier1,3, Philippe Parola1,2, Van Thuan Le1,2, Line Meddeb1, Jacques Sevestre1, Morgane Mailhe1, Barbara Doudier1, Camille Debelle1, Sophie Amrane1, Piseth Seng1, Marie Hocquart1, Julie Finance1, Vera Esteves1, Tissot Dupont1,*, Stéphane Honore2,*, Andreas Stein1,3, Mathieu Million1,3, Philippe Roger1,3, Jean-Paul Renoux1,3, Sylvain Chartier1,3, Philippe Piroir1,3, * Correspondence: Philippag@lacassine-paris6.fr

Vasilicos Athans @AthansID · Mar 28
Live look at new HCQ/azithromycin studies being published.
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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<tbody>
<tr>
<td>Age, years ± SD</td>
<td>44 ± 16</td>
<td>45 ± 15</td>
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<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>
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</table>

***Not yet peer reviewed***

https://www.medrxiv.org/content/10.1101/2020.03.22.20040758v1
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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
Q: Could #ibuprofen worsen disease for people with #COVID19?

A: Based on currently available information, WHO does not recommend against the use of ibuprofen.

Could ibuprofen worsen disease for people with COVID-19?

At present, based on currently available information, WHO does not recommend against the use of ibuprofen. We are also consulting with physicians treating COVID-19 patients and are not aware of reports of any negative effects of ibuprofen, beyond the usual known side effects that limit its use in certain populations. WHO is not aware of published clinical or population-based data on this topic.

#coronavirus

18 March 2020
[3/19/2020] FDA is aware of news reports stating the use of non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, could worsen coronavirus disease (COVID-19). These news reports followed a March 11, 2020 letter in The Lancet medical journal, which hypothesized that an enzyme (a molecule that aids a biochemical reaction in the body) is increased by NSAIDs and could aggravate COVID-19 symptoms.
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

Fang L, et al. Published online March 11, 2020  https://doi.org/10.1016/S2213-2600(20)30116-8
Bottom Line: NSAIDs and COVID-19

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

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SARS-CoV-2 and the RAAS are Related!

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

- 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**

Expert Opinions: ACEi/ARB and COVID-19

<table>
<thead>
<tr>
<th>Society</th>
<th>Update</th>
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<tbody>
<tr>
<td>European Society of Hypertension</td>
<td>March 12, 2020</td>
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<tr>
<td>European Society of Cardiology Council on Hypertension</td>
<td>March 13, 2020</td>
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<tr>
<td>Hypertension Canada</td>
<td>March 13, 2020</td>
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<tr>
<td>Canadian Cardiovascular Society</td>
<td>March 15, 2020</td>
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<tr>
<td>The Renal Association, United Kingdom</td>
<td>March 15, 2020</td>
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<tr>
<td>International Society of Hypertension</td>
<td>March 16, 2020</td>
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<tr>
<td>American College of Physicians</td>
<td>March 16, 2020</td>
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<tr>
<td>Spanish Society of Hypertension</td>
<td>March 16, 2020</td>
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<tr>
<td>American Heart Association/Heart Failure Society of America/American College of Cardiology</td>
<td>March 17, 2020</td>
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<tr>
<td>European Renal Association/European Dialysis and Transplant Association</td>
<td>March 17, 2020</td>
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<tr>
<td>American Society of Pediatric Nephrology</td>
<td>March 17, 2020</td>
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<tr>
<td>High Blood Pressure Research Council of Australia</td>
<td>March 18, 2020</td>
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<tr>
<td>Australian Diabetes Society</td>
<td>March 29, 2020</td>
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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 other-wise stable patients

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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)
What is CPS doing?

- 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
Continuing Education

How to claim credit (pharmacists & pharmacy technicians)

1. Navigate to UCDenver.edu/pharmacy/continuingeducation
2. Select Online CE
3. Select Today’s Webinar

Questions: sop.continuingeducation@cuanschutz.edu

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