Systemic Medications for the Dermatology Toolbox: Hydroxychloroquine

American Academy of Dermatology
03/04/2019

Nicole Fett MD MSCE
Associate Professor of Dermatology
Oregon Health and Science University
Conflicts of Interest and Disclosures

• I have no conflicts of interest
• I have no pertinent disclosures
  – UpToDate author and peer reviewer
  – Investigator for Hoffman-La Roche and Pfizer
  – Assistant Section Editor JAMA Derm
  – Education and Program Committee Medical Dermatology Society
  – Education and Program Committee Rheumatologic Dermatology Society
  – Materials review panel medical expert in dermatology for the Lupus Foundation of America
  – Board of Directors Association of Professors of Dermatology
  – President Elect Rheumatologic Dermatology Society
  – AAD Editor, Medical Dermatology Online Board Prep Question Bank
  – Associate Professor of Dermatology, OHSU
  – Dermatology Residency Program Director
  – Packer’s fan and owner
• I will be discussing off-label uses of hydroxychloroquine
Hydroxychloroquine Clinical Questions

• What dose do I prescribe?
• Does it really cause cardiomyopathy?
Hydroxychloroquine Outline

• Uses for the medication
• Brief review of absorption/metabolism/excretion
• Mechanism of action
• Contraindications
• Pregnancy risks
• Adverse effects
• Formulations
• Dosing
• Medication interactions
• Monitoring guidelines
• Key points slide
• Review clinically relevant questions
Hydroxychloroquine Outline

• Uses for the medication
  – Interface issues: Cutaneous lupus, dermatomyositis, lichen planus
  – Granulomatous issues: sarcoidosis, PNGD, IGD

• Brief review of absorption/metabolism/excretion

• Mechanism of action

• Contraindications

• Pregnancy risks

• Adverse effects

• Formulations

• Dosing

• Medication interactions

• Monitoring guidelines

• Key points slide

• Review clinically relevant questions
Hydroxychloroquine Outline

• Uses for the medication
• Brief review of absorption/metabolism/excretion
• Mechanism of action
• Contraindications
• Pregnancy risks
• Adverse effects
• Formulations
• Dosing
• Medication interactions
• Monitoring guidelines
• Key points slide
• Review clinically relevant questions
Hydroxychloroquine Outline

• Uses for the medication
• Brief review of absorption/metabolism/excretion
• Mechanism of action
• Contraindications
• Pregnancy risks
• Adverse effects
• Formulations
• Dosing
• Medication interactions
• Monitoring guidelines
• Key points slide
• Review clinically relevant questions
TLR-independent mechanisms of antimalarial therapy

- UV protection
  - Local anti-inflammatory effects and upregulation of the protective c-Jun-encoding gene
  - Control of photosensitivity and cutaneous lupus

- Antilipidaemic effects
  - Act at the lipid receptor level to regulate enzyme activity and possibly also through TLRs
  - Reduce LDL, VLDL and cholesterol, and increase HDL levels

- Antiangiogenic effects
  - Reduce epidermal expression of VEGF
  - In vitro anti-proliferative and apoptotic effects on ECs
  - Possible mode of action in discoid lupus

Hydroxychloroquine Outline

- Uses for the medication
- Brief review of absorption/metabolism/excretion
- Mechanism of action
- **Contraindications**
  - Retinal disease
  - Hypersensitivity
  - Older age, liver dz, renal dz, LBW, tamoxifen
- Pregnancy risks
- Adverse effects
- Formulations
- Dosing
- Medication interactions
- Monitoring guidelines
- Key points slide
- Review clinically relevant questions
Hydroxychloroquine Outline

• Uses for the medication
• Brief review of absorption/metabolism/excretion
• Mechanism of action
• Contraindications
• Pregnancy risks
• Adverse effects
• Formulations
• Dosing
• Medication interactions
• Monitoring guidelines
• Key points slide
• Review clinically relevant questions
Hydroxychloroquine Outline

• Uses for the medication
• Brief review of absorption/metabolism/excretion
• Mechanism of action
• Contraindications
• Pregnancy risks
• **Adverse effects**
• Formulations
• Dosing
• Medication interactions
• Monitoring guidelines
• Key points slide
• Review clinically relevant questions
Antimalarials: New screening tests and retinopathy risk

- Real body weight predicted risk better than ideal body weight
  - Recommending $\leq 5$ mg/kg/day of REAL body weight
  - Max 400 mg/day

Your patient is a 45 year old female with a history of DLE well controlled on hydroxychloroquine. She has been on hydroxychloroquine for 15 years at a dose of < 5 mg/kg/day. What is her current risk of retinopathy?

A.) 0%
B.) 3%
C.) 5%
D.) 7.5%
Hydroxychloroquine Retinal Toxicity

# Hydroxychloroquine Retinal Toxicity

## Table 1. Major Risk Factors for Toxic Retinopathy

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dosage</td>
<td></td>
</tr>
<tr>
<td>HCQ</td>
<td>&gt;5.0 mg/kg real weight</td>
</tr>
<tr>
<td>CQ</td>
<td>&gt;2.3 mg/kg real weight</td>
</tr>
<tr>
<td>Duration of use</td>
<td>&gt;5 Yrs, assuming no other risk factors</td>
</tr>
<tr>
<td>Renal disease</td>
<td>Subnormal glomerular filtration rate</td>
</tr>
<tr>
<td>Concomitant drugs</td>
<td>Tamoxifen use</td>
</tr>
<tr>
<td>Macular disease</td>
<td>May affect screening and susceptibility to HCQ/CQ</td>
</tr>
</tbody>
</table>

CQ = chloroquine; HCQ = hydroxychloroquine.
Hydroxychloroquine Retinal Toxicity

Table 3. Clinical Examination Techniques

Recommended Screening Tests
Primary tests: ideally do both
  Automated visual fields (appropriate to race)
  SD OCT
Other objective tests (as needed or available):
  mfERG
  FAF
  Newer tests of possible value in future
  Microperimetry
  Adaptive optics retinal imaging
Not Recommended for Screening
  Fundus examination
  Time-domain OCT
  Fluorescein angiography
  Full-field ERG
  Amsler grid
  Color testing
  DMEQ

Hydroxychloroquine Cardiomyopathy

• Conduction abnormalities
• Cardiomyopathy

• American Heart Association:
  
  “Hydroxychloroquine has been determined to be an agent that may either cause direct myocardial toxicity or exacerbate underlying myocardial dysfunction (magnitude: major). Consider chronic toxicity if conduction disorders (eg, bundle branch block, atrioventricular heart block) as well as biventricular hypertrophy are diagnosed. May also be associated with QT interval prolongation; ventricular arrhythmia and torsades de pointes have been reported (avoid concurrent use of other medications which may prolong the QT interval).”
Hydroxychloroquine Cardiomyopathy Risk

Which patient is at highest risk of developing cardiomyopathy on hydroxychloroquine?

A.) 55 yo African American male with RA on 400 mg/day HCQ for 2 years

B.) 60 yo African American woman with SScl on 400 mg/day HCQ for 5 years

C.) 45 yo Caucasian woman with SLE on 400 mg/day HCQ for 15 years

D.) 33 yo Caucasian male with malaria on 800 mg/day HCQ for malaria treatment
Hydroxychloroquine Cardiomyopathy

Hydroxychloroquine Cardiomyopathy

Table 1  Drugs with proportional reporting ratios greater than 10 calculated from MedWatch database

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Proportional reporting ratio (PRR)</th>
<th>( \chi^2 )</th>
<th>Potential cardiomyopathy mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin</td>
<td>77.4</td>
<td>24,712.2</td>
<td>Higher digoxin levels toxic to myocardium</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>54.8</td>
<td>792.8</td>
<td>Unknown</td>
</tr>
<tr>
<td>Alglucosidase alfa</td>
<td>45.7</td>
<td>1224.8</td>
<td>Unknown</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>36.7</td>
<td>2847.6</td>
<td>HER2 receptors in myocardium</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>28.2</td>
<td>262.4</td>
<td>Inhibition of lysosomal hydrolases (7)</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>27.3</td>
<td>1088.9</td>
<td>Anthracycline oxidative stress in myocytes (7)</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>23.2</td>
<td>7635.1</td>
<td>PPAR-( \gamma )-deficiency in myocytes</td>
</tr>
<tr>
<td>Propofol</td>
<td>22.8</td>
<td>2802.6</td>
<td>Unknown</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>16.9</td>
<td>806.9</td>
<td>Unknown</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>15.6</td>
<td>309.4</td>
<td>Tyrosine kinase inhibitor myocyte toxicity (7)</td>
</tr>
<tr>
<td>Clozapine</td>
<td>15.6</td>
<td>388.9</td>
<td>Direct myocyte toxicity, unknown mechanism</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>14.3</td>
<td>156.9</td>
<td>Antimetabolite</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>12.6</td>
<td>148.9</td>
<td>Coronary ischemia and vasospasm</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>12.2</td>
<td>619.8</td>
<td>Ubiquitin-proteasome inhibition</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>12.2</td>
<td>227.5</td>
<td>Unknown</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>11.8</td>
<td>259</td>
<td>Antimetabolite (alkylating agent) myocyte death</td>
</tr>
<tr>
<td>Betaseron</td>
<td>11.2</td>
<td>427.9</td>
<td>Myocarditis by immune overstimulation</td>
</tr>
<tr>
<td>Rituximab</td>
<td>10.2</td>
<td>391.7</td>
<td>Cytokine release cardiomyopathy</td>
</tr>
<tr>
<td>Imatinib</td>
<td>10</td>
<td>391.6</td>
<td>Tyrosine kinase inhibitor myocyte toxicity (7)</td>
</tr>
</tbody>
</table>

Hydroxychloroquine Cardiomyopathy

- 42 cases confirmed via histopathology
- Mean age = 56 years (31 to 81 yrs)
- 83% women
- SLE, SScl, RA, malaria
- Mean duration tx = 13 yrs (2-35 yrs)
- Mean cumulative dose CQ = 1277 g
- Mean cumulative dose HCQ = 1843 g

Hydroxychloroquine Cardiomyopathy

Hydroxychloroquine Cardiomyopathy

• What should we do?
  – MI vs toxicity
  – ?ECG annually after three years?
    • MRI and biopsy
  – Drug holidays?
Hydroxychloroquine Neuromyotoxicity

Hydoxychloroquine Cutaneous Toxicity

- “Rash”
- SJS/TEN
- AGEP

- Hair bleaching
- Dyschromia
Which dermatomyositis associated auto-antibody increases the risk of HCQ rash?

A. SAE-1/2
B. Jo-1
C. MDA5
D. Mi2
Hydroxychloroquine Hypoglycemia

- Irritability
- Confusion
- Dizziness, shakiness
- Sweating or cold, clammy skin
- Headache
- Tingling feeling
- Low glucose symptoms
- Hard, fast heartbeat
Hydroxychloroquine Outline

• Uses for the medication
• Brief review of absorption/metabolism/excretion
• Mechanism of action
• Contraindications
• Pregnancy risks
• Adverse effects
• Formulations
• Dosing
• Medication interactions
• Monitoring guidelines
• Key points slide
• Review clinically relevant questions
Hydroxychloroquine Outline

- Uses for the medication
- Brief review of absorption/metabolism/excretion
- Mechanism of action
- Contraindications
- Pregnancy risks
- Adverse effects
- Formulations
- Dosing
- Medication interactions
- Monitoring guidelines
- Key points slide
- Review clinically relevant questions

Hydroxychloroquine Outline

- Uses for the medication
- Brief review of absorption/metabolism/excretion
- Mechanism of action
- Contraindications
- Pregnancy risks
- Adverse effects
- Formulations
- Dosing
- Medication interactions
- Monitoring guidelines
- Key points slide
- Review clinically relevant questions
Hydroxychloroquine Interactions

• Other antimalarials
• Dapsone: Hemolytic anemia
  – *Risk D*: Consider therapy modification

• Risk C: rate control, QT prolongation, hypoglycemics
Hydroxychloroquine Outline

- Uses for the medication
- Brief review of absorption/metabolism/excretion
- Mechanism of action
- Contraindications
- Pregnancy risks
- Adverse effects
- Formulations
- Dosing
- Medication interactions
- Monitoring guidelines
- Key points slide
- Review clinically relevant questions
Hydroxychloroquine Outline

- Uses for the medication
- Brief review of absorption/metabolism/excretion
- Mechanism of action
- Contraindications
- Pregnancy risks
- Adverse effects
- Formulations
- Dosing
- Medication interactions
- Monitoring guidelines
- Key points slide
- Review clinically relevant questions

- Dose < 5 mg/kg/day REAL weight
  - Max 400 mg/day
- Retinopathy
- Neuromyopathy
- Cardiomyopathy
- Consider drug holiday
- Cessation in those without benefit
Hydroxychloroquine Clinical Questions

• What dose do I prescribe?
• Does it really cause cardiomyopathy?