Hydroxychloroquine and Chloroquine

Chloroquine has been used for years as an antimalarial. However, with increasing Plasmodium resistance, it has fallen out of favor for chloroquine derivatives and artimeter compounds. Hydroxychloroquine is used mostly for inflammatory and rheumatologic conditions including lupus, rheumatoid arthritis, and dermatomyositis. It can be life changing for lupus. Maximal daily dose is around 400-800 mg.

I. Clinical Presentation:

A. CNS: Sedation, coma, seizures, myopathy. Psychosis and hallucinations may occur in pediatric patients. Tinnitus and hearing loss as these medications are derived from cinchona tree bark and cause cinchonism (which looks a lot like aspirin).
Less common and associate more with therapeutic chloroquine use: dystonia, extrapyramidal symptoms, and myasthenia gravis like syndrome
B. Optic: causes retinal artery spasm and visual changes ("boxcars on a train") even in therapeutic dosing
C. Resp: Respiratory depression, apnea
D. CV: Hypotension, bradycardia, ventricular tachycardia, ventricular fibrillation, torsades de pointes, wide QRS
E. Electrolytes: Hypokalemia, **hypoglycemia**
F. GI: Nausea, vomiting, diarrhea
G. Heme: Hemolytic anemia, particularly in patients with G6PD deficiency, methemoglobinemia

II. Drug Interactions:

A. Chloroquine and Hydroxychloroquine are substrates of CYP 2C8 and 3A4, medications that inhibit these enzymes may cause or worsen toxicity. This includes antidepressants, antipsychotics, antiarrhythmics, buprenorphine, HIV medications, oral hypoglycemics, and some antibiotics. Please run a drug interaction program if the patient is taking other medications.
B. **Will cause hemolysis in G6PD deficient patients**

III. Treatment:

A. Gastric Decontamination
1. Activated charcoal is most effective within 1 hour of ingestion. The magnitude of its benefit has not been established. It should be reserved for patients with potential for serious toxicity. Avoid giving to a patient who cannot protect their airway. COMPLICATIONS: Pulmonary aspiration, GI obstruction.
1) Adult: 50-100 grams in 240 mL fluid PO/NG/OG
2) Pediatric: 1 gram/kg (50 gm max) in 240 mL fluid PO/NG/OG

B. High Dose Diazepam-preferred as there is some suggestion that there may receptors in the myocardium. Maximal dose predicated on toxicity to the drug and carrier liquid (propylene glycol).
1. Indications: Seizures, hypotension, cardiogenic shock, ventricular dysrhythmias, QRS and QT prolongation, consider for ingestion of >5 grams in adults or 30 mg/kg in pediatric patients.
a. Loading dose: **2 mg/kg** over 30 minutes (anticipate respiratory and cardiovascular support to maintain a SBP > 90 mmgHg. Epinephrine is the inopressor of choice)
b. Maintenance dose for ongoing cardiotoxicity 1-2 mg/kg/day

C. Seizures refractory to diazepam

1. Lorazepam-maximal dose predicated on toxicity to the drug. The need for intubation is not a contraindication to its use
   a. Adult: 1-4 mg IV
   b. Pediatric 0.05-0.1 mg/kg (4 mg max per dose) IV
2. Phenobarbital (anticipate respiratory support)
   a. Adult and Pediatric: 10-20 mg/kg IV
3. Propofol (anticipate respiratory support)
   a. Adult and Pediatric: load 1-2 mg/kg, then 20 mcg/kg/min and titrate to effect

D. QRS prolongation (QRS>120 msec) OR Ventricular tachycardia
   1. Sodium Bicarbonate
      a. 1-4 mEq/kg IV (max 200 mEq per dose).
      b. 150 mEq in 1 liter D_5W with 20 mEq/L KCl, titrate to pH 7.45-7.55
      c. Monitor potassium, sodium, and pH
      d. Anticipate worsening of hypokalemia and supplement with KCl oral/IV immediately

E. QT prolongation (QTc > 500 msec) OR torsades de pointes
   1. If serum potassium < 3.5 mmol/L, correct to 3.5-4.0 mmol/L, proceed cautiously due to potential rebound hyperkalemia as toxicity resolves
   2. Magnesium sulfate 2-4 gm IVPB over 30 minutes
   3. For torsades refractory to magnesium therapy would recommend overdrive pacing or pharmacologic pacing with isoproteronol

F. Hypotension
   1. IV fluid bolus: 1-2 L of crystalloid (10-20 mL/kg for pediatric patients)
   2. Vasopressors
      a. **Epinephrine** (historically first line for chloroquine and hydroxychloroquine toxicity)
         1) Adult and Pediatric: Start at 0.1-1 mcg/kg/min and titrate to maintain BP and perfusion
         2) Anticipate worsening of hypokalemia
      b. Norepinephrine
         1) Adult: Start at 8-12 mcg/min and titrate to maintain BP and perfusion
         2) Pediatric: Start at 0.05-0.1 mcg/kg/min and titrate to maintain BP and perfusion

G. Refractory ventricular arrhythmia, cardiogenic shock, cardiac arrest
   1. ECMO (limited evidence, with a few cases of successful use in both chloroquine and hydroxychloroquine)
   2. 20% Lipid Emulsion (limited evidence of effect)
      a. 1.5 mL/kg over 2-3 minutes, may repeat X 1 if no effect, then can titrate dose between 0.025-0.25 mL/kg/min based on clinical response.
      b. Hemodynamic parameters should be monitored at least Q 15 minutes
      c. **Maximum total dose of 10 mL/kg**
      d. **Lipid Emulsion should be discontinued after 1 hour or less**

H. Hypokalemia
   1. Potassium supplementation oral or IV. Watch K levels as it may rebound as toxicity resolves

I. Dystonic Reaction
   1. Diphenhydramine (preferred agent in children)-use with caution as this is a sodium channel blocker. If patient develops QRS >110 msec, do not use

a. Adult Dose: 25-50 mg IV
b. Pediatric Dose: 1.25 mg/kg/IV (max 50 mg)

2. Benztropine
   a. Adult Dose: 1-4 mg IV
   b. Pediatric Dose (> 3y): 0.02-0.05 mg/kg IV (max 2mg)
3. Lorazepam, If anticholinergic or not responding/contraindicated to use of diphenhydramine or benztropine
   a. Adult: 1-4 mg IV
   b. Pediatric 0.05-0.1 mg/kg (4 mg max per dose) IV

J. Myasthenia Gravis Like Syndrome
   1. If suspected, consult neurology to discuss treatment and the use of acetylcholinesterase inhibitors

IV. Laboratory studies:

A. Basic metabolic panel and 12-lead EKG
B. Trend serum glucose and hypokalemia every 1-6 hours depending on clinical status
C. CBC for hemolysis
   1. Peripheral smear, haptoglobin, recticulocyte count if hemolysis is suspected
D. Methemoglobin level if unexplained hypoxia
E. CPK recommended if patient has seizures
F. Chloroquine and hydroxychloroquine levels are not clinically useful
G. Urine Pregnancy test in females of child-bearing age
H. For patients with self-harm intent
   1. Aspirin level
   2. Acetaminophen level at least 4 hours post ingestion

Adapted from and with appreciation to the Indiana Poison Center who shared their guideline with the rest of the AAPCC community