Hydroxychloroquine and Hallucinosis: a Case Report

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Background

- **Hydroxychloroquine (HCQ):** Synthetic anti-malarial used widely in rheumatic diseases, generally well-tolerated
- Common side effects include rash, GI upset, headache, dizziness; rarely psychosis, convulsions, heart arrhythmias
- Metabolized by liver with elimination half-life of 40 days due to wide tissue distribution, but concentration in neural tissue can reach 10-20x plasma levels[1]
- Pathophysiology for neuropsychiatric side effects unknown, but proposed mechanisms include:
  1. Cholinergic imbalance resulting from acetylcholinesterase inhibition by chloroquine[2]
  2. HCQ is lysosomotropic, and accumulates within lysosomes leading to dysfunction from build up of toxic metabolites[3]
  3. Inhibition of P-glycoprotein at the blood brain barrier[4]
- Risk Factors: female sex, co-administration of CYP3A4 inhibitors, co-administration of low-dose GCCs, alcohol intake, low body weight, administration of dose exceeding maximum therapeutic dose[4]
- Can address with risperidone or other atypical antipsychotics

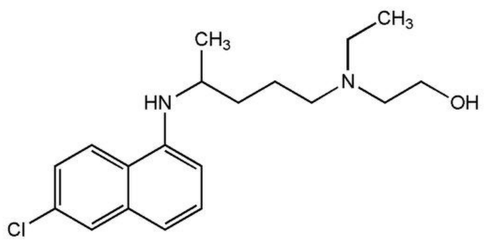


Figure 1. Chemical structure of hydroxychloroquine, a 4-aminoquinoline medication with wide uses in rheumatology, and as an anti-malarial[5]

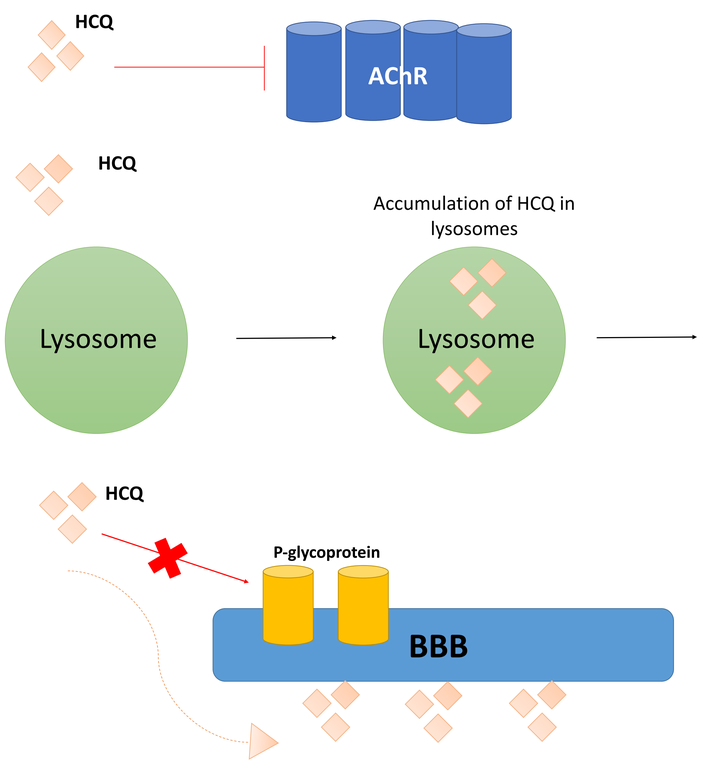
Methods

- Case report; patient's case was reviewed using electronic medical record, Cerner
- Brief review of literature conducted using Rutgers University electronic library resources and PubMed online database

Case Report

A 55-year-old woman with past medical history of dermatomyositis and recent history of domestic abuse presented to the ED with a four-week history of altered mental status, visual hallucinations, and acute behavioral changes including inability to maintain activities of daily life, aggression, and banging her head against walls. In the ED, the patient was pleasant but incoherent, and could not corroborate the events leading to her admission. Urine drug screen and urinalysis were within normal limits. Given the acute change in mental status, CMP, CBC, RPR, B12, Folate, thyroid panel, CXR and CT head were all performed, but were unremarkable. ESR was 76, and CRP was 4.44. On physical exam, she was visibly dysphoric with circumstantial thought process, but without objective evidence of hallucinations. A Montreal Cognitive Assessment (MoCA) was performed with a resulting score of 8. Home dose of medications was confirmed as methotrexate 2.5mg PO weekly, prednisone 20mg PO BID, hydroxychloroquine 200mg PO daily. Given relative normality of labs, suspicion for hydroxychloroquine-associated psychosis arose. Hydroxychloroquine was discontinued and risperidone 0.5mg PO BID was started with improvement in mental status.

Hypothesized Pathophysiology



1. HCQ, like chloroquine, may block acetylcholine receptors
2. This can lead to anticholinergic effects causing altered mental status

1. Increased lysosome pH
2. Disruption of lysosomal enzymes
3. Accumulation of toxic metabolites

1. P-glycoprotein = efflux pump
2. HCQ inhibits p-glycoprotein at BBB → increased concentration HCQ in neural tissue

Figure 2. The three main proposed mechanisms for the neuropsychiatric effects of HCQ. From top to bottom: blockage of acetylcholine receptor leading to cholinergic imbalance, accumulation of toxic metabolites in lysosomes, endosomes, and Golgi apparatus, and interaction with p-glycoprotein, an efflux pump, at the blood-brain barrier, which may exacerbate already elevated neural tissue concentration of HCQ.

Discussion

- Antimalarials as a class have been known to cause toxic psychosis
- Few cases reported of HCQ-associated psychosis, and pathophysiology still unclear
- Spectrum of psychotic symptoms includes delirium, delusions, auditory/visual hallucinations, depersonalization, ideas of reference
- Adverse effects may be delayed from initiation of HCQ due to long half-life, large volume of distribution, increased concentration in neural tissue
- Family history/presence of previous psychiatric illness may increase risk, especially in patient w/ history of trauma, abuse
- Other risk factors: co-administration of steroids, though patient's prednisone dose was consistently low
- Psychotic symptoms may self-resolve after withdrawal of drug, usually ~1 week
- Low doses of antipsychotic can be used for symptom mitigation
- Future studies directed at elucidating mechanism of neuropsychiatric side effects

Conclusion

- Evaluation of new-onset psychosis should include thorough review of current medications as well as labs and imaging to rule out organic causes
- Even patients dosed within normal therapeutic range of HCQ are at risk for neuropsychiatric side effects
- Withdraw of HCQ and initiation of antipsychotic effective in treatment

Literature Cited

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