When COVID-19 prophylaxis leads to hydroxychloroquine poisoning

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Abstract

Hydroxychloroquine overdose was a relatively uncommon event prior to the COVID-19 pandemic. However, due to the massive increase in prescriptions, coupled with the search for possibly effective treatment of COVID-19 infection, these overdoses have become more frequent. The management of severe hydroxychloroquine overdose does not have any well-established protocols. This report highlights the clinical course and successful management of a life-threatening hydroxychloroquine overdose. An 80-year-old man was admitted to the ICU in shock after a potentially lethal ingestion of hydroxychloroquine for COVID-19 prophylaxis in a COVID-19 negative patient. Treatments included sodium bicarbonate infusion, high dose diazepam, norepinephrine and epinephrine, and continuous electrolyte repletion. After 5 days in the intensive care unit, the patient recovered and was discharged home. In conclusion, hydroxychloroquine overdose can result in life-threatening rapid decompensation requiring gastric decontamination, alkalization, high dose diazepam, hemodynamic support, and frequent electrolyte replacement.

Keywords: Hydroxychloroquine, overdose, management

Introduction

Hydroxychloroquine has become a highly controversial topic given the rise of SARS-CoV-2 virus (COVID-19) and the resulting global pandemic. This result is due to a strong urge by the general public to find any potential treatment, often without adequate concern for possible harms. At the center of this early debate was the use of the medication hydroxychloroquine. This drug is commonly used as an antimalarial medication that functions by interfering with vacuole digestive functions in malarial parasites. It also inhibits the locomotion of neutrophils and chemotaxis of eosinophils.[1] For this reason, it is FDA approved for prevention and treatment of malaria and the treatment autoimmune conditions, such as systemic lupus erythematosus and rheumatoid arthritis.

Early in the pandemic, hydroxychloroquine was given emergency use authorization for the treatment COVID-19; however, this was rescinded when subsequent studies failed to demonstrate a reduction in morbidity or mortality and found a threefold increase in adverse events compared to placebo.[3] Despite this, hydroxychloroquine remained a highly requested medication by patients. New prescriptions rates for hydroxychloroquine during the COVID-19 pandemic soared from 1,143 prescriptions in March 2019 to 75,569 in March 2020, an 80-fold increase compared to pre-pandemic levels.[3]

Hydroxychloroquine has been associated with numerous significant adverse effects, such as cardiomyopathy, cardiac conduction abnormalities, severe hypoglycemia, retinopathy, hemolysis in G6PD patients, and multiple drug-drug interactions.[2] As the case below demonstrates, current circumstances with high

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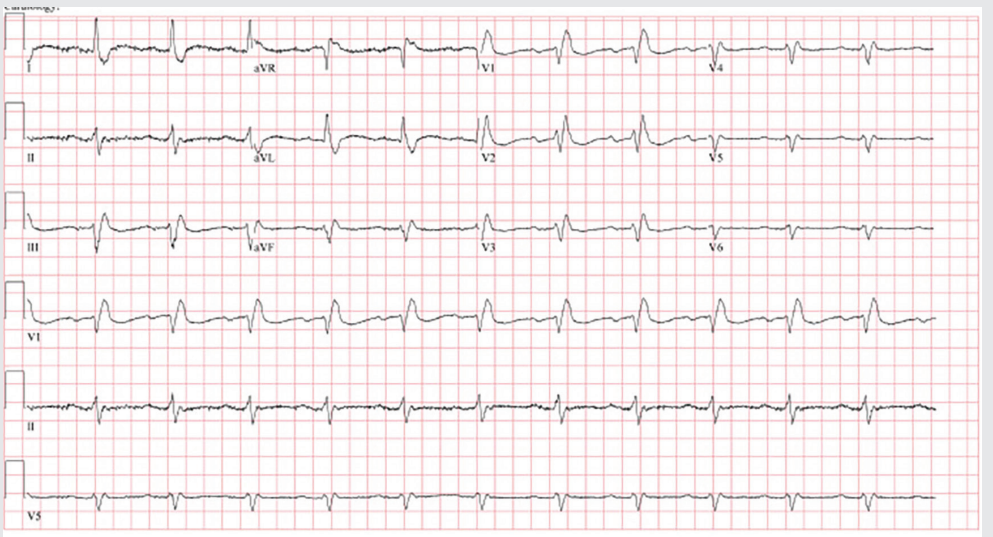

Figure 1. ECG upon Arrival to Emergency Department.
Note: Sinus rhythm with 1°AV Block and right bundle branch block. Ventricular rate 71 beats per minute, PRI 256 msec, QRS 210 msec, QTc 534 msec.

levels of hydroxychloroquine prescription and misunderstanding of its efficacy increases the possibility of dangerous and potentially fatal overdoses.

Case

An 80-year-old man with a past medical history of hypertension and hyperlipidemia presented to the Emergency Department with a chief complaint of dizziness after ingestion of 6 grams of hydroxychloroquine. The patient stated that he was prescribed the hydroxychloroquine as prophylaxis against COVID-19, and after exposure to a coworker with symptomatic COVID-19, the patient took the full bottle for prophylaxis. He presented to the Emergency Department approximately one hour after ingestion. On initial evaluation, the patient was noted to have cardiovascular instability with hypotension and reported feeling lightheaded. The electrocardiogram (ECG) obtained at that time showed a sinus rhythm with 1° AV block, RBBB, prolonged QRS (210 ms) and prolonged QTc (534 ms) (Figure 1).

Poison Control was contacted and recommended multi-dose activated charcoal every 2 hours for 3 doses, sodium bicarbonate infusion with a goal of a serum pH of 7.5, high dose intravenous diazepam, normal saline infusion, and norepinephrine for hypotension. Central access was obtained, a norepinephrine infusion was initiated, and epinephrine was quickly added given a worsening shock state. Patency of the airway was maintained, requiring only supplemental oxygen through the nasal cannula. Patient received 15 mg of IV diazepam (200 mcg/kg) and was transferred to the intensive care unit in critical condition.

The hospital course was complicated by a small bowel obstruction and persistent severe electrolyte abnormalities. Hypokalemia in the 1.0–2.0 range required continuous PO and IV potassium replacement, more than 130 mEq daily. In addition, profound hypomagnesemia and hypocalcemia with arrhythmias occurred throughout hospital stay requiring comprehensive metabolic panels every 4-6 hours and continuous replacement of both magnesium and calcium. In addition, the patient developed hyperglycemia with values above 400 mg/dL shortly after admission and required continuous insulin infusion for 2 days.

On hospital day 2, he was titrated off vasopressor support. The patient became hypervolemic secondary to continuous bicarbonate infusion and developed oliguric acute renal failure requiring diuresis to optimize respiratory function. The small bowel obstruction gradually resolved with electrolyte replacement, bowel rest, and gastric decompression.

On hospital day 5, the patient's potassium level stabilized; he had gradual resolution of oliguric acute renal failure and did not require dialysis. The patient's QRS and QTc returned to baseline (Figure 2). Sodium

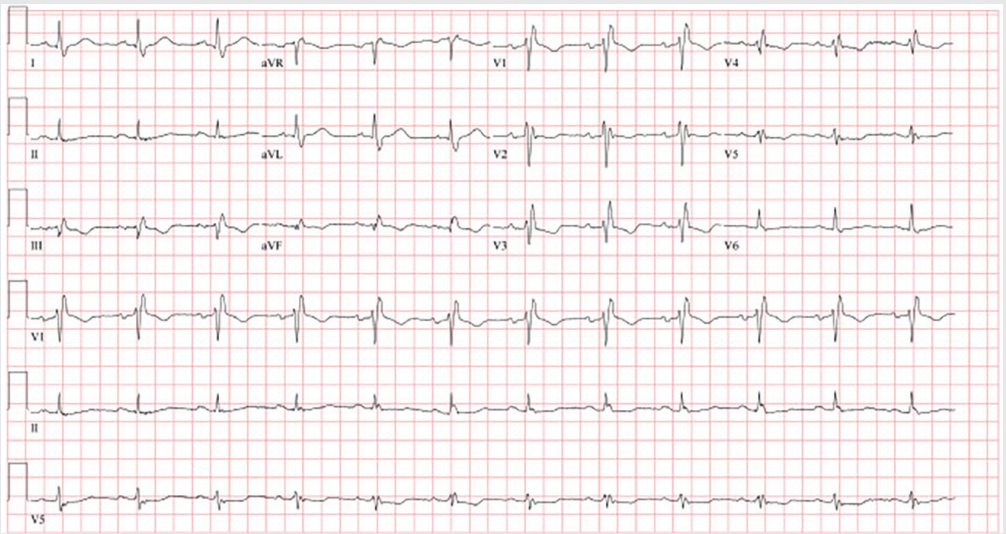

Figure 2. ECG on Day of Discharge.
Note: Normal Sinus Rhythm with Right bundle branch block. Ventricular rate 72 beats per minute, PRI 180 msec, QRS 134 msec, QTc 457 msec. Interval resolution of 1° AV block, prolonged QTc and reduction in QRS interval to pre-ingestion baseline.

bicarbonate infusion was then stopped, and the patient was transferred out of the ICU. He was discharged on hospital day 6 and continued to be in good health at scheduled follow-up. The patient tested negative for COVID-19 at time of admission and did not develop symptoms of infection throughout admission. A summary of the patient's daily electrolyte values throughout hospitalization are displayed in Table 1.

Discussion

While there is no well-established lethal dose of hydroxychloroquine, animal trials and case studies have suggested that toxic doses can occur in the 20 mg/kg range with lethal doses potentially as low as 30 mg/kg.[4] Our patient ingested approximately 85 mg/kg, placing him well within the range of a potentially lethal ingestion. Symptoms after overdose tend to begin early, generally within the first three hours after ingestion.[4] The drug undergoes extensive metabolism into multiple active metabolites and has a long half-life in acute ingestions in the range of 170 hours.[4] Mild toxicity is primarily associated with gastrointestinal symptoms, such as nausea, vomiting, diarrhea, and weakness. Severe life-threatening toxicity is generally marked by altered mental status, cardiac dysrhythmias secondary to myocardial irritability, QRS/QTc prolongation secondary to sodium channel blockage, and life-threatening electrolyte abnormalities, such as hypokalemia and hypoglycemia.[5,6] However, our

Table 1. Electrolytes During Hospital Course

Hospital Day	Sodium (mmol/L)	Potassium (mmol/L)	Chloride (mmol/L)	Carbon Dioxide (mmol/L)	Magnesium (mmol/L)	Phosphorous (md/dL)	Calcium Total (mg/dL)
Arrival	134	4.1	102	24	2.0	4.0	9.0
Day 1	143–147	2.5–1.4	108–104	30–20	2.6–1.7	4.0	8.8
Day 2	142–134	3.9–1.9	101–96	32–25	2.3–1.9	*	7.5–6.8
Day 3	147–137	4.5–2.5	104–94	34–30	2.3–1.7	*	7.9–6.8
Day 4	137–134	3.5–3.0	96–93	37–34	2.0–1.7	*	7.9
Day 5	138–135	4.0–3.4	98–95	36–32	1.7–1.6	*	9.1
Discharge	135	4.4	98	27	1.9	*	8.5

* not measured

patient developed hyperglycemia requiring an insulin infusion for several days. This is a previously unreported complication in hydroxychloroquine toxicity and differs from the known toxidrome.

Given early gastrointestinal symptoms and the potential for a significantly altered mental status, early definite airway management should be considered if presenting with these symptoms. An ECG should be obtained early to evaluate for QRS widening and QTc prolongation, which should be managed with sodium bicarbonate and magnesium sulfate, respectively. Standard supportive care, including frequent electrolyte monitoring and replacement, is critical. Profound hypocalcemia and hypomagnesemia were a cornerstone of treatment plan this patient. While mild hypokalemia is an expected result of bicarbonate infusion, these electrolyte abnormalities are infrequently mentioned in the management of hydroxychloroquine overdose.[7] An emphasis should be placed on obtaining frequent electrolyte panels that include magnesium and calcium to ensure that these potentially life-threatening abnormalities do not go unrecognized. In addition, hemodynamic instability frequently occurs and should be managed with intravenous fluids with a low threshold to start vasopressors.[8]

An additional therapy that has been used is high dose intravenous diazepam (2 mg/kg).[9] Our patient received 15 mg (200 mcg/kg) with close monitoring without requiring intubation or respiratory support. This is a unique therapy that can be considered in patients with severe, life-threatening ingestions, typically, large doses more than 30mg/kg in patients presenting with dysrhythmias, hypotension and respiratory failure. Diazepam may reduce myocardial irritability in massive overdoses and has shown a survival benefit in these cases. Additional therapies for refractory cases, such as ECMO and intravenous lipid emulsion therapy, have been proposed; however, limited evidence to support their use and has not shown improved outcomes.[10] Hypertonic saline has also been proposed and used in a small number of case studies in place of sodium bicarbonate to avoid increasing hypokalemia and dysrhythmias.[10] More published research on the treatment of this toxidrome is critical to improve the clinician's understanding and management of cases with severe toxicity.

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References

1. Tett SE. Clinical pharmacokinetics of slow-acting antirheumatic drugs. Clin Pharmacokinet. 1993 Nov;25(5):392–407. doi: 10.2165/00003088-199325050-00005.
2. FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems. FDA Drug Safety. US Food and Drug Administration.
3. Singh B, Ryan H, Kredo T, et al. Chloroquine or hydroxychloroquine for prevention and treatment of COVID-19. Cochrane Database of Systemic Reviews 2021, Issue 2. Art. No.: CD013587. DOI: 10.1002/14651858.CD0135787.pub2. Accessed 18 April 2022.
4. Rainsford KD, Parke AL, Clifford-Rashotte M, et al. Therapy and pharmacological properties of hydroxychloroquine and chloroquine in treatment of systemic lupus erythematosus, rheumatoid arthritis and related diseases. Inflammopharmacology. 2015;23(5):231–69.
5. Barry JD. Antimalarials. In: Nelson LS, Howland MA, Lewin NA, et al. Goldfrank's Toxicologic Emergencies. 11th ed. New York, NY: McGraw-Hill Education, 2019:836–49.
6. Marquardt K, Albertson TE. Treatment of hydroxychloroquine overdose. Am J Emerg Med 2001 Sep;19(5):420–4.

7. Ndukwu I, Ghahramani M. Hydroxychloroquine overdose presenting as acquired qt interval prolongation and torsade de pointes. J Am Coll Cardiol. 2017 Mar, 69 (11_Supplement) 2340.
8. McBeth PB, Missirlis PI, Brar H, et al. Novel therapies for myocardial irritability following extreme hydroxychloroquine toxicity. Case Rep Emerg Med. 2015;2015:692948. doi: 10.1155/2015/692948.
9. Lee HM, Archer JR, Dargan PI, et al. What are the adverse effects associated with the combined use of intravenous lipid emulsion and extracorporeal membrane oxygenation in the poisoned patient? Clin Toxicol (Phila). 2015;53(3): 145–50.
10. Mahan KM, Hayes BD, North CM, et al. Utility of hypertonic saline and diazepam in COVID-19-related hydroxychloroquine toxicity. J Emerg Med. 2021 Mar;60(3):359–64.