



# Intentional Hydroxychloroquine Overdose Treated with High-Dose Diazepam: an Increasing Concern in the COVID-19 Pandemic

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## Abstract

**Introduction** Recent attention on the possible use of hydroxychloroquine and chloroquine to treat COVID-19 disease has potentially triggered a number of overdoses from hydroxychloroquine. Toxicity from hydroxychloroquine manifests with cardiac conduction abnormalities, seizure activity, and muscle weakness. Recognizing this toxidrome and unique management of this toxicity is important in the COVID-19 pandemic.

**Case Report** A 27-year-old man with a history of rheumatoid arthritis presented to the emergency department 7 hours after an intentional overdose of hydroxychloroquine. Initial presentation demonstrated proximal muscle weakness. The patient was found to have a QRS complex of 134 ms and QTc of 710 ms. He was treated with early orotracheal intubation and intravenous diazepam boluses. Due to difficulties formulating continuous diazepam infusions, we opted to utilize an intermitted intravenous bolus strategy that achieved similar effects that a continuous infusion would. The patient recovered without residual side effects.

**Discussion** Hydroxychloroquine toxicity is rare but projected to increase in frequency given its selection as a potential modality to treat COVID-19 disease. It is important for clinicians to recognize the unique effects of hydroxychloroquine poisoning and initiate appropriate emergency maneuvers to improve the outcomes in these patients.

**Keywords** COVID-19 · hydroxychloroquine · Chloroquine · Drug-Related Side Effects · Adverse Reactions

## Introduction

Hydroxychloroquine and chloroquine are widely used in the treatment of malaria as well as chronic inflammatory conditions such as rheumatoid arthritis and systemic lupus erythematosus (SLE). At the time of this case, human trials found some efficacy and improved survival in individuals with COVID-19

disease treated with chloroquine, although hydroxychloroquine is preferred given its lower side effect profile [1–3]. These recent investigations had several limitations, including a small sample size, limited long-term outcome follow-up, and dropout of a substantial proportion of study participants, including death [4, 5]. While the use of hydroxychloroquine to treat COVID-19 remains debated, recent attention in the USA on the possible

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use of hydroxychloroquine and chloroquine to treat COVID-19 also sparked concern among medical professionals about decreased availability of hydroxychloroquine for individuals with chronic inflammatory conditions and the potential for unintentional toxicity or overdose of hydroxychloroquine [6, 7]. Here, we describe the case of an intentional overdose of hydroxychloroquine requiring a high-dose diazepam regimen and describe the implications of managing this overdose for clinicians.

## Case Report

A 27-year-old man with a history of rheumatoid arthritis and untreated depression presented to a community emergency department (ED) with nausea and nonbloody emesis. He reported an intentional overdose of approximately 20 hydroxychloroquine 200 mg tablets, 30 methotrexate 2.5 mg tablets, and 30 prednisone 10 mg tablets, approximately 8 hours prior to presentation. He divulged his attempt to family who brought him to the ED. On arrival, his vital signs were a heart rate of 63 beats per minute, blood pressure of 95/55 mmHg, respiratory rate of 23 breaths per minute, and an oxygen saturation of 99% on room air. His weight was approximately 80 kg. On exam, his pupils were 3 mm bilaterally without nystagmus. He had a normal skin exam without diaphoresis. His heart sounds were normal and regular, and his lungs were clear to auscultation. The abdomen was nontender with normal active bowel sounds, no masses, and no hepatosplenomegaly. No clonus, tremor, or hyperreflexia were noted. His neurologic examination demonstrated diffuse weakness of all four extremities. The patient was somnolent but arousable to voice. When interviewed, he divulged his suicide attempt. Initial electrocardiogram (ECG) demonstrated a widened QRS complex of 134 ms and a QTc interval of 710 ms. There were no prior ECGs for comparison. In the ED, he was noted to have several episodes of non-sustained ventricular tachycardia. He developed progressive somnolence, and due to this, his QTc prolongation and subsequent episodes of non-sustained ventricular tachycardia, he was electively orotracheal intubated using etomidate 20 mg and succinylcholine 120 mg. Laboratory analysis demonstrated undetectable concentrations of acetaminophen and salicylates, and a methotrexate concentration of 0.35  $\mu\text{mol/L}$  (ref 0–1  $\mu\text{mol/L}$ ). Aside from hypokalemia (potassium 2.0  $\text{mmol/L}$ ), the remainder of his electrolytes were within normal range (Table 1), hepatic and renal function were normal, and an initial complete blood count showed no signs of pancytopenia.

Given the widened QRS, prolonged QTc, and concomitant hypokalemia, the diagnosis of hydroxychloroquine poisoning was made. Due to his initial findings of cardiac conduction abnormalities, the decision was made to transfer him to a tertiary care center with the availability of advanced cardiology subspecialty support. Intravenous (IV) potassium replacement was

started at 10 mEq/h. The patient also received a bolus of 100 mEq of sodium bicarbonate 8.4%, after which his QRS improved to a 128 ms, with QTc of 639 ms calculated using the Bazett's formula. Given his improvement in his cardiac conduction, the decision was made to maintain him on a sodium bicarbonate infusion for ground ambulance transport from the community hospital to our tertiary center (150 mEq/L in dextrose 5% water) at 150 mL/h. On arrival to the tertiary care center, an IV diazepam bolus of 1 mg/kg was administered over 30 minutes, approximately 4 hours into his hospital course. Intermittent, diazepam boluses were initiated at 6.5 mg every 2 hours, with a goal to decrease and maintain his QRS under 100 ms. Epinephrine was initially started at 0.25 mcg/kg/min; however, it was subsequently discontinued per hospital protocol as the patient was able to maintain adequate systolic arterial pressure ( $\geq 100$  mm Hg) without additional hemodynamic support and in order to avoid unnecessary beta-1 agonism since the burden of non-sustained ventricular tachycardia had greatly decreased after initiation of diazepam [8]. The patient was admitted to the intensive care unit (ICU) for continued management.

In the ICU, the patient was initiated on continuous propofol and fentanyl infusions for sedation and analgesia. Hypokalemia was treated with 120 mEq of potassium chloride via orogastric tube and 40 meq of IV potassium chloride. Nineteen hours after initiation of diazepam treatment, the QRS narrowed to 94 ms, and QTc decreased to 487 ms. Diazepam was discontinued after a cumulative dose of 124 mg over 12 hours (5 mg IV once at the community hospital, 80 mg IV bolus, plus 39 mg IV from the intermittent boluses every 2 hours at our center), with ECG showing QRS narrowed to 88 ms and QTc decreased to 499 ms. Despite an initial complete blood count within normal range, subsequent blood draws showed a rapid decrease in hemoglobin and platelet count (Table 1), which raised concern for medication-induced hematologic toxicity. He was given 25 mg of leucovorin every 6 hours while monitoring his methotrexate concentrations, which decreased from 0.35 to 0.15  $\mu\text{mol/L}$ . Given low methotrexate concentration and stable markers of acute hemolytic processes (Table 1), leucovorin was discontinued.

On extubation, the patient confirmed his ingestion of hydroxychloroquine and methotrexate. He described nonadherence to both xenobiotics during the COVID-19 pandemic, despite receiving monthly refills of hydroxychloroquine and methotrexate by mail. The patient stockpiled these medications and decided to ingest them in whole on the day of presentation to the ED. Consent for publication of this case was obtained from this patient and provided to the journal in accordance with JMT policy.

## Discussion

Hydroxychloroquine and chloroquine poisoning results in hypokalemia and widened QRS interval leading to ventricular

**Table 1** Selected laboratory values of patient.

	Reference values	Time since ingestion (hours)									
		Hospital day 1					Hospital day 2				
		8 h*	12 h	16 h	20 h	24 h	28 h	32 h	36 h	42 h	
<b>Laboratory values</b>											
Sodium (mmol/L)	136–145	144	146	146	146	145	147	144	145	143	
Potassium (mmol/L)	3.4–5.1	2.0	2.2	2.5	3.6	5.9	4.7	5.6	6.0	4.6	
Chloride (mmol/L)	98–107	102	103	106	109	111	113	111	112	110	
Carbon dioxide (mmol/L)	22–31	22	27	27	24	23	22	22	22	22	
Anion gap	7–17	20	16	13	13	11	12	11	11	11	
BUN (mg/dL)	6–23	16	13	11	9	9	8	8	8	8	
Creatinine (mg/dL)	0.50–1.20	1.26	1.18	1.10	1.03	1.00	1.05	1.05	1.05	1.17	
Glucose (mg/dL)	70–100	168	139	153	109	97	87	113	112	113	
Phosphorus (mg/dL)	2.4–4.3	1.5	1.1	0.6	1.5	–	3.8	3.2	3.4	3.5	
AST (SGOT) (U/L)	10–50	29	22	22	24	24	23	24	23	21	
ALT (SGPT) (U/L)	15–41	36	30	34	35	32	28	26	25	22	
CK (U/L)	39–308	–	65	75	73	73	–	–	–	–	
Hs-TnT (ng/L)	0–14	–	<6	–	–	–	–	<6	–	–	
Lactic acid (mmol/L)	0.2–2.0	3.3	1.9	1.6	2.0	2.2	3.4	1.9	2.7	1.7	
Lipase (U/L)	13–60	–	17	–	–	–	–	–	–	–	
WBC (K/ $\mu$ L)	4.00–10.00	11.03	11.22	8.29	8.84	9.11	12.97	11.13	12.03	11.94	
Hgb (g/dL)	13.5–18.0	14.4	12.3	11.3	10.9	10.8	11.1	11.4	11.9	11.4	
PLT(K/ $\mu$ L)	150–450	166	139	132	129	127	144	145	155	135	
PT-INR	0.9–1.1	1.1	1.2	1.2	1.2	1.3	1.2	1.2	1.2	1.2	
Fibrinogen (mg/dL)	200–450	–	188	185	175	168	166	171	188	186	
VBG pH	7.30–7.40	7.43	7.42	7.58	–	–	–	–	–	–	
VBG pCO <sub>2</sub> (mmHg)	38–50	32	48	32	–	–	–	–	–	–	
VBG HCO <sub>3</sub> <sup>–</sup> (mmol/L)	–	21	–	–	–	–	–	–	–	–	
ABG pH	7.35–7.45	–	–	7.63	–	7.51	7.42	7.45	7.40	7.40	
ABG pCO <sub>2</sub> (mmHg)	36–47	–	–	25	–	28	35	32	39	41	
ABG pO <sub>2</sub> (mmHg)	65–95	–	–	178	–	177	137	163	120	118	
Methotrexate ( $\mu$ mol/dL)	0.00–1.00	–	0.35	0.15	0.10	–	–	–	–	–	
Acetaminophen ( $\mu$ g/mL)	10.00–20.00	< 5.0	–	–	–	–	–	–	–	–	
Ethanol (mg/dL)	0–10	< 10	–	–	–	–	–	–	–	–	
<b>EKG parameters</b>											
QRS (ms)	< 120	134	–	116	102	–	88	94	92	92	
QTc (ms)	< 430	710	–	663	559	–	499	487	464	474	
<b>Interventions</b>											
IV Diazepam (mg)	–	5	80	2	2	2	2	–	–	–	
IV Bicarbonate (mEq/h)	–	100	150	150	150	–	–	–	–	–	
Leucovorin (mg)	–	–	–	–	–	25	–	25	–	25	

ABG, arterial blood gas; ALT, alanine aminotransferase; AST, aspartate transaminase; BUN, blood urea nitrogen; CK, creatine kinase; Hgb, hemoglobin; hs-TnT, high-sensitivity troponin T; INR, international normalized ratio; IV, intravenous; PLT, platelets; PT, prothrombin time; QTc, corrected QT interval; VBG, venous blood gas; WBC, white blood cells; \*Ingestion occurred at 2 AM on the day of presentation to the emergency room. The patient presented to the emergency room at 10 AM, approximately 8 hours since ingestion

tachycardia, cardiac irritability from sodium and potassium channel blockade [8, 9]. Neurotoxicity including seizures and hypotension is also common. Hydroxychloroquine and

chloroquine poisoning are relatively rare in the USA; with increased media attention focused on its potential use to treat and prevent COVID-19 disease, however, we anticipate

increased prevalence of unintentional and intentional poisoning from these agents. Even though its use is now discouraged in most COVID-19-related clinical circumstances based on newer data, there may still be a large supply in homes due to its popularity early on in the pandemic. Healthcare providers should recognize the clinical features of hydroxychloroquine poisoning and understand the medical interventions that improve outcomes in these potentially unstable patients.

Hydroxychloroquine is an orally administered 4-aminoquinone, which was first synthesized by introducing a hydroxyl group to chloroquine and was demonstrated to be about 40% less toxic than chloroquine in animal models [10]. Given its lower toxicity and more readily availability, hydroxychloroquine is preferred in the treatment of malaria and rheumatoid arthritis. Nonetheless, the two drugs have similar structural, therapeutic, pharmacokinetic, and toxicological properties. Therefore, prolonged hydroxychloroquine use or overdose may have potentially fatal depressant effects on the myocardium, similar to those caused by chloroquine [11]. As a result, the two drugs have nearly identical clinical features of poisoning, and recommended management is the same for both drugs [12]. Following oral administration, absorption is rapid and near-complete; rapid distribution in the body lead to cardiac and neurotoxicity effects that develop as rapidly as 30 minutes after ingestion. It has a large volume of distribution (5522 L), is metabolized in the liver, and renally excreted [13].

Hydroxychloroquine increases lysosomal pH in antigen-presenting cells and decreases toll-like receptor signaling, features that make it an attractive drug for chronic inflammatory conditions like rheumatoid arthritis. Hydroxychloroquine inhibits glycosylation of angiotensin-converting enzyme-2 (ACE2), a cell surface receptor thought to facilitate entry of SARS-nCoV-2 into cells [1, 3]. Recently, the ability of hydroxychloroquine to downregulate this inflammatory pathway was postulated to improve survival in individuals with acute respiratory distress syndrome (ARDS) caused by the novel coronavirus SARS-nCoV-2 [3]. Hydroxychloroquine exerts its toxicity through blockade of cardiac and cerebral sodium channels. This competitive blockade is potent, resulting in depolarization delays in cardiac myocytes and manifesting as a widened QRS complex over 100 ms on ECG. In large doses, hydroxychloroquine also binds cerebral sodium channels, resulting in epileptiform seizures, and in skeletal muscle, resulting in weakness. Death occurs in the setting of ventricular dysrhythmias and intractable seizures.

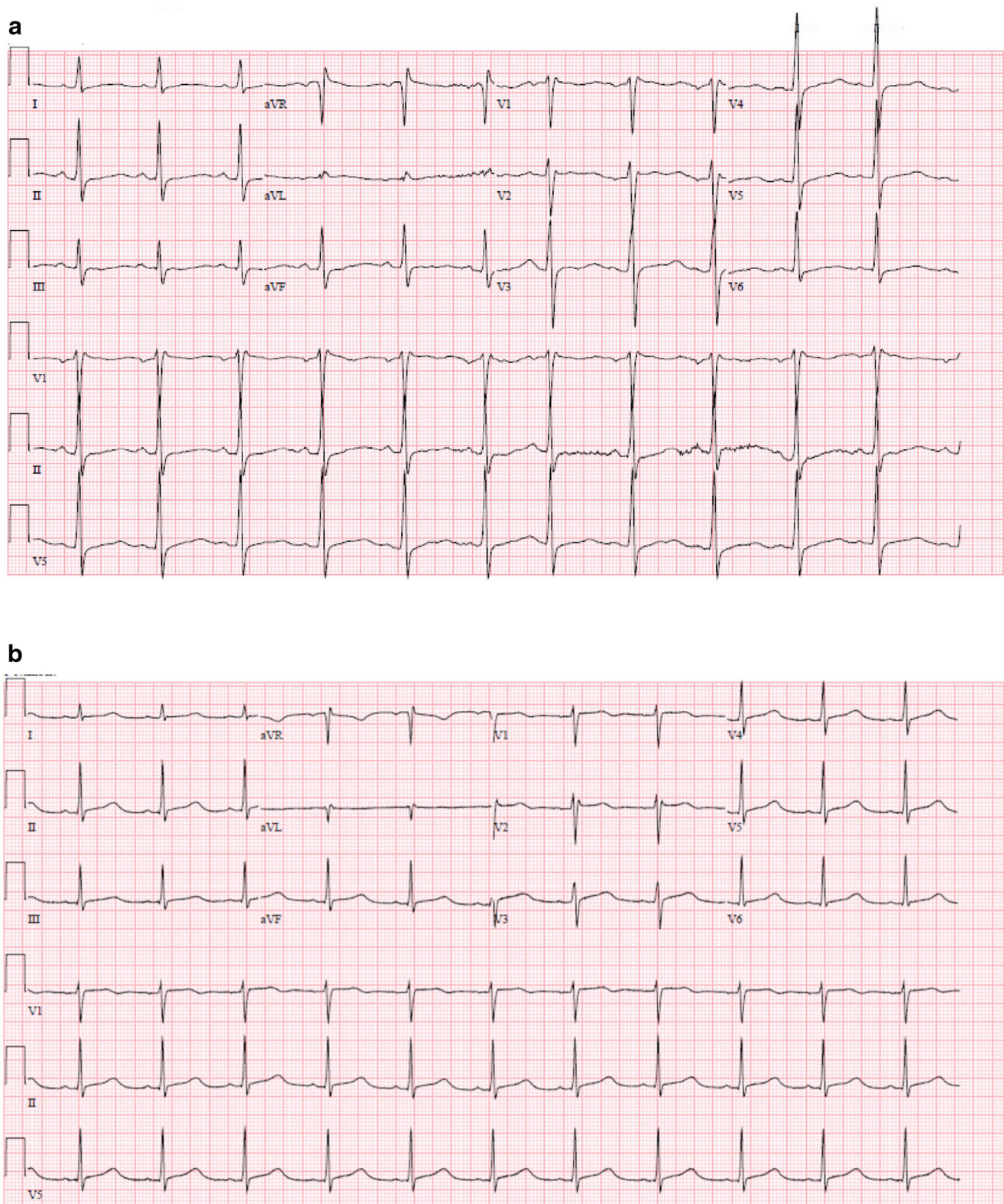
Laboratory evaluation should examine other potential co-ingestants and include a basic metabolic panel with a focus on potassium concentrations. Hydroxychloroquine or chloroquine drug concentrations are unavailable immediately and are not helpful in guiding treatment. An ECG should be obtained to assess for effects of sodium channel blockade and hypokalemia. The history, presence of key physical exam

features, hypokalemia (U waves), a prolonged QRS complex, and QTc interval on ECG should prompt the clinician to consider the possibility of poisoning from hydroxychloroquine.

Treatment of moderate and severe hydroxychloroquine poisoning centers has two predominant features. First, supportive care and airway management, including IV crystalloid volume resuscitation, is important to permit renal clearance of hydroxychloroquine. Additionally, early orotracheal intubation in individuals with muscle weakness or seizures may improve survival [8, 9]. In individuals who have mild poisoning exhibited by mild hypokalemia and some QTc prolongation without sedation or weakness, aggressive supportive care with potassium replacement and close monitoring of the QTc on telemetry may suffice.

Replacement of potassium should occur early in the clinical course, as hydroxychloroquine and chloroquine overdoses may cause profound hypokalemia. This can be confounded and exacerbated if sodium bicarbonate infusions are initiated to maintain QRS < 100 ms and/or epinephrine infusion to maintain adequate systolic arterial pressure. In our case, the severe hypokalemia predated any initiation of treatment with these agents, further supporting the causal relationship of hypokalemia with hydroxychloroquine intoxication. Most institutions have IV electrolyte replacement guidelines that limit the amount of parenteral potassium replacement in a given period. However, traditional IV replacement pathways may be inadequate to counteract the synergistic effect of hydroxychloroquine intoxication and treatment-induced hypokalemia; additional oral potassium may be needed on an ad hoc basis—together with frequent monitoring—to ensure serum concentrations are sufficiently raised and minimize the risk of ventricular dysrhythmias (Fig. 1). Post-poisoning monitoring should include assessment for hyperkalemia after intracellular potassium shifts occur. Orally administered activated charcoal can enhance biliary clearance of hydroxychloroquine and decrease toxicity but only should be considered if the patient is awake, alert, and cooperative [7]. Seizures, respiratory depression, or altered mental status may lead to aspiration of activated charcoal. The risks and benefits should be weighed prior to administration.

The second component involves directed therapy with high-dose IV diazepam and epinephrine. The recommended dose of diazepam involves IV bolus administration of 1–2 mg/kg body weight, followed by a continuous infusion of 1–3 mg/kg over 24 hours [8, 14]. The suggested epinephrine dose is 0.25 mcg/kg/minute, titrating to a systolic blood pressure > 90 mmHg [8]. These drugs directly affect the pharmacologic mechanisms through which hydroxychloroquine exerts its toxicity [15]. Although the mechanism by which diazepam addresses cardiac conduction abnormalities from hydroxychloroquine is controversial, animal models of chloroquine overdose demonstrate that when diazepam is administered, whole blood concentrations of chloroquine increase,



**Fig. 1** Table of pertinent laboratory values, electrocardiogram intervals and pharmacologic interventions

while cardiac myocyte concentrations of chloroquine decrease [16]. This suggests that diazepam may mediate displacement of chloroquine from sodium channels in the heart [15].

Second, diazepam may exert an antiarrhythmic effect by binding cardiac myocyte GABA receptors, although this hypothesis does not explain why other benzodiazepines lack efficacy

in treating chloroquine poisoning [17]. Despite this, a double-blind, placebo, case-controlled trial of diazepam infusion compared with standard supportive care suggested that the addition of diazepam does not alter the course of patients with moderate chloroquine poisoning [16]. This investigation only included individuals with moderate overdose without significant dysrhythmias, seizures, or hypotension at presentation. It is plausible that in more severely poisoned individuals, diazepam may have an additional mortality or morbidity benefit. Epinephrine increases inotropy and improves cardiac output in the hydroxychloroquine-poisoned heart. Given its large volume of distribution and significant protein binding, hydroxychloroquine is not amenable to clearance via hemodialysis [18]. Intravenous lipid emulsion (ILE) has also been suggested as treatment, by acting as a “lipid sink” and redistributing lipophilic hydroxychloroquine from tissues into the plasma [9, 19]. However, ILE may exert a paradoxical effect by pulling toxins out of the gut and increasing their systemic circulation. Since the marginal effect of hemodialysis and ILE is unclear, if not paradoxically harmful, the current consensus recommends against their use, especially if the patient condition improves or remains stable with standard therapy [8, 18]. In this case, the use of leucovorin to address potential concomitant methotrexate poisoning did not affect the pharmacodynamics and toxicokinetics of hydroxychloroquine [20, 21].

Like in high-dose insulin euglycemic therapy for calcium channel blocker overdoses, initiation of large doses of diazepam boluses and infusions may be difficult for some clinicians. We recommend early communication with hospital pharmacists and recognition of the logistical challenges of preparing a diazepam continuous infusion. In our case, a continuous infusion of diazepam at 1 mg/kg over 24 hours was ordered, but safety and operational considerations were encountered, forcing us to pursue an alternative strategy of administering intermittent IV doses of 6.5 mg diazepam every 2 hours for 24 hours. Although a continuous diazepam infusion remains the standard of care, this intervention may not be available for several reasons. Diazepam has a long half-life (33–45 hours) with an active metabolite, nordiazepam (half-life 87 hours), and the IV formulation contains 40% propylene glycol [22]. Patients requiring high-dose diazepam regimens should be monitored for lactic acidosis, for which patients with renal or hepatic impairment are at increased risk [23, 24]. Due to its high lipophilicity, diazepam does not incorporate into solution well and is adsorbed by standard plastic infusion bags resulting in less drugs being administered to the patient [25, 26]. Dilution in IV fluids, especially if performed at the bedside due to emergent need of infusion over 30 minutes, may cause the drug precipitate out of solution [27]. A diazepam infusion would therefore likely need to be prepared undiluted in a glass container, which is rarely available [28]. Fortunately, this case demonstrates that intermittent

IV boluses of diazepam can achieve the desired outcome of improving the QRS complex and QTc interval and preventing dysrhythmias.

If diazepam injection is unavailable due to drug shortages or if procurement would result in significant treatment delay, phenobarbital can also be considered [29]. The efficacy of alternative benzodiazepine therapy in improving ECG abnormalities in hydroxychloroquine overdose is unknown. While other benzodiazepines like midazolam may be used to achieve sedation in intubated individuals, it is unknown whether these benzodiazepines will be effective in addressing cardiac conduction abnormalities described in hydroxychloroquine poisoning.

This case had several limitations. First, we were not able to obtain a confirmatory hydroxychloroquine level; since this does not help guide clinical care, the focus was on aggressively managing this patient. Without a quantitative level, it is difficult to qualify the severity of this patient’s ingestion. Nevertheless, we encourage medical toxicologists and physicians who encounter individuals with hydroxychloroquine poisoning to utilize the physical exam, laboratory analysis, and ECG to guide choice of therapies for these patients. Second, we did not obtain a comprehensive toxicology screen to describe the absence of other drugs of abuse in this patient. We felt that the history provided by the patient and family and the presence of exam findings consistent with hydroxychloroquine poisoning were reliable enough to initiate hydroxychloroquine-specific therapy.

Overall, this case demonstrates the importance of rapid recognition and treatment of hydroxychloroquine poisoning. We anticipate that clinicians may be asked to recognize and manage this toxidrome in increasing frequency as attention on hydroxychloroquine as potential pharmacotherapy for COVID-19 disease may be popularized, despite an increasing concern on the increased mortality associated with this treatment [4, 5]. Various world leaders have repeatedly touted the use of hydroxychloroquine to manage COVID-19 disease despite the lack of rigorous clinical trial data to support its use. Personal anecdotes from world leaders may have the untoward effect of promoting the use of hydroxychloroquine in the treatment and prevention of COVID-19. In addition to the association of hydroxychloroquine use in the context of the COVID-19 pandemic, it is important to recognize unique sources of chloroquine exposure like aquarium cleaners (chloroquine phosphate) and initiate prompt treatment for individuals who present with findings consistent with toxicity. [6]

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## Compliance with Ethical Standards

Consent for publication of this case was obtained and provided to the journal in accordance with JMT policy.

**Conflict of Interest** None.

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