



Toxicokinetics of hydroxychloroquine following a massive overdose

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ABSTRACT

Background: We report a patient with a massive hydroxychloroquine overdose manifested by profound hypokalemia and ventricular dysrhythmias and describe hydroxychloroquine toxicokinetics.

Case report: A 20-year-old woman (60 kg) presented 1 h after ingesting 36 g of hydroxychloroquine. Vital signs were: BP, 66 mmHg/palpation; heart rate, 115/min; respirations 18/min; oxygen saturation, 100% on room air. She was immediately given intravenous fluids and intubated. Infusions of diazepam and epinephrine were started. Activated charcoal was administered. Her initial serum potassium of 5.3 mEq/L decreased to 2.1 mEq/L 1 h later. The presenting electrocardiogram (ECG) showed sinus tachycardia at 119 beats/min with a QRS duration of 146 ms, and a QT interval of 400 ms (Bazett's QTc 563 ms). She had four episodes of ventricular tachydysrhythmias requiring cardioversion, electrolyte repletion, and lidocaine infusion. Her blood hydroxychloroquine concentration peaked at 28,000 ng/mL (therapeutic range 500–2000 ng/mL). Serial concentrations demonstrated apparent first-order elimination with a half-life of 11.6 h. She was extubated on hospital day three and had a full recovery.

Conclusion: We present a massive hydroxychloroquine overdose treated with early intubation, activated charcoal, epinephrine, high dose diazepam, aggressive electrolyte repletion, and lidocaine. The apparent 11.6 hour half-life of hydroxychloroquine was shorter than previously described.

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1. Introduction

Hydroxychloroquine was initially marketed as an antimalarial treatment, however due to its significant anti-inflammatory properties, it is now also used for rheumatological disorders. While rare, hydroxychloroquine overdose carries a significant risk of morbidity and mortality. Toxicity resembles chloroquine overdoses with profound electrolyte shifts and cardiovascular collapse. Similarly, the management of patients with hydroxychloroquine overdoses is based on animal and human data for chloroquine toxicity which demonstrate improved outcomes with high dose diazepam, epinephrine and early intubation [1,2]. Data for hydroxychloroquine overdoses are limited to case reports and case series, with only three prior reports of its toxicokinetics [3–5]. We report a patient with a massive hydroxychloroquine overdose manifested by profound hypokalemia and ventricular dysrhythmias and describe hydroxychloroquine toxicokinetics following the ingestion.

2. Case presentation

A 20-year-old woman (60 kg) presented to the emergency department 1 h after ingesting 36 g of hydroxychloroquine by history. The patient was a college student with a past psychiatric history of untreated depression but otherwise had no past medical history and was not taking any medications at baseline. She intercepted a package with medications meant for another student. There was no report of a coingestant or history of drug abuse. On arrival, she was afebrile with the following vital signs: blood pressure, 66 mmHg/palpation; heart rate, 115/min; respirations, 18/min; oxygen saturation, 100% on room air; and glucose, 92 mg/dL. Her physical examination was remarkable for tachycardia and decreased mental status. She was immediately started on 2 L of normal saline and received two doses of 40 µg of epinephrine intravenously for hypotension. The regional poison control center was called and recommended epinephrine intravenously, diazepam and early intubation. Diazepam (2 mg/kg IV over 30 min) and an epinephrine infusion (7.5 µg/min IV) were started. Activated charcoal was administered through an orogastric tube. Orogastric lavage was recommended, however it was not

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performed due to the inability to obtain a large bore lavage tube at the hospital where the patient presented. Suction from an 18F orogastric tube did not return any pill fragments. The initial venous blood gas analysis showed: pH, 7.44; PCO₂, 38 mmHg; bicarbonate, 25 mEq/L; and lactate, 4.8 mmol/L. Her initial serum potassium was 5.3 mEq/L, which decreased to 2.1 mEq/L 1 h later. Other laboratories were essentially unremarkable, and acetaminophen, salicylates, and ethanol were undetectable. The initial electrocardiogram (ECG) showed sinus tachycardia 119 beats/min, QRS duration of 146 ms, and QT interval of 400 ms (Bazett's QTc 563 ms), with a left axis deviation. Serial ECGs showed a QRS duration of 128 ms, and widening of her QTc interval to 684 ms, with a right axis deviation (Fig. 1). The patient received three ampules (150 mEq) of sodium bicarbonate in an attempt to correct the sodium channel blockade on the ECG with no improvement in the QRS. Due to the concern of worsening the existing hypokalemia and prolonged QT interval, and the lack of response to the initial bolus, no additional sodium bicarbonate was given. While still in the emergency department, the patient developed four episodes of ventricular tachydysrhythmias requiring electrical cardioversion followed by the administration of 2 g of magnesium sulfate.

Blood hydroxychloroquine concentrations were measured by high performance liquid chromatography/tandem mass spectrometry (Quest Diagnostics). Her initial hydroxychloroquine concentration was 27,000 ng/mL (therapeutic concentration 500–2000 ng/mL) 4 h post ingestion and peaked at 28,000 ng/mL 5 h post ingestion. Serial hydroxychloroquine concentrations over the first 24 h following the overdose demonstrated apparent first-order elimination with a half-life of 11.6 h (see Fig. 2). The patient received a total of 200 mEq of potassium chloride in the first 12 h of her hospital stay, at which point, her serum potassium normalized to 4.0 mEq/L. The serum potassium rebounded to 6.5 mEq/L at 16 h post ingestion, and was only treated with 1 g of calcium gluconate. In the initial 12 h she had multiple episodes of non-sustained ventricular tachycardia and was treated with a lidocaine infusion. Serial ECGs demonstrated continued prolongation of her QRS duration and QT intervals even with normal serum potassium and magnesium concentrations (see Fig. 3). The ECG finally normalized 36 h post ingestion. She was extubated on hospital day 3 and had a full neurological recovery without any deficits. After her acute care hospitalization, the patient was transferred to an inpatient psychiatry unit.

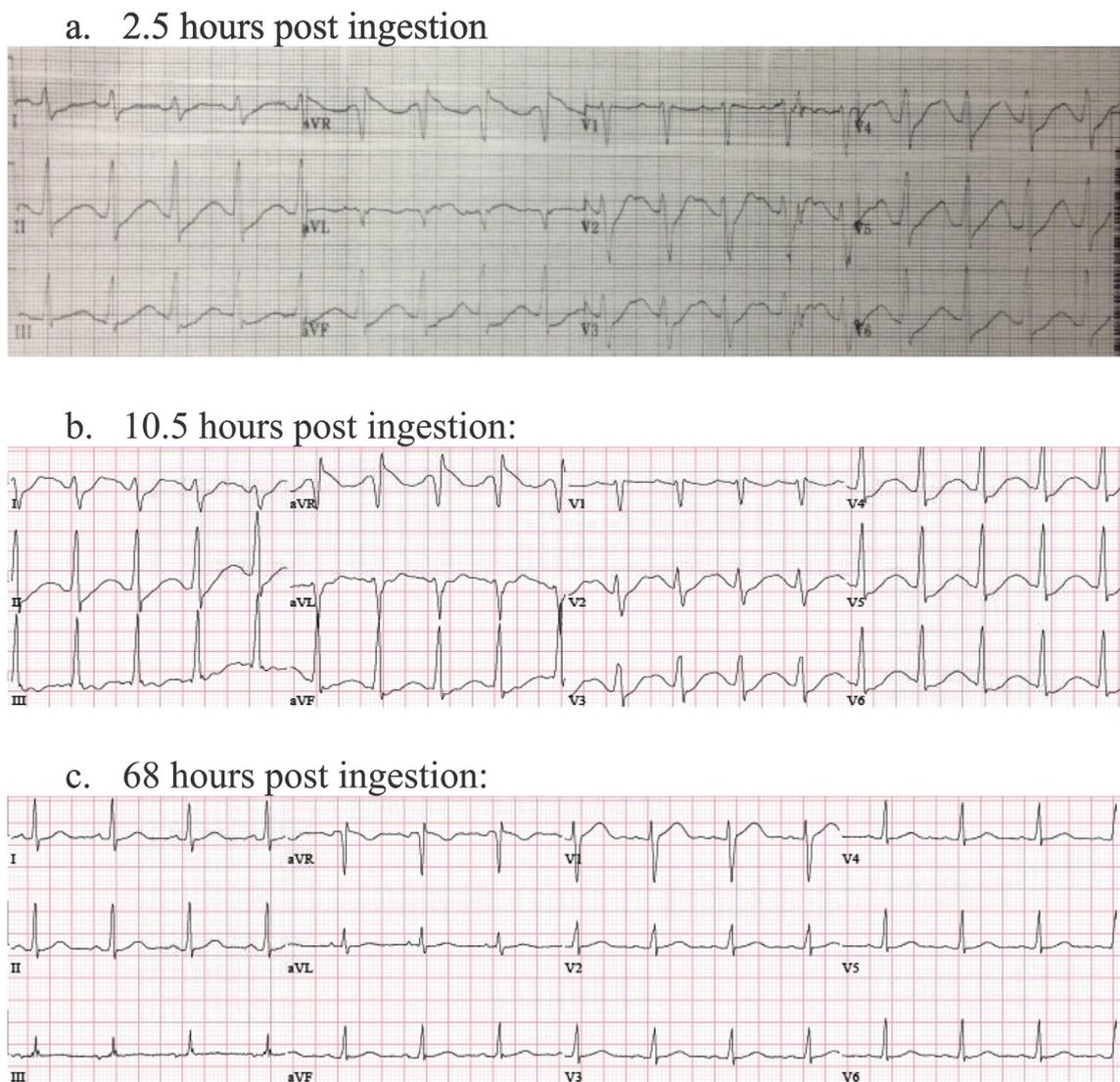


Fig. 1. ECG progression post hydroxychloroquine overdose: (a) initial ECG at 2.5 h post ingestion demonstrates a QRS of 128 ms and a Bazett's QTc of 684 ms; (b) ECG at 10.5 h with a QRS of 125 ms and a Bazett's QTc of 524; (c) ECG at 68 h post ingestion with a QRS of 82 ms and a Bazett's QTc of 462 ms.

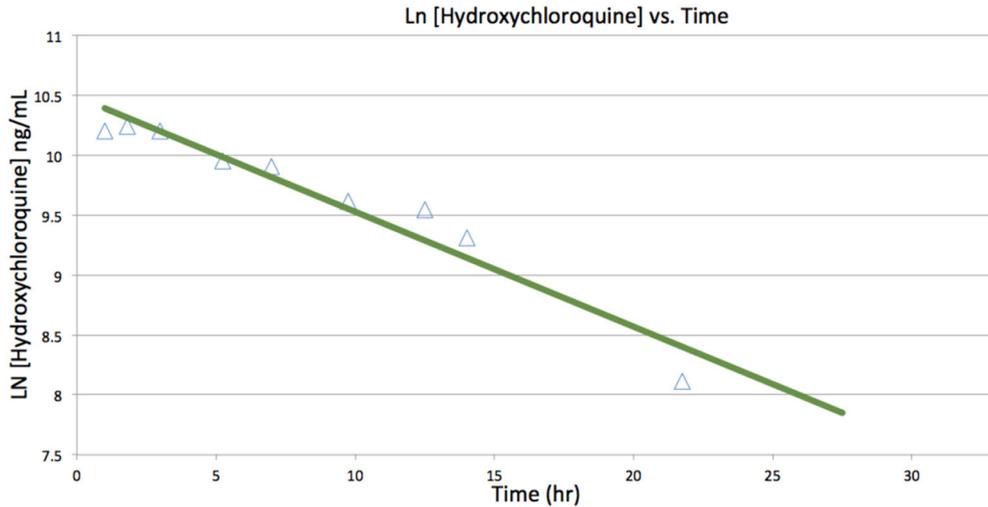


Fig. 2. Toxicokinetics of hydroxychloroquine: natural log of hydroxychloroquine concentration over time for first 22 h post ingestion. The equation for the line above is: $y = -0.0595x + 10.513$; and a $R^2 = 0.94508$. The half-life of hydroxychloroquine was calculated to be 11.6 h using equation $t_{1/2} = 0.693/ke$, where $ke = 0.0595$.

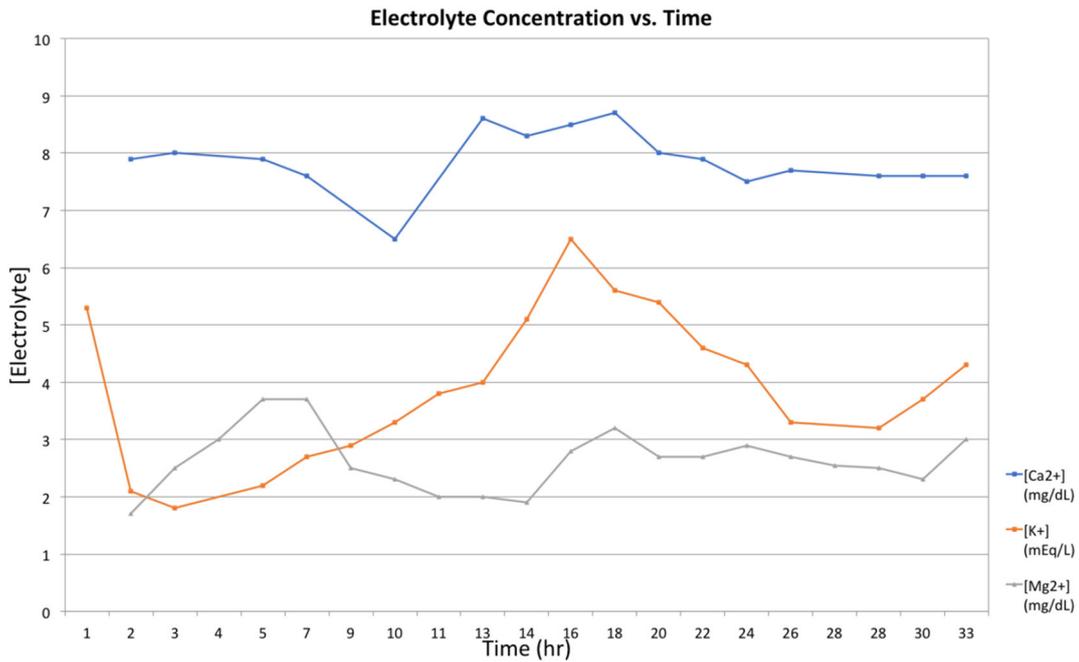


Fig. 3. Electrolyte shifts of potassium, calcium, and magnesium over time. The potassium was noted to drop precipitously to a low of 1.8 mEq/L at 3 h and peaked at 6.5 mEq/L at 16 h post ingestion.

3. Discussion

Hydroxychloroquine and chloroquine are 4-aminoquinolines with similar patterns of toxicity. At therapeutic doses, hydroxychloroquine has a bioavailability of approximately 70% (with a range of 25–100%) with a very large volume of distribution of approximately 800 L/Kg [6,7]. Hydroxychloroquine pharmacokinetics are similar to chloroquine with peak plasma concentration between 3 and 12 h post ingestion and is highly adsorbed to activated charcoal (95–99%) [8]. It is primarily metabolized by the liver and has an estimated elimination half-life of 40 days [9]. While the pharmacokinetics of hydroxychloroquine is most commonly described as a two compartment model, some authors consider a three compartment model more appropriate [7,10,11]. The multi-compartment model may help explain the difference between

the duration of toxicity and the elimination half-life in hydroxychloroquine overdoses. As the drug is absorbed and enters the circulation, it rapidly distributes into tissue compartments, such as the brain and heart, leading to toxicity.

In our case report, we collected nine serial concentrations of hydroxychloroquine over a 22-hour period with an observed half-life of 11.6 h. This is lower than previously described toxicokinetics studies which report half-lives between 15.5 and 31 h [3,4]. Various confounding variables affect the toxicokinetics, such as patient hemodynamics, bowel perfusion, the quantity of the ingested drug, and possibly the administration of activated charcoal. It is unknown if hydroxychloroquine undergoes enterohepatic or enteroenteric recirculation. Regardless, it is unlikely that a single dose of activated charcoal affected the toxicokinetic half-life in our patient. Assuming hydroxychloroquine follows a two-

compartment pharmacokinetic model, the half-life we observe over the first 22 h likely represents the initial alpha phase of distribution. Prior case reports recorded concentrations over a longer period of time (between 33 and 68 h) which may have contributed to a longer observed half-life as it may have captured both an initial alpha distribution as well as early beta elimination phase of the drug [3,4].

Electrolyte, cardiac and central nervous system abnormalities are characteristic of massive hydroxychloroquine overdoses. Hypokalemia is thought to occur due to intracellular shifts in potassium and not total body depletion. In chloroquine overdoses, the degree of hypokalemia is associated with the severity of toxicity [12]. There is debate regarding how aggressive hypokalemia should be managed. While there are risks for dysrhythmias with severe hypokalemia, animal models suggest hypokalemia is protective for QRS widening in quinine toxicity [12,13]. Furthermore, rebound hyperkalemia is reported following aggressive potassium repletion [5]. Our patient received 200 mEq of potassium chloride and the serum potassium increased from 1.8 mEq/L to 6.5 mEq/L 16 h post overdose.

The electrocardiogram is an important tool in the assessment of sodium channel and HERG potassium channel blockade in 4-aminoquinoline overdoses. The data evaluating the prevalence of ECG abnormalities specific to hydroxychloroquine overdoses are limited. In a retrospective regional poison control center study, 64% of patients treated in a healthcare facility after a reported hydroxychloroquine ingestion had recorded ECG abnormalities [14]. Prolongation of either the QRS duration or QT interval was noted in 13% and 17% of patients, respectively [14]. In those who received an ECG, the QTc was greater than 500 ms in 13–18% of patients [14,15]. Our patient had both QRS and QT interval prolongation that resolved after 24 and 48 h, respectively. Interestingly, the initial widened QRS did not respond to the bolus administration of 150 mEq of sodium bicarbonate. No further sodium bicarbonate was given because of concern for potentiating QT interval prolongation. Lidocaine, a type IB sodium channel blocker, was given in consultation with cardiology for recurrent non-sustained ventricular tachycardia. While the rate of PVCs and non-sustained ventricular tachycardia diminished, the efficacy of lidocaine in hydroxychloroquine toxicity is unclear. Lastly, the QT interval was prolonged even after electrolyte correction likely due to the drug's HERG channel blockade.

Management of patients with hydroxychloroquine overdoses is largely based on experience with chloroquine overdosed patients. Riou et al. demonstrated a mortality benefit in patients with chloroquine overdoses by treating with the combination of early intubation, high dose diazepam, and epinephrine [1]. While there are case reports of patients receiving intravenous fat emulsion in hydroxychloroquine overdoses, there is no clear evidence that it

improves outcomes [16,17]. We recommended against the use of intravenous fat emulsion due to the high gastrointestinal burden and concern for redistribution of the drug from the gastrointestinal tract into the bloodstream.

4. Conclusion

We present a case of a massive hydroxychloroquine overdose treated successfully with early intubation, activated charcoal, epinephrine, high dose diazepam, aggressive electrolyte repletion, and lidocaine. Additionally, abnormal cardiac conduction and dysrhythmias were present even after the correction of electrolyte abnormalities. The apparent half-life of hydroxychloroquine was 11.6 h in this massive overdose, which is shorter than previously described in the literature.

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