Review Article

# Hydroxychloroquine Toxicity Management: A Literature Review in COVID-19 Era

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## Abstract

**Background:** Hydroxychloroquine (HCQ) has been widely investigated for the treatment of COVID-19. Although it is rare, several case reports of acute toxicity of HCQ due to overdose have been reported during the last two decades. The aim of this review is to summarize the management options of acute HCQ toxicity. **Methods:** A literature review that was conducted using an electronic search in the Google Scholar search engine. The inclusion criteria include any patient over 12 years old presenting with HCQ intoxication symptoms from January 1999 to January 2020. **Results:** Sixteen cases were found that have the inclusion criteria of this study. Most patients presented with altered mental status, electrocardiogram abnormalities, visual disturbance, and decrease cardiac output. Activated charcoal was the first line of management in nearly two-thirds of patients whereas 93.8% received fluid resuscitation and 81.3% of the patients need at least one type of vasopressor agent. Furthermore, potassium is given for 93.8% of the patient while 75% of the patients need sodium bicarbonate and intubation, lipid emulsion was used in three patients only and 13 patients survived. **Conclusion:** The acute HCQ toxicity may result during the treatment period of COVID-19. The most common options can use in this situation include included gastric lavage and decontamination, IV fluid resuscitation, potassium replacement, sodium bicarbonate, intravenous lipid emulsion, and extracorporeal circulation membrane oxygenation. The role of diazepam is not clear but can be used in the significant toxicity while hyperkalemia associated with severe ingestions.

**Keywords:** Hydroxychloroquine, overdose, toxicity

## Introduction

Hydroxychloroquine (HCQ) is a commonly prescribed medication for both treatment and prophylaxis of malaria, rheumatoid arthritis, and systemic lupus erythematosus. It has been approved in the United States since 1955 and widely investigated for the treatment of COVID-19. Based on early reports of efficacy in COVID-19 management, the FDA issued an emergency use authorization to allow HCQ sulfate donation to the Strategic National Stockpile to be distributed and used for certain patients hospitalized with COVID-19.[1]

The safety profile of HCQ shows that it is well tolerated with adverse effects (e.g., retinopathy) when it is used chronically (>5 years).[2] However, serious and acute consequences have occurred following HCQ overdose and the first case report of acute toxicity was published in 1960.[3] Although it is rare, several case reports of acute toxicity of HCQ due to overdose have been reported during the last two decades. Of 1408 fatalities were reported to the American Association of Poison Control Centers during the year 2014, two of them were HCQ toxicity.[4]

### Pharmacokinetics and pharmacodynamics properties of hydroxychloroquine

HCQ is made up of the group's contribution hydroxy-on the parent compound of chloroquine to reduce the toxicity. Its half-life ranges from 15.5 to 31 h. The gastrointestinal (GI) absorption is rapid, and the maximum plasma concentration is reached within 1–2 h and is prolonged by binding to plasma proteins. HCQ undergoes hepatic (alkylation and glucuronoconjugation) and renal metabolism, and its renal

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elimination is relatively slow as 6% of the dose ingested is eliminated in 10 days. On the other hand, fecal elimination represents 25% of the ingested dose. As a result, a massive overdose may lead to accumulation in plasma resulting in serious adverse effects.[5]

Experts have discussed several options to treat acute toxicity of HCQ through published case reports. The purpose of this review is to summarize the pharmacological options used in the management of acute HCQ toxicity among 16 published case reports during the last two decades.

## Methods

An electronic search of the literature was performed through January 1999 until March 2019 by using Medline, Scopus, and PubMed. We used the following MeSH terms HCQ and toxicity, management, overdose, or poising in different permutations. In addition, we reviewed all the relevant citations from all reviewed articles that appear in our research for any additional references.

Our inclusion criteria include the presence of HCQ intoxication with the management steps taken so only articles including HCQ intoxication in adults (above 18 years old) or adolescents (12–17 years old) patients were obtained for analysis.

All the studies that met the inclusion criteria were analyzed after that, demographic data and clinical data for each article were tabulated, the following data were extracted:[1] toxic dose, [2] the clinical features[3] HCQ level in the blood,[4] glasgow coma scale,[5] electrocardiogram changes (QRS widening and QTc prolongation),[6] need intubation and time of extubation,[7] using gastric lavage (GL),[8] using activated charcoal,[9] using fluid resuscitation,[10] pressor infusion,[11] using high-dose diazepam[12] potassium replacement[13] giving sodium bicarbonate and its indication[14] giving intravenous (IV) lipid emulsion (ILE)[15] using extracorporeal circulation membrane oxygenation (ECMO)[16] the outcome.

## Results and Discussion

A total of 16 studies met the inclusion criteria from 1999 to 2019, 87.5% of them were female (14/16) with mean age 29.8 years old range from 16 to 64 years old, 7 forms 16 cases (43%) took the HQC for suicide purpose whereas 25% received it as a treatment for SLE [Table 1].

### Clinical features of Hydroxychloroquine toxicity

Among the 16 identified case reports, the total ingested amount of HCQ ranged from 3 to 40 g (Median is 20 g). Patients may present with altered mental status, prolonged QTc (increases ≥60 ms from baseline or QTc ≥500 ms) ventricular dysrhythmias, hypotension, visual disturbances, and decreased cardiac output. Patients may develop both profound hypokalemia and rebound hyperkalemia.

### Management of hydroxychloroquine acute toxicity

Among the 16 cases, 75% of patients were intubated and required supportive management. One patient was put on ECMO, and three deaths were documented. QTc prolongation was reported in 15 cases. The most common dose, which was ingested by the patients (31%), is 20 g. The overdose ingestion ranged from as low as 3 g till 40 g. Seven cases reported HCQ postingestion serum levels ranging from 5.5 to 27 mg/L (normal 0.5–2 mg/L). The management of these cases includes several conventional and nonconventional treatment modalities.

### Modalities of conventional treatment

#### *Gastrointestinal Decontamination*

The decision to perform GI decontamination (GL and activated charcoal) is based on the specific poison (s) ingested, the time from ingestion to presentation, presenting symptoms, and the predicted severity of poisoning. The patients who will benefit from GI decontamination at most who present for care as soon as possible after ingestion (usually within 1–2 h), who do not have clinical factors (e.g., somnolence) that makes the decontamination dangerous.[5]

Among the 16 cases, five patients (31%) had received GL and ten patients (62%) had received activated charcoal (AC).[6-9] The most common dose reported for AC is 50 g used as a single-dose[5,9-11] [Table 2]. One patient had received multidose AC as 50 g once and then 10 g repeated hourly for an unreported duration.[12] Aspiration is the most often cited concern when clinicians chose not to administer AC. However, among the case reports, there were no documented incidences of aspiration.

Based on that, GL is not recommended for routine decontamination compared to AC. Rarely, GL may be helpful if the patient has ingested a toxic amount of poison and the procedure can be performed within 1 h of ingestion. When performed, GL should be followed by AC administration, as the HCQ is well adsorbed by AC.[2]

#### *Intravenous fluid resuscitation*

Following an overdose of HCQ, patients may present with severe hypotension requiring fluid resuscitation. Our review found that colloid[5,12] and crystalloid (primarily normal saline) fluids were used to manage the hypotension. Out of the reported patients, 12 patients (75%) required fluid administration, out of them, four patients (33%) received normal saline, two patients received a not-specified colloidal fluid, one patient received lactated Ringer's, and the rest did not specify the type of fluid used. Ten out of the 12 patients (83%) failed regarding this option and required vasopressors [Table 2].

#### *Intravenous vasopressors*

Vasopressors are used to antagonize the vasodilatation and myocardial depression by acting as a powerful inotrope (reduces the intraventricular conduction time) and vasoconstrictor to overcome the depressive cardiovascular effects of chloroquine.[13,14]

**Table 1: Summary of study characteristics include in this review**

| Reference | Year | Type of study | Gender | Age (year) | Country of report | Indication of HQC |
|---|---|---|---|---|---|---|
| Jordan | 1999 | Case report | Female | 18 | Australia | SLE |
| Marquardt | 2001 | Case report | Female | 16 | USA | None |
| Yanturali | 2004 | Case report | Female | 17 | Turkey | RA |
| Fung | 2007 | Case report | Female | 28 | Hong Kong | SLE |
| Mongenot | 2007 | Case report | Female | 39 | France | Suicide |
| Ling Ngan Wong | 2008 | Case report | Male | 49 | Hong Kong | Suicide |
| Gunja | 2009 | Case report | Female | 16 | Australia | Suicide |
| Gunja | 2009 | Case report | Female | 45 | Australia | RA |
| Wong | 2011 | Case report | Female | 37 | Hong Kong | Suicide |
| Wong | 2011 | Case report | Female | 29 | Hong Kong | SLE |
| McBeth | 2015 | Case report | Female | 23 | Canada | Pruritus |
| Broek | 2016 | Case report | Female | 25 | Netherland | Suicide |
| Broek | 2016 | Case report | Male | 25 | Netherland | Suicide |
| Chansky | 2017 | Case report | Female | 64 | USA | Nail psoriasis |
| Murphy | 2017 | Case report | Female | 26 | USA | SLE |
| De Olano | 2019 | Case report | Female | 20 | USA | Suicide |

SLC: Systemic lupus erythematosus, RA: Rheumatoid arthritis, HQC: Hydroxychloroquine

**Table 2: Summary of conventional treatment**

| Modalities of conventional treatment | Given (%) | Not given (%) |
|---|---|---|
| Gastric lavage | 5 (31.3) | 11 (68.7) |
| Activated charcoal | 11 (68.7) | 5 (31.3) |
| Fluid resuscitation | 15 (93.8) | 1 (5.2) |
| Pressor infusion | | |
| Epinephrine | 9 (56) | 3 (18.7) |
| Norepinephrine | 2 (12.5) | |
| Dopamine | 2 (12.5) | |
| High-dose diazepam | 9 (56) | 7 (44) |
| Potassium replacement | 15 (93.8) | 1 (5.2) |
| Sodium bicarbonate | 12 (75) | 4 (25) |

In our review, epinephrine was the most commonly reported vasopressor as it was used in nine patients (75%). Maximum doses ranged from 5 to 160 mcg/min (median 20 mcg/min) with initial titration starting from 1.5 mcg/kg/min. No adverse effects were reported. The other vasopressors that have been used are dopamine in two patients and norepinephrine in one patient, and two patients needed to be on epinephrine and norepinephrine [Table 2].

### *High-dose diazepam*

The use of diazepam for a HCQ overdose is controversial. Many theories have been showed for the probable favorable effect of diazepam, including: (1) a central antagonist effect; (2) anticonvulsant effect; (3) antiarrhythmics effect by an electrophysiologic action inverse to chloroquine; (4) pharmacokinetic interaction between diazepam and chloroquine; and (5) decrease in chloroquine-induced vasodilatation. Animal models of chloroquine toxicity have shown that high doses of diazepam decreased mortality significantly and also improved the cardiovascular parameters and increased the excretion of chloroquine.[15,16]

The role of high-dose diazepam is not well established but most authors still recommend its use for the treatment of significant HCQ poisoning. For example, patient with hypotension, QTc prolongation, hypokalemia in combination with other supportive measures such as mechanical ventilation, epinephrine, and cardiovascular monitoring; however, it is not known whether this influenced clinical outcomes.[6,10,15-17] The recommended dose is 2 mg/kg IV administered over 30 min, followed by 1–2 mg/kg/day for 2–4 days.[10,17] When using these high doses, one must be sure that the patient is intubated and ventilated. It should be remembered not to exceed the 5 mg/min maximum infusion rate of diazepam or cardiotoxicity from the propylene glycol may ensue.[10]

In the cohort of 16 cases included in this review, diazepam was administered to nine patients (75%), and one case survived without any use of diazepam in the treatment.[18] The findings of this review showed variability of the required infusion rate and no referenced range was followed or reported [Table 2].

### *Potassium replacement therapy*

Profound hypokalemia is a known complication of HCQ and CQ overdoses. It is unknown whether HCQ causes direct cardiotoxicity or if it is partly due to hypokalemia. Potassium replacement may be required; however, monitoring for rebound hyperkalemia with resultant dysrhythmias is important.[16]

Hypokalemia is thought to be secondary to potassium channel blockade rather than potassium depletion and is a good index of severity of chloroquine and HCQ overdoses.[12,19] The severity of hypokalemia closely correlates with the level of chloroquine and HCQ toxicity. Potassium concentrations <1.9 mEq/L is correlated with severe, life-threatening ingestion. Hypokalemia <3.0 mEq/L should be corrected carefully. To avoid iatrogenic hyperkalemia, potassium levels should be frequently monitored, as

chloroquine-induced hypokalemia tends to self-correct from the redistribution of intracellular potassium. The infusion should not exceed 10–15 mEq KCl per hour.[11]

Rebound hyperkalemia was reported to occur in about 16 h post-HCQ overdose, and the consequences of this level elevations ranged from an easily corrected level with no arrhythmias to the occurrence of ventricular fibrillation in 36 h post-HCQ overdose.[9,12,20]

In a nutshell, the dosing of the potassium varied widely among the cases reviewed and cases of overcorrection were thought to be associated with overcorrection late in the course. In the absence of data showing a benefit of potassium supplementation in the HCQ overdose, careful replacement should be entertained.

### *Sodium bicarbonate*

The concern about giving sodium bicarbonate in HCQ poisoning is the potential for a further intracellular shift of potassium exacerbating the marked hypokalemia.[9] No present studies are supporting its use in patients overdosed of chloroquine or HCQ.[10] Since alkalization may worsen preexisting hypokalemia, it should be used with great care.[14] Ling demonstrated two case reports successfully used bicarbonate in conjunction with other agents for massive HCQ overdoses.[6]

Twelve case reports through this review have used 100 mEq of sodium bicarbonate as boluses with close monitoring of potassium level. Among the 12 cases, nine patients received sodium bicarbonate for narrowing the QRS widening with only case report documented no improvement. 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.[20] Out of the 12, three patients were dead.

## Modalities of nonconventional treatment

### *Intravenous lipid emulsion*

One of the hypothesized mechanisms of ILE therapy in reversing drug toxicities is the "lipid sink" effect in which the lipophilic drugs are sequestrated into a newly created intravascular lipid compartment. Moreover, ILE has been suggested to have a direct inotropic effect on the depressed myocardium secondary to the cardiotoxic drug intoxications by overcoming the inhibition to the oxidative phosphorylation and enhancing the myocyte carbohydrate use. The efficacy of ILE for the treatment of HCQ overdose has never been studied.[21]

The evidence for the use of ILE for HCQ toxicity is limited. Three case reports involving ILE have been published. In one patient, the administration of ILE in the form of propofol within1–to 2 h of HCQ ingestion could have played a role in the patient's survival.[13] ILE was administered as the last resort in two other cases and neither patient survived[16] [Table 3].

ILE use should be discussed with a toxicologist in patients with a known large ingested dose of HCQ or signs of severe poisoning. Further information elucidating the use and effectiveness of this therapy should be sought.[4]

**Table 3: Nonconventional treatment**

| Modalities of nonconventional treatment | Given | Not given |
|---|---|---|
| Intravenous lipid emulsion | 3 (18.7) | 13 (81.3) |
| ECMO | 1 (6.3) | 15 (93.7) |
| Outcome | | |
| Survive | 13 (81.3) | |
| Dead | 3 (18.7) | |

ECMO: Extracorporeal circulation membrane oxygenation

### *Extracorporeal circulation membrane oxygenation*

ECMO can be used as a rescue treatment following inotropic agents and HCQ overdoses. Its use must be early before the development of advanced multi-organ failure.[5] This method was thought to help remove chloroquine or HCQ, but both drugs have very large volumes of distribution and rapidly distribute to the intracellular space.[10] It was considered in case reports; however, due to the patients' rapid improvement, the need for ECMO was obviated. ECMO has also been successfully demonstrated in an isolated case of severe HCG toxicity.[16] In the case of acute respiratory distress syndrome or refractory circulatory shock, treatment with ECMO could be considered.[13]

Among the 16 case reports, only one case used ECMO and the patient survived. ECMO can be considered as the last option in managing patients with HCQ overdose when other options have failed [Table 3].

## Conclusion

The widespread availability of and interest in HCQ as a result of an international COVID-19 pandemic has the potential to result in increased cases of acute HCQ toxicity. This review demonstrated the most common options used in the supportive management of patients presenting with acute HCQ overdose included GL and decontamination, IV fluid resuscitation, potassium replacement, sodium bicarbonate, ILE, and ECMO. Hyperkalemia is associated with severe ingestions and cautious replacement with frequent monitoring is needed due to the risk of overcorrection. The role of diazepam is not clear but could be considered with significant HCQ poisoning in combination with other supportive measures. Early patient assessment is crucial to determine the feasibility of the individual treatment modalities.

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## Conflicts of interest

There are no conflicts of interest.

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