

## Massive Hydroxychloroquine Overdose in an Uncontrolled Diabetic Patient: A Case Report, Complications and Management

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### Abstract

#### Introduction

Hydroxychloroquine (HCQ) is an antimalarial agent that has been tried out in the treatment of COVID-19, however, evidence of efficacy remains limited. Although Hydroxychloroquine overdose is not common, growing cases of poisoning with HCQ have been reported during recent years. HCQ toxicity is characterized by life-threatening symptoms which require immediate medical intervention. This report presents a suicide attempt in a hyperglycemic patient, massive ingestion of HCQ manifested by hypokalemia and acidosis.

#### Case summary

A 47-year-old man presented at the hospital hours after massive ingestion of HCQ (100 tablets), with generalized weakness and dizziness which had led to a fall. He was drowsy and had experienced episodes of nausea/vomiting. His past medical history was remarkable for uncontrolled diabetes mellitus, confirmed by the blood glucose of 345 mg/dL, and a previous history of hospitalization a few months ago, due to a suicide attempt. He developed marked hypokalemia accompanied by acidosis, plasma potassium of 2.8 mmol/L and pH 7.34, and hypotension, blood pressure of 80/51 mm Hg, but survived with close cardiac monitoring and immediate intervention including aggressive potassium replacement, bicarbonate infusion, and charcoal administration.

#### Conclusion

Considering the significantly increased off-label use of HCQ during the COVID-19 pandemic, this report alerts the potential for HCQ to be associated with severe electrolyte disorders, especially in predisposing conditions like diabetes. Clinicians should keep in mind the possibility of hypoglycemia in diabetic patients under hypoglycemic medications and concurrent use of chloroquine/HCQ. This therapeutic approach also suggests the benefit of even a delayed activated charcoal administration in the treatment of HCQ poisoning.

**Key Words:** hydroxychloroquine, overdose, poisoning, hyperglycemia, hypokalemia

#### Competing Interests

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## Introduction

Hydroxychloroquine (HCQ), available under the trade name Plaquenil, was developed in 1934 to treat autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus, as well as malaria. Recently, the possible potential of HCQ in the treatment of COVID-19 has been discussed, but no reliable result has been achieved yet [1].

The main toxic effect of Hydroxychloroquine is on the heart. Blockage of  $\text{Na}^+$  and  $\text{K}^+$  channels results in prolonged QRS and QT, a risk for cardiac arrhythmia and hypotension. Potassium efflux is also manifested by hypokalemia [2]. Irreversible retinal damage is an Ophthalmologic complication followed by chronic exposure to Hydroxychloroquine [3]. Due to the life-threatening Symptoms of poisoning with Hydroxychloroquine and the importance of detoxification and prompt treatment, further understanding of the symptoms, complications, and treatment recommendations is necessary.

## Reason for report

Although few cases of overdose with this drug have been published, there is still no detailed information on how to manage patients referred to the hospital [4, 5]. As far as we know, there are no reports of HCQ overdose in an uncontrolled diabetic patient. So, here we report massive Hydroxychloroquine ingestion in a hyperglycemic patient who suffers hypokalemia and acidosis.

## Case Presentation

A 47-year-old man was transferred to Emam Reza hospital after an intentional overdose of hydroxychloroquine. In January 2021. He had ingested about 100 hydroxychloroquine tablets at 11 the last night in a suicide attempt. During the night, he experienced frequent nausea/vomiting episodes about eight times in 8 hours. After a fall followed by dizziness in the morning, he contacted the Emergency center and was brought to the Emergency Department at 7 am. On admission, he presented lethargic but alert and awakened with a Glasgow Coma Scale score of 15 (out of a maximum of 15), his blood pressure was 80/51 mm Hg, pulse rate 91/min, respiratory rate 18/min, and  $\text{O}_2\text{sat}$  97% (

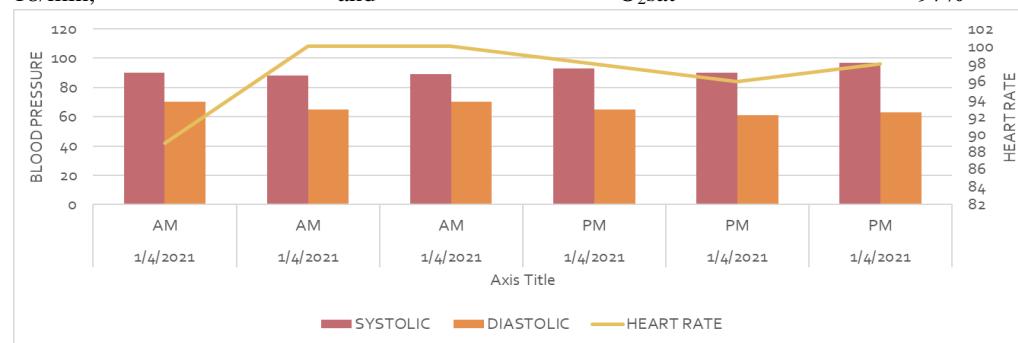
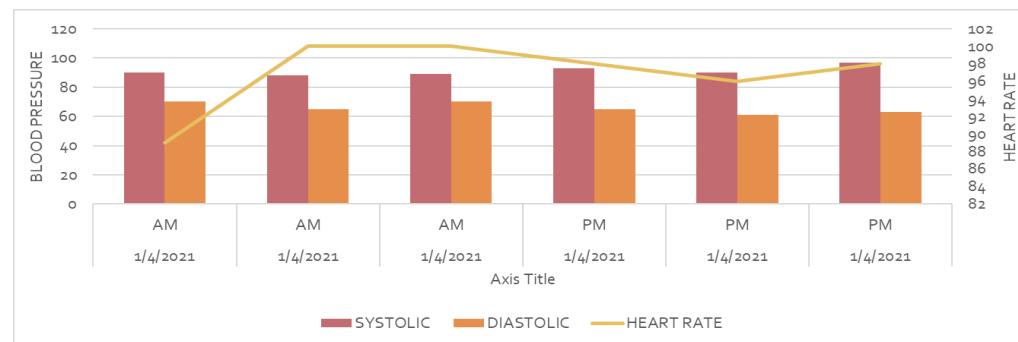


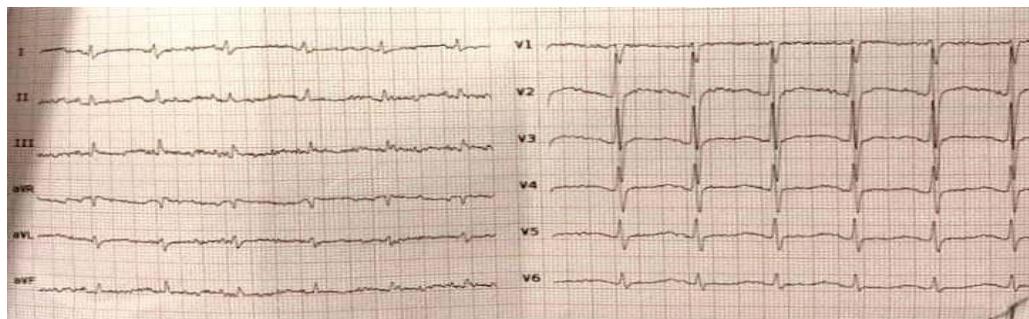
Figure 1). The examination was unremarkable aside from a small laceration on the left eyebrow from the fall, which a consequent head computerized tomography (CT) scan turned out clear. He declared his hospitalization a few months ago due to his suicide attempt. Other than that, his past medical history did not include anything relative; only diabetes was confirmed by the person accompanying the patient (Blood glucose level: 345 mg/dL). Ophthalmology and psychology consults were ordered before transferring to inpatient poisoning care.



**Figure 1** Vital signs record of the patient during hospitalization

Charcoal (50 cc) was administered with a nasogastric tube (NG tube). Due to the patient's charcoal intolerance. He received intravenous (I.V) ondansetron (4 mg) and pantoprazole (40 mg). Serum therapy, including a vial of bicarbonate and 10 ccs of potassium chloride, had been ongoing since the early admission.

The initial laboratory studies (**Error! Reference source not found.**) were notable for plasma potassium of 2.8 mmol/L and pH 7.34. His doctor ordered an electrocardiogram (ECG) observation due to his hypokalemic status and monitoring of plasma potassium every 4 hours (Figure 2). Repeated blood glucose monitoring was also conducted to look for any possible complications caused by his hyperglycemia. The patient had an almost uneventful hospital course.



**Figure 2** Twelve-lead ECG of a 47-year-old male patient showed sinus rhythm and normal intervals during his initial presentation

**Table 1** Selected laboratory values of patient

Laboratory values	9:57 am	1:25 pm	Reference-values
<b>Temperature (°C)</b>	37	37	97°F (36.1°C)-99°F (37.2°C)
<b>Hb-std(g/dl)</b>	15	15	Male: 14-18 Female: 12-16
<b>FiO2(%)</b>	20.9%	20.9%	21%
<b>Blood glucose (mg/dL)</b>	345	-	70-110
<b>PO2(mmHg)</b>	50.8	44.0	80-100
<b>PCo2(mmHg)</b>	-	33.3	35-45
<b>PH</b>	7.34	7.314	7.35-7.45
<b>K<sup>+</sup> (mmol/L)</b>	2.8	-	3.5-5.0
<b>HCo3S(mmol/L)</b>	0.1	17.9	22-28

<b>P50(mmHg)</b>	28.7	29.5	24-28
<b>H<sup>+</sup>(mmol/L)</b>	45.7	48.5	40
<b>Acidosis</b>	+	+	-/+

## Discussion

Hydroxychloroquine is mainly used in rheumatologic disease treatment and malaria prophylaxis [6]. HCQ holds a narrow therapeutic window. The toxic dose is 20 mg/kg since the therapeutic dose is defined as 10 mg/kg [7]. HCQ overdose holds a considerable mortality rate among adults, estimated at 10–30% [8].

Many different drugs for other diseases have been tried out in COVID-19, including HCQ [9]. In vitro studies have suggested that both chloroquine and hydroxychloroquine can inhibit fusion between SARS-CoV-2 and the host cell membrane by increasing the endosomal pH and glycosylation of the cellular angiotensin-converting enzyme-2 receptors. Despite their antiviral activity in some in vitro models, randomized clinical trials have provided no viral load reduction in the respiratory tract in their administration. Thus the COVID-19 treatment guidelines strongly recommend against their use [10]. But still, hydroxychloroquine and chloroquine's off-label use has led to a rise in their poisoning cases all around the world [11].

The most common signs and symptoms of Hydroxychloroquine overdose are drowsiness, nausea/vomiting, abdominal pain, visual/ auditory disturbances, agitation, respiratory/cardiac arrest, and hypokalemia [12]. Some clinical criteria associated with HCQ poisoning fatal outcome include; ingestion of greater than 5 gr, hypotension defined as systolic blood pressure lower than 80 mmHg, QRS prolongation more than 120 ms, ventricular arrhythmia, and blood concentration upper than 8 mg/ml [8].

Recommended treatment for HCQ overdose focuses mainly on good supportive care; Meticulous cardiovascular monitoring along with hemodynamic observation [13]. The intensity of HCQ toxicity is directly related to the level of plasma potassium, thus fluid balance control and intravenous (I.V) Potassium chloride treatment can play an important role [14]. Although no clinical studies support the beneficial use of sodium bicarbonate in improving QRS widening, two studies have successfully used bicarbonate in patients with hydroxychloroquine overdose [15]. These results are in line with our above observations.

In the cases of hypotension, vasopressor therapy like epinephrine should be used. A unique use of diazepam is marked in HCQ overdose cases to treat dysrhythmias, QRS widening, circulatory collapse, and seizures; however, no records have been reported on seizures after an HCQ overdose [16]. Gastric lavage and more effectively activated charcoal can be helpful in gastrointestinal decontamination only if done within the first hour of ingestion. Accordingly, giving an NG charcoal hours after the exposure might not be the best decision in our case. Nevertheless, a meta-analysis study on the activated charcoal on drug exposure showed that the effect of its use could be continued significant when administered up to 4 hours after drug intake [17].

Both hypo- and hyperkalemia are associated with diabetes; insulin deficiency is also involved in the development of hyperkalemia. Recently, emerging evidence suggests the beneficial use of HCQ in diabetic patients, which has led to its approval for the treatment of type 2 diabetes. Therefore, subsequent to the synergic effect of HCQ and blood-glucose-lowering agents, in patients with diabetes and concurrent use of chloroquine/HCQ, hypoglycemia must be thought of [18]. Our patient, a confirmed diabetic with a blood glucose of 345 mg/dl, with a current HCQ overdose, still showed no hypoglycemia. It is probably because he was not under any hypoglycemic medications. However, his condition Required special attention and strict monitoring of blood glucose and potassium level to avoid any complications, which makes our case distinctive from others.

A case report on HCQ overdose associates the severity of the hypokalemia with the acute poisoning cases [19]. In comparison, two other studies reported extreme hypokalemia in patients on chronic hydroxychloroquine therapy [4]. In our case, as the first exposure to the HCQ as an overdose, the patient lacks severe hypokalemic status. Due to a lack of laboratory facilities, urine analysis, and enzyme immunoassay, we could not evaluate the

serum/urine level of HCQ to verify the reliability of his report. Nevertheless, considering his symptoms and the other laboratory test results, it comes to mind that he could be exaggerating about the number of the pills.

Despite the long half-life of HCQ, most studies have reported the early onset of symptoms [3], different from our case in which the patient was hospitalized hours after ingestion of a large amount of the drug, another reason to suspect the accuracy of patient's claims. The patient had an early recovery and a short hospital stay, consistent with other cases [2, 20].

Although we cannot recommend treatment plans only based on a single case, it seems that following the guidelines developed for HCQ poisoning plays a critical role in HCQ overdose case management.

## Outcome

In our case, the patient presented with the typical symptoms of HCQ overdose, including drowsiness, hypotension, and minor hypokalemia with a rapid recovery. We believe, prompt management played a crucial role in surviving a potentially lethal hydroxychloroquine overdose.

## Conclusion

This study indicates that excessive consumption of Hydroxychloroquine can lead to life-threatening symptoms. Due to the possible fatal outcomes of Hydroxychloroquine poisoning and its wide use in treating autoimmune diseases and currently COVID-19, further studies to investigate treatment modalities and Combination therapy would evolve as experience accumulates.

## Statements and Declarations

### Informed consent

Written informed consent from the patient was also obtained.

### Author contributions

All authors contributed to the study's conception and design. Oversight and leadership responsibility for the research was provided by [E.V.M] and [M.H. K]. Data collection was performed by [S.Y. T], and [M. Z]. The first draft of the manuscript was written by [H. S. I], [S. KH], and [S. A] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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