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Pharmacological Management after Administration of High-Dose Aminoquinoline: Case Report

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ABSTRACT

Hydroxychloroquine (HCQ) is approved for treatment of malaria and rheumatic diseases such as systemic lupus erythematous (SLE), rheumatoid arthritis, Q-fever and juvenile idiopathic arthritis. HCQ consider to be safe medication with narrow safety margin. Cardiovascular and cerebrovascular effects may result as from HCQ overdose. It is often fatal due to cardiovascular toxicity. We present a case for a young female who survived after HCQ intoxication with discussion about the possible recommendation for management. The cardiovascular complications were the main symptoms of toxicity that resulted in cardiac failure with atrio-ventricular block, ventricular arrhythmias torsade de points and QT- interval prolongation. The main goal of HCQ intoxication treatment is to prevent the hemodynamic complications. Treatment recommendations are established based on limited clinical experience. The main effective treatment consists of epinephrine, diazepam and mechanical ventilation. Close clinical monitoring and early recognition of toxicity symptoms and immediate withdrawal of HCQ is important approach in management of HCQ toxicity and it is essential for reversibility of cardiomyopathy. In conclusion, HCQ toxicity is not commonly seen in clinical practice, the reported cases in the literature are few. It is considered fatal as it leads to cardiac complications, therefore, effective therapy is important to stabilize the heart functions and minimize the severe complications.

Key words: Case Report; Hydroxychloroquine; Aminoquinoline; HCQ toxicity; Cardiovascular toxicity

INTRODUCTION

Hydroxychloroquine (HCQ) is an aminoquinoline that have similar pharmacokinetic of chloroquine (CQ). It is approved for treatment of malaria and rheumatic diseases such as systemic lupus erythematous (SLE), rheumatoid arthritis, Q-fever and juvenile idiopathic arthritis.[1,2] HCQ consider to be safe medication, but its safety margin is narrow, single dose of 30 mg/kg or higher can be fatal. Cardiovascular effects including hypotension, vasodilation, suppressed myocardial functions, cardiac arrhythmias, and eventual cardiac arrest. Confusion, convulsions, and coma may also result as cerebrovascular effects from HCQ overdose. Dosing is calculated based on patient weight, the standard dose is 200 mg twice daily or 400 mg daily (maximum dose = 6.5 mg/kg/d).[3]

HCQ toxicity is infrequent although it is commonly used in rheumatological disorders, there are limited number of reported cases, and it is often fatal due to cardiovascular toxicity. We present a case for a young female who survived from HCQ intoxication with discussion about the possible recommendation for management.

CASE REPORT

A 22 years old female patient, known to have guttate psoriasis on betamethasone 0.05%/ calcipotriol 0.005% ointment. Presented to emergency department (ER) after one hour from ingestion of 10 tablets of HCQ (200mg per tablet). She experienced three episodes of nausea and vomiting, epigastric discomfort, dizziness, headache, blurred vision and pre-syncope attacks.

In ER, patient was hypotensive, blood pressure (BP) reached 85/59 with generalized chest pain, dull ache, dyspnea and fatigue. Two liters of intravenous normal saline (NaCl 0.9%) bolus infusion was given followed by maintenance infusion 80ml/hour in addition to a single dose of activated charcoal 50g orally. There was no history of seizure, limb weakness orthopnea, palpitation, wheezeing, cough or urinary symptoms. The patient was admitted under general internal medicine team as a case of HCQ overdose. Intensive care unit (ICU) was consulted regarding low BP, they recommended to continue on maintenance intravenous fluid (IVF). Basic screen, bone panel, electrocardiography (ECG) every 6 hours, troponin- I and lactic acid every 8 hours and echocardiography (ECHO) were ordered. Cardiology team was consulted, ECG showed QT wave prolongation (480/507) and QRS 108, ECHO showed suspicion of secundum isolated atrial septal defects (ASD) versus patent foramen ovale (PFO), which investigated later by trans-esophageal ECHO and prove to be small PFO with mild mitral regurgitation, mild to moderate tricuspid regurgitation and mild pulmonic valvular regurgitation. Psychiatric team was consulted, their impression was self-harm behavior with mild to moderate suicidal risk for daily follow up and monitoring.

In the following day, patient was clinically and vitally stable, tolerating orally, no vomiting or loss of appetite. Same management was completed by internal medicine team to continue on intravenous hydration, ECG monitoring, basic screen and bone panel every 6 hours, troponin- I and lactic acid every 8 hours and liver functions test with close observation for any visual changes, and to consult ophthalmology team urgently if happened. Psychiatry team recommended to follow up the patient through outpatient clinic and no psychotropic treatment was needed. Patient

was kept for one more day under observation then discharged from hospital, to be returned to cardiology clinic after 7 days and psychiatric clinic after 4 days.

Upon discharge, safety precaution was provided to the patient's family and advised to bring the patient to ER in case of self-harm intent and to observe her behavior. Patient was educated about other coping strategies to deal with stressful events, and was informed that she can come to ER at any time if she has suicidal thoughts that are uncontrollable.

DISCUSSION

HCQ is an aminoquinoline that have similar pharmacokinetic of chloroquine (CQ). Both are indicated for treatment of malaria. HCQ known to have less toxic effect than CQ. Both can cause blockade in sodium and potassium channels which proposed the mechanism of cardiovascular collapse. The onset of toxicity is commonly rapid, it can happened within 30 minutes, death can occur within one to three hours from cardiac arrest.[4] The clinical criteria that associated with fatal outcomes included ingestion of more than 5 g of HCQ that leads to hypotension (systolic BP <80 mmHg), prolongation of the QRS interval (>120ms), ventricular dysrhythmias and HCQ blood level >8 mg/ml.[5] Dosing are expressed as HCQ- sulfate salt. HCQ- sulfate 200mg is equivalent to HCQ-base 155mg. The standard recommended dose is 200 to 400 mg daily as once daily dose or in two divided doses, not exceed 5mg/kg/day of actual body weight to avoid toxicity symptoms.[2] An article review done by Jaeger. A, et al, and published in 1987, it found that the toxic dose of HCQ is 20 mg/kg, while the fatal dose is 30 mg/kg.[6] Survival after ingestion of more than 20 grams has been reported by Yanturali S, et al.[7] Due to few number of reported cases, fatal or toxic dose in humans has not been well established.

HCQ intoxication is rarely occur but it is often fatal mainly due to cardiovascular toxicity. There are limited number of reported cases in Middle East. This case is the first case reported in Saudi Arabia. The cardiovascular complications was the main symptoms of toxicity due to HCQ overdose that resulted in cardiac failure with atrio-ventricular block, ventricular arrhythmias torsade de points and QT- interval prolongation due to sodium channel blocking activity as same as class 1a antiarrhythmic drugs. The cardiovascular collapse mainly results from negative inotropic effects and peripheral vasodilation which lead to hypotension, in addition to hypokalemia which occur mainly due to increased intracellular distribution.[2,8,9] ECG is an essential test for assessment of sodium and potassium channels blockade in HCQ overdose cases. The reports that evaluating the incidence of ECG abnormalities due to HCQ overdose are limited. A retrospective study done by regional poison control center showed that 64% of patients in healthcare facility who are treated with HCQ had recorded ECG abnormalities. QRS or QTc prolongation was noted in 13% and 17% of patients, respectively. The QTc was greater than 500 ms in 18% of patients.[10] Our patient had both QRS and QT interval prolongation that resolved after 24 and 48 hours, respectively. American Heart Association recommended to monitor for cardiac sign and symptoms, discontinue treatment promptly if cardiomyopathy sign and symptoms occur.[6]

HCQ may cause irreversible retinopathy which usually associated with high daily dosing and longer duration of more than 5 years of treatment.[2] American Academy of Ophthalmology recommended a maximum dose of 5mg/kg/day using actual body weight with baseline retinal screening and annual screening starting after 5 years of treatment or earlier if risk factors are available. Ophthalmological screening is recommended in those cases to rule out irreversible retinal toxicity.[11]

The main goal of HCQ intoxication treatment is to prevent the hemodynamic complications. Treatment recommendations are established based on limited clinical experience. Most reported cases commented that, the management of HCQ intoxication is demonstrated upon the management of CQ intoxication. [Table 1]. The main effective treatment consists of epinephrine, diazepam and mechanical ventilation. [12,13] Hemodynamic support including intubation and mechanical ventilation are recommended if severe symptoms accured. Gastric decontamination by gastric lavage and administration of activated charcoal are suggested during the first hour after HCQ overdose ingestion.[14,15,16] One study done by Kivisto KT, et al, published in 1993, showed that activated charcoal prevented absorption of 95% - 99% of the ingested CQ when given within 5 minutes.[17] HCQ as CQ have very large volume of distribution and rapidly distributed intra-cellularly. Close clinical monitoring and early recognition of toxicity symptoms and immediate withdrawal of HCQ is important approach in management of HCQ toxicity and it is essential for reversibility of cardiomyopathy. Regular screening with ECG and ECHO to identify conduction system diseases, ventricular morphology or functional changes are important in patients receiving HCQ therapy.[18]

The conduction abnormalities like QRS prolongation can be treated by alkalization of blood by sodium bicarbonate, this treatment modality is controversial as alkalanization of blood will exacerbate hypokalemia. Most of HCQ toxicity cases developed hypokalemia, which is mainly due to increased intracellular distribution, and this will increase the risk of arrhythmia. The treatment of hypokalemia doesn't require aggressive potassium replacement as depletion is not excessive.[19] HCQ is highly lipophilic substance, therefor, intravenous lipid emulsion has been used successfully and it's one of the possible effective treatment in HCQ toxicity cases.[20]

In conclusion, HCQ toxicity is not commonly seen in clinical practice, the reported cases in the literature are few.
It is considered fatal as it leads to cardiac complications, therefore, effective therapy is important to stabilize the heart functions and minimize the severe complications.

Table 1: Treatment of Chloroquine intoxication:

Symptoms	Therapeutic management
Loss of consciousness	Hemodynamic support including intubation and mechanical ventilation, if acidaemia occurs, administer sodium bicarbonate 1 – 2 mmol/kg intravenously (IV) to prevent further toxicity while intubation process. The goal is to maintain a narrow QRS (<100ms) and pH >7.45
Arrhythmias	Sodium bicarbonate 1 – 2 mmol/kg IV to maintain a narrow QRS (<100ms) and a pH

	>7.55, repeat doses as required
Hypotension	Fluid resuscitation plus sodium bicarbonate. In case of resistance, vasopressors, noradrenaline or adrenaline should be used. Noradrenaline: 0.15mg/kg in 50ml dextrose 5% at rate 0.05 – 0.5 mcg/kg/min Adrenaline: 0.15mg/kg in 50ml dextrose 5% at rate 0.05 – 0.5 mcg/kg/min
Seizures	IV benzodiazepines every 5 minutes to effect, check for dysrhythmia Lorazepam: 0.1mg/kg (maximum dose: 4mg) Diazepam: 0.15mg/kg (maximum dose: 10mg) Midazolam: 0.2mg/kg (maximum dose: 10mg)
Renal replacement therapy	No role for hemodialysis, peritoneal dialysis or hemo-perfusion

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