Original Article

Hydroxychloroquine from Safety to Death: Case Series

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ABSTRACT

Introduction: Hydroxychloroquine (HCQ) has been used to treat many autoimmune diseases. Early in the era of the COVID-19 pandemic, HCQ was an essential arm in its management. Later, updated evidence had recommendations against its use in cases of COVID-19; however, its abundance in homes raised the risk of its misuse. **Aim**: This study aimed to describe patients with acute hydroxychloroquine toxicity who presented to the Poison Control Centre Ain Shams at University Hospitals (PCC-ASUH) including the management and the outcomes. **Method:** Medical records of patients with acute HCQ toxicity presented to PCC-ASUH from the beginning of December 2020 to the end of December 2021 were reviewed. Patients' demographics, clinical parameters, laboratory investigations, electrocardiography (ECG) findings, treatment were presented and interpreted. **Results**: Eleven patients of acute HCQ poisoning during the study duration; ten survived, and one died. The most common presenting symptoms were vomiting and hypotension. The ECG abnormalities observed in two patients were wide QRS complexes and prolonged QT intervals. Patients were treated symptomatically. Hypotension was initially treated by intravenous (IV) fluids. Vasopressors were used in three patients. **Conclusion**: Although the incidence of acute HCQ toxicity is low, it can be fatal. The treatment is based mainly on early IV fluid resuscitation. The vasopressors were added to patients after the failure of fluid therapy. Patients required meticulous ECG and serum electrolytes monitoring, particularly serum Potassium (K) levels. **Recommendations**: The study recommended the early use of epinephrine as a vasopressor after the failure of IV fluid therapy to correct the hypotension in HCQ-poisoned patients. Intravenous diazepam should be considered with endotracheal intubation (ETT) and mechanical ventilation (MV) in the treatment of the severe cases.

KEYWORDS: Hydroxychloroquine; COVID-19 Treatment; SLE Treatment; High Dose Diazepam.

I. INTRODUCTION:

Hydroxychloroquine (HCQ); one of 4-aminoquinoline drugs, is currently used to treat autoimmune illnesses such as systemic lupus erythematosus (SLE), rheumatoid arthritis, and others (Watson et al., 2020).

According to anecdotal reports and preliminary data in early 2020, the prescription of HCQ and chloroquine for reducing viral loads and manifestations in patients with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infections has increased (Porta et al., 2020).

With the release of the initial reports indicating the efficacy of 4-aminoquinolines in the prevention and treatment of COVID-19 infection, cases of acute HCQ toxicity started to be reported in many countries, particularly with the media attention on their role in this issue **(**Lebin & LeSaint, 2020; Schilling & White, 2021).

Aminoquinoline drugs, including HCQ have recorded significant toxicity in both therapeutic use and overdose settings (Porta et al., 2020).

The aim of this case series was to describe hydroxychloroquine poisoning cases presented to the Poison Control Centre at Ain Shams University Hospitals (PCC-ASUH) including the management and the outcome in the period from the beginning of December 2020 to the end of December 2021.

II. PATIENTS AND METHODS

Study design: A retrospective case series was conducted.

Study setting and time: the study was carried out at the PCC-ASUH from the beginning of December 2020 to the end of December 2021.

Study population: Patients admitted to the PCC-ASUH with acute HCQ toxicity.

Study procedure and data collection tool: Medical records of patients with acute HCQ toxicity at the PCC-ASUH in previously determined duration were retrieved and reviewed. Demographics, clinical manifestations, laboratory investigations, electrocardiogram (ECG) findings, and the outcome were extracted through using extraction sheets. Patients were classified according to the Poisoning Severity Score (PSS); PSS (0) included asymptomatic patients, PSS (1) (patients with minor presentations), PSS (2), (patients with moderate presentations), PSS (3) (patients with severe manifestations), and PSS (4) (fatal: included dead patients). The PSS should involve the overall clinical course and should be applied according to the most severe symptomatology either subjective symptoms or objective signs. Therefore it is normally a retrospective process. Severe cases resulting in death are graded separately in the score as PSS 4 (fatal) to allow a more accurate presentation of data (World Health Organization (WHO), 2007).

Data management and analysis: Data were analyzed by SPSS package (Version 20). Quantitative data were presented as mean and standard deviation (SD), while, qualitative data were summarized as frequencies (n) and percentage (%).

Ethical considerations: the study was approved by the Research Ethics Committee (FMASU REC) at Faculty of Medicine Ain-Shams University (Approval Number: R130/1023). The gathered data were used anonymously to maintain confidentiality.

III. RESULTS

According to the annual reports from the PCC-ASUH, no cases of acute HCQ toxicity were reported before 2020. With the increase of HCQ use during the COVID-19 pandemic, cases of acute poisoning have started to emerge.

The cases started to present in December 2020. The PCC-ASUH received eleven patients with acute HCQ toxicity during the study period from the beginning of December 2020 to the end of December 2021. One patient presented in December 2020, and the rest of the patients presented in 2021. The patients were classified according to the outcome into ten survivors (improved and were discharged from the hospital) and one non-survivor (died).

According to the poisoning severity score (PSS), the cases were classified as asymptomatic (PSS 0) (1 patient), minor (PSS 1) 6 patients, moderate (PSS 2) 2 patients, severe (PSS 3) one patient and one case was classified as PSS 4 (fatal) (figure 1).

Table (1) summarizes the ten survivors' demographic information, clinical features, and management. The mean age was 23 (± 6) years. Most of the patients were females (n= 9, 90%). All patients used HCQ in suicidal attempts in amounts ranging between 6 and 40 tablets. The mean delay time until their hospital arrival was 3.3 (± 1.6) hours. The most common presenting symptom was vomiting (n=7, 70%). Other findings were hypotension (n=5, 50%), hypokalemia (n=3, 30%), leukocytosis (n=3, 30%), and arrhythmia (n=2, 20%).

At the emergency room (ER), all patients in the current study received activated charcoal. All hypotensive survivors in the present study responded to fluid resuscitation except for two cases, one patient was PSS 2 (moderate toxicity), and the other was PSS 3 (severe), who required vasopressor. Epinephrine (vasopressor) was used immediately after the failure of fluid therapy without delay. The severely poisoned patient was a 39 years old female who arrived at the ER 4 hours after attempting suicide by taking 40 hydroxychloroquine tablets. The patient presented with vomiting and hypotension (90/60 mmHg). Electrocardiogram showed wide QRS complexes (120 msec), and prolonged QTc intervals (671 msec) (corrected according to Bazett's formula). The laboratory findings revealed hypokalemia (serum K^+ 2.3 mEq/l), slightly elevated lactate level (4 mg/dl), and

leukocytosis (total leukocytic count (TLC) 14×103/mm3). Other laboratory parameters were within normal ranges.

The patient received fluid resuscitation (20 ml/kg) and potassium replacement by KCl solution (10mEq/hr). Intravenous sodium bicarbonate ($NaHCO_3$) 100 mEq of 8.4% solution was given to correct the wide QRS complexes shown in the ECG. The Epinephrine infusion was started (0.25 mcg/kg/min) and titrated to correct the hypotension after the failure of the fluid therapy.

The patient did not respond to the Epinephrine (80 mic/min), so a high dosage of diazepam was added (4 ampules of 15 mg midazolam) over 30 minutes, and the patient was intubated and mechanically ventilated. The patient improved after the first bolus of diazepam infusion. The hypotension was corrected. Four days later, the patient was improved and ECG corrected and the patient was discharged from the hospital.

The non-survived patient was the first case presented with acute HCQ toxicity during the COVID-19 pandemic. She was a 28-year-old female patient who arrived at the ER 4 hours after suicidal ingestion of 60 tablets of Plaquenil (hydroxychloroquine 200 mg), it was her treatment for SLE, and she was kept on one tablet per day. The patient complained of vomiting and diarrhea. She was given activated charcoal before being admitted to the hospital.

The patient was conscious and alert (Glasgow Coma Scale (GCS) 15/15), with a heart rate of 58/minute (min), regular rhythm, a systolic blood pressure of 60mmHg, a respiratory rate of 26 breath/min, and a body temperature of 37^{o} C axillary. The rest of the physical examination was unremarkable.

A wide pore cannula was placed, a blood sample was collected, and an intravenous fluid (20ml/kg normal saline) was started before being admitted to the intensive care unit (ICU) for further evaluation of the case. After ICU admission, the ICU physician inserted the central venous catheter. The systolic blood pressure remained low (60 mmHg) without response to fluid resuscitation, so a vasopressor (norepinephrine) was added and titrated to 50 mcg/min in addition to intravenous fluids, proton pump inhibitors, and antiemetic. Electrocardiogram revealed a wide QRS complex (120 msec) and a prolonged corrected QT (Qtc) interval (680 msec corrected according to the Bazett formula) (Figure 2). NaHCO3 (100 mEq) and magnesium sulfate (MgSO4) 2mg were given.

Laboratory tests were done on admission (table 2). The patient had elevated

serum creatinine (2.8 mg/dl), elevated liver enzymes (ALT and AST were 202 and 195 IU/l, respectively), and high blood lactate (5.2 mg/dl). No other abnormalities were observed in the laboratory investigations at hospital admission.

After Five hours, the patient suddenly developed cardiac arrest, so the intensive care team started cardiopulmonary resuscitation (CPR) and direct current defibrillation (DC) shock. They also add Antiarrhythmic drugs (lidocaine) to control the ventricular tachycardia (VT) (Figure 3).

The patient was recovered and mechanically ventilated. The physician started an epinephrine infusion (40mcg/min) to control shock and replaced Potassium (10mEq/hr) with Potassium chloride (KCl) solution to correct the hypokalemia (3mEq/l). Twelve hours later, the patient developed torsade de point and died despite IV MgSO4 therapy and conventional advanced cardiac life support (ACLS) procedures.

Table 1. Demographic, intoxication, clinical findings and the management of ten Survived hydroxychloroquine cases in the current study.

	N	**%**
Demographic data		
Age *[Mean ± SD (min – max)]*	23 ± 6 (18 – 39)	
Gender		
Female	9	90.0%
Male	1	10.0%
Intoxication data and Clinical finding		
Delay (hr) *[Mean ± SD (min – max)]*	3.3 ± 1.6 (2 – 7)	
No. of Tablets *[Mean ± SD (min – max)]*	16.9 ± 10.4 (6 – 40)	
Blood pressure		
Low	5	50.0%
High	5	50.0%
Pulse rate (beats / minute) *[Mean ± SD (min – max)]*	84 ± 8 (70 – 100)	
GIT symptoms		
No symptoms	3	30.0%
Vomiting only	5	50.0%
Vomiting with diarrhea or colic	2	20.0%
ECG findings		
No	8	80.0%
Yes	2	20.0%
Leukocytosis		
No	7	70.0%
Yes	3	30.0%
Hypokalemia		
No	7	70.0%
Yes	3	30.0%

Poisoning Severity Score (PSS)		
None	1	10.0%
Minor	6	60.0%
Moderate	2	20.0%
Severe	1	10.0%
Case Management		
IV fluid/K		
Fluids	7	70.0%
Fluids with k	3	30.0%
Epinephrine		
No	8	80.0%
Yes	2	20.0%
Diazepam		
No	9	90.0%
Yes	1	10.0%
NaHCO3		
No	8	80.0%
Yes	2	20.0%
Hospital stays (days) *[Mean ± SD (min – max)]*	2 ± 1 (1 – 4)	

- N: number SD: standard deviation ECG: Electrocardiogram

Table 2. Laboratory Investigation results on admission of the non-survived hydroxychloroquine case in the current study.

Laboratory investigation	On admission
RBS (mg/dl)	75
BUN (mg/dl)	22
Serum creatinine (mg/dl)	2.8
Serum ALT (IU/l)	195
Serum AST (IU/l)	202
Na (mEq/l)	144
K (mEq/l)	3.6
pH	7.34
PCO_2 (mmHg)	43
HCO_3 (mEq/l)	23.3
Serum lactate (mg/dl)	5.2
T.CPK (mg/dl)	197
Hb (g/dl)	13.3
PLT/mm^3	298
TLC/mm^3	9

- ***Abbreviations*** *(RBS: random blood sugar, BUN: blood urea nitrogen, ALT: alanine transaminase, AST: aspartate transaminase, pH: negative log of hydrogen ion, PCO_2: Partial pressure of carbon dioxide, T.CPK: creatinine phosphokinase, Hb: hemoglobin, PLT: platelet count, and TLC: total leukocyte count).*

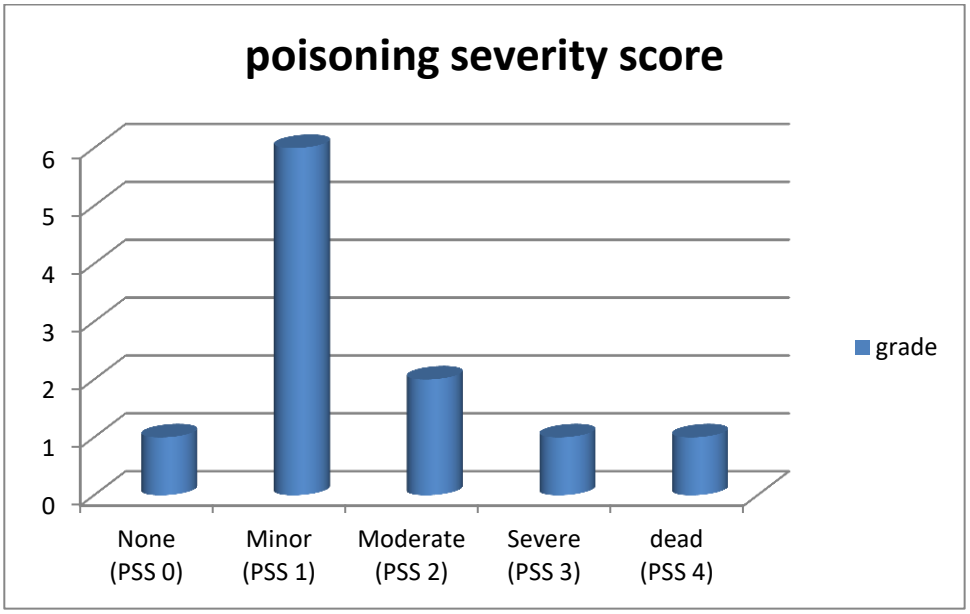

Figure (1) Bar chart shows the severity of HCQ intoxicated cases in the current study.

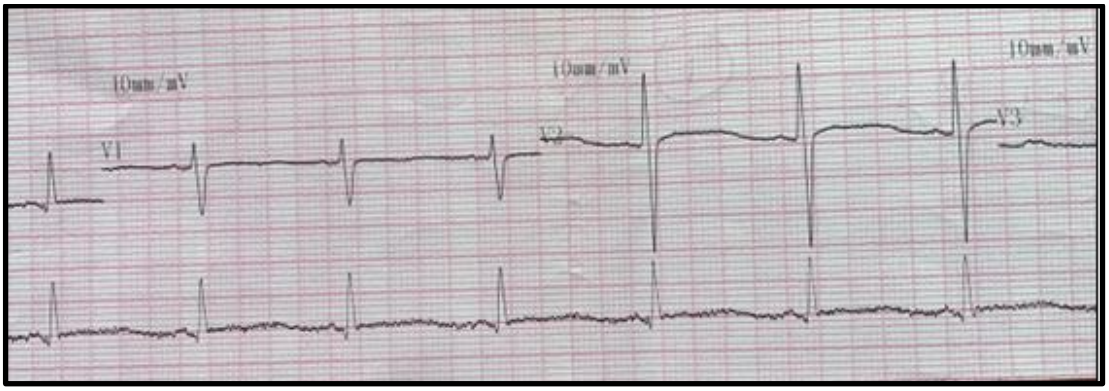

Figure (2): ECG of the non-survived HCQ toxicity case shortly after ICU admission showed wide QRS and prolonged QT interval

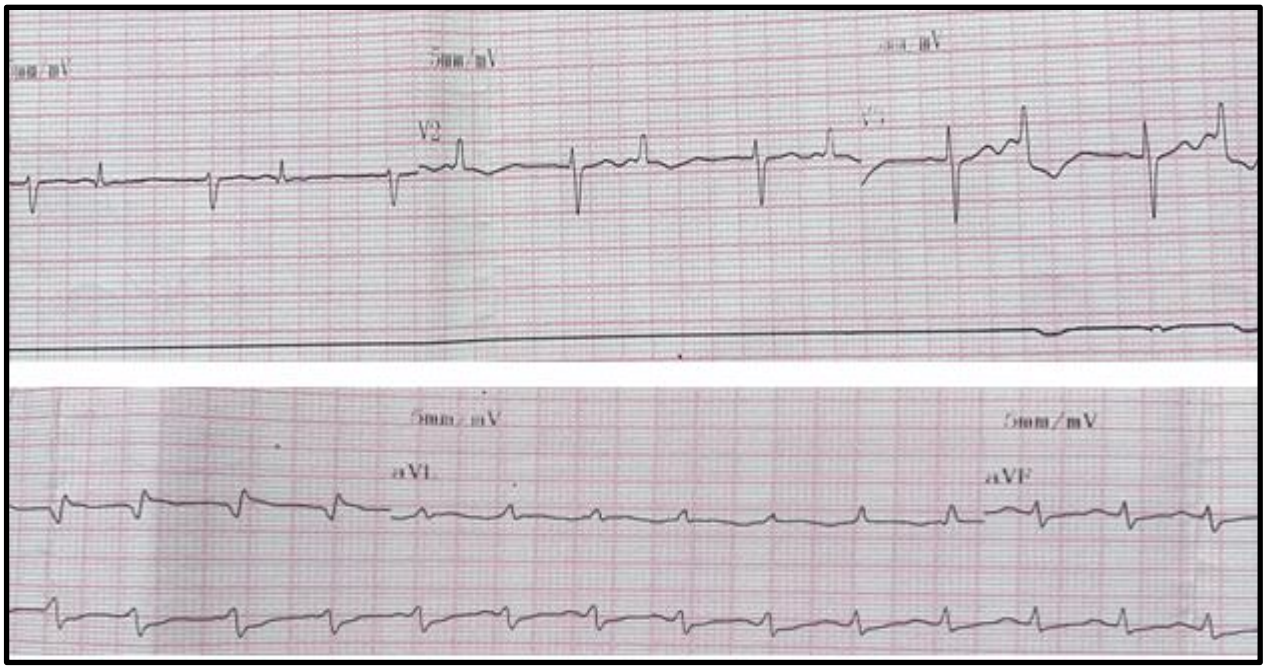

Figure (3): ECG of the non-survived case shows ventricular tachycardia 5 hours after ICU admission

IV. DISCUSSION

Chloroquine and hydroxychloroquine are closely related 4-aminoquinoline drugs. Hydroxychloroquine (HCQ) is a chloroquine derivative and has the same medical effects but with fewer toxic effects. Based on its immunity regulation properties, anticoagulation activity, and amelioration of inflammation, HCQ has been used in the treatment of SLE and recently in the treatment of COVID-19 infection (Chen et al., 2020& Porta et al., 2020).

Although its use has been discouraged in the COVID-19 cases based on updated data, it is still available in homes due to its publicity early in the pandemic (Chai et al., 2020). That led to the use of hydroxychloroquine in suicide attempts, as shown in the present study.

Most of the patients in the current series arrived hospital within 4 hours after exposure, and this could be related to the rapid and complete absorption of hydroxychloroquine from the gastrointestinal tract (GIT) with whole blood levels peaked 1–3 hours after ingestion, resulting in rapid onset of severe symptoms and increased risk of death in severe poisoning (Lebin and LeSaint, 2020).

In the present study, vomiting was observed in most of the patients. It is reported

that HCQ causes nausea and vomiting due to direct gastric irritation besides stimulation of emetic centers in the brain, and this is usually transient following acute intoxication (Porta et al., 2020).

Hypokalemia was one of the observed finding in the current study. Hypokalemia is likely due to potassium channel blockage causing increased intracellular potassium (Stevenson et al., 2020). The extent of hypokalemia is an indicator of the severity of toxicity. The treatment of resistant hypokalemia is often one of the most common features following acute HCQ poisoning and is usually related to cardiac manifestations, including arrhythmias (Porta et al., 2020).

The first experience with acute HCQ patients in the PCC-ASUH during the COVID-19 pandemic started at the end of 2020. The patient presented with severe cardiovascular toxicity (resistant hypotension and ECG changes progressed to VT). Cardiovascular complications are among the leading causes of death in acute HCQ toxicity.

Hydroxychloroquine causes cardiovascular toxicity by direct suppression of cardiac voltage-dependent sodium and potassium channels. This effect causes QRS widening and prolongation of the QT intervals. Direct cardiac depression causes hypotension and cardiogenic shock rather than its peripheral vasodilator effect (Chai et al., 2020 & Stevenson et al., 2020).

Norepinephrine was used as a vasopressor in that patient after the failure of fluid therapy. Epinephrine and mechanical ventilation were considered after recovery from cardiac arrest. The poor outcome for that patient encouraged a change in the management strategy of acute HCQ toxicity patients presented later on.

The updated treatment protocol has included aggressive supportive treatment using early fluid resuscitation by 10-20 ml/kg normal saline over 20 minutes if systolic blood pressure is less than 90 mmHg after airway and breathing stabilization. Correct hypoglycemia if present. Epinephrine is the first choice vasopressor for resistant hypotension (after the failure of fluid therapy) in a dose of 0.25 mcg/kg/min increased by 0.25 mcg/kg/min until adequate blood pressure is obtained. Early endotracheal intubation (ETT) and mechanical ventilation (MV) should be considered. High-dose diazepam (1-2mg/kg) over 30 minutes is used after ETT and MV to relieve cardio-toxicity and resistant hypotension. This treatment strategy is consistent with the treatment addressed by Porta et al., (2020).

Vasopressors counteract the vasodilation and myocardial depressant effect of HCQ by acting as a potent inotrope (reduces the intra-ventricular conduction time) and vasoconstrictor to inhibit the depressive cardiovascular effects of HCQ. Diazepam has been recommended to treat severe acute HCQ poisoning as adjunctive therapy in resistant cases. The effects of diazepam can be mediated via a central antagonist effect, an anticonvulsant effect, an electrophysiologic impact that prevents arrhythmia, a pharmacokinetic interaction with HCQ, or a reduction in HCQ-induced vasodilatation (Bakhsh, 2020).

By application of the updated treatment strategy for acute HCQ toxicity, the rest of the patients in the current study gave good responses with better outcomes.

Most of the patients responded to the initial fluid resuscitation. The same results were in the previous study by Lebin and LeSaint, (2020) which reported that, the stabilization of the airway, respiration, and circulation, as well as the initiation of fluid resuscitation with ongoing cardiovascular monitoring, are considered the cornerstone treatment in acute HCQ poisoning.

A high dose of diazepam, ETT, and MV were added to treat the severely poisoned patient in this series after failure of intravenous fluid and a high dose of vasopressor (epinephrine) to correct the hypotension. The patient improved and recovered, although the severity of toxicity.

After stabilization, decontamination measures including gastric lavage and activated charcoal could be used as early as within the first hour due to its rapid and complete absorption from GIT (Lebin and LeSaint, 2020). Hydroxychloroquine has a high volume of distribution and high protein binding, which makes the modalities of enhanced elimination useless (Porta et al., 2020).

Although the lethal or toxic dose of HCQ in adults has not yet been determined, and the treatment should be based on observed toxicity manifestations (Porta et al., 2020), it was observed in the current study, that the dose was related to the severity of toxicity as the severe and the fatal cases consumed higher doses (40 and 60 tablets respectively) than the other patients.

V. CONCLUSION

Although hydroxychloroquine toxicity instances are not frequent, the poisoning with this drug have increased, particularly since the COVID-19 pandemic and the increase in its use. In the current study, the treatment of the patients was mainly supportive. The treatment included fluid replacement therapy to correct

the hypotension which is one of the most recorded signs of HCQ toxicity. Vasopressors were used to treat patients with resistant hypotension. High-dose diazepam, ETT, and mechanical ventilation were used to treat the severely poisoned patient. Follow-up and correction of hypokalemia should be initiated as soon as possible. A wide QRS complexes and prolonged QTc intervals were observed with increased poisoning severity.

VI. RECOMMENDATIONS

The study recommended early use of fluid resuscitation for hypotensive patients with acute HCQ toxicity. Epinephrine was the first choice vasopressor to be used early after the failure of fluid therapy to treat resistant hypotension. High-dose diazepam, ETT, and MV should be considered early in patients with acute HCQ with resistant cardiotoxicity. Follow up of the ECG and serum K-level is very important as both are related to the severity of HCQ poisoning.

VII. CONFLICT OF INTEREST

The authors state that they have no conflict of interest.

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هيدروكسيكلوروكين من الأمان إلى الموت: سلسلة حالات

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الملخص العربى

المقدمة: تم استخدام الهيدروكسيكلوروكين في علاج العديد من أمراض المناعة الذاتية. كما كان الهيدروكسيكلوروكوين, في وقت مبكر من جائحة كورونا ، ذراعًا أساسيًا في العلاج. في وقت لاحق ، ولكن الأدلة المحدثة أعطت توصيات ضد استخدامه في حالات كورونا ؛ ومع ذلك ، فإن توفره في المنازل زادت من مخاطر إساءة استخدامه. ***الهدف***: تهدف هذه الدراسة إلى وصف مرضى تسمم الهيدروكسيكلوروكين الحاد الذين أستقبلهم مركز علاج التسمم بمستشفيات جامعة عين شمس متضمنا العلاج ونتائج التسمم . ***طريقة البحث***: تمت مراجعة السجلات الطبية لمرضى التسمم الحاد بعقار الهيدروكسيكلوروكوين الذين تم حجزهم بمركز علاج التسمم بمستشفيات جامعة عين شمس عام من بداية ديسمبر ٢٠٢٠ إلى نهاية ديسمبر ٢٠٢١ حيث تم عرض و تحليل البيانات الديموغرافية للمرضى والمعايير السريرية والفحوصات ونتائج تخطيط القلب والعلاج. ***النتائج***: خلال فترة الدراسة تم حجز إحدى عشر مريضا بالتسمم الحاد لعقار الهيدروكسيكلوروكوين ؛ نجا منهم عشرة ومات مريض واحد. كانت الأعراض الأكثر شيوعًا هي القيء وانخفاض ضغط الدم. ولقد لوحظ تغيرات فى رسم القلب فى أثنان من المرضى وكانت على هيئة زيادة فى وقت مركب QRS وفترات QT انخفاض ضغط الدم. تم علاج المرضى في المقام الأول حسب الاعراض. تم علاج . الدم في البداية عن طريق تعويض السوائل,و تم استخدام ضاغطات الأوعية فى ثلاث حالات و قد ساعد الاستخدام المبكر للإيبنفرين بعد فشل تعويض السوائل وكذلك إستخدام جرعة عالية من الديازيبام مع تركيب انبوبة التهوية والوضع على جهاز فى تحسن الحالة التى كانت تعانى من التسمم الشديد. ***الخلاصة***: على الرغم من أن نسبة حدوث تسمم التنفس الصناعى الهيدروكسيكلوروكين الحادة منخفضة ، إلا أنها قد تكون مميت و.يعتمد العلاج بشكل أساسي على الإنعاش المبكر باستخدام السوائل الوريدية ثم إضافة الادوية القابضة للاوعية الدموية بعد فشل السوائل كما ان المرضى احتاجوا إلى مراقبة دقيقة لتخطيط القلب ومراقبة الاملاح في الدم ، وخاصة مستويات البوتاسيوم. ***التوصيات***: اوصت الدراسة بالاستخدام المبكر للبينفرين كقابض لعلاج انخفاض ضغط الدم فى مرضى تسمم الهيدروكسيكلوروكين كما يجب أخذ للاوعية الدموية بعد فشل السوائل الوريدية الديازيبام فى الاعتبار مع تركيب أنبوبة التهوية بالقصبة الهوائية والتنفس الصناعى فى علاج الحالات شديدة التسمم.