CHLOROQUINE OVERDOSE

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ABSTRACT

Chloroquine, a well-known anti-malarial drug may be lethal when ingested in large amount. We report the case of a 45 year-old patient who ingested 10 g of chloroquine in a suicidal attempt, 3 h prior to presentation. Despite aggressive management, the patient died on the third day. The ingested dose (> 4 g), the QRS duration (> 0.10 sec), and the onset of hypotension (systolic blood pressure < 100 mmHg) are the established prognosticators. The delay in management, the blood chloroquine concentration on admission, and the onset of cardiovascular complications also influence the final outcome. The treatment consists in tracheal intubation, mechanical ventilation, epinephrine and diazepam in the presence of any bad prognostic factor as well as 8.4% sodium bicarbonate in case of QRS complex enlargement on EKG. The chloroquine is not dialyzable nor hemofiltrated. extracorporeal membrane oxygenation (ECMO) might be helpful in the most severe case refractory to the pharmacological treatments.

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INTRODUCTION

Chloroquine has always been used as a treatment and prevention for malaria infection. In case of massive ingestion, intoxication can be harmful if not lethal. The first cases of chloroquine intoxication were reported in the literature in 1978 [1]. Additionally, there are few case-series from Africa including women who ingested higher dose as abortive measures [2]. In France, chloroquine overdose remains uncommon even though in the 80s, the number has increased following the publication of a book "suicide, instruction" which was rapidly withdrawn from publication.

Chloroquine overdose has a fast onset (1-3 hours) and high mortality (10% above 4 g). Being an over-the-counter medication (in several countries and in the past in France) and sold on internet and some countries in boxes of 100 tablets of 100 mg made it easy to ingest a lethal dose. Conventional therapy did improve prognosis of the patient. However mortality is still elevated with severe overdose, hence triggering development of new unconventional therapies.

CASE REPORT

We report the case of a 45-year-old man with major depression, status post mitral valve replacement treated with fluindione (Previscan ®) who called the prehospital emergency services after the ingestion three hours prior of 100 tablets of 100 mg of chloroquine. A medical team was directed to his home. On arrival the patient was lying down with a Glasgow coma scale (GCS) of 11 (eye opening = 3, verbal response = 4 motor response = 4).

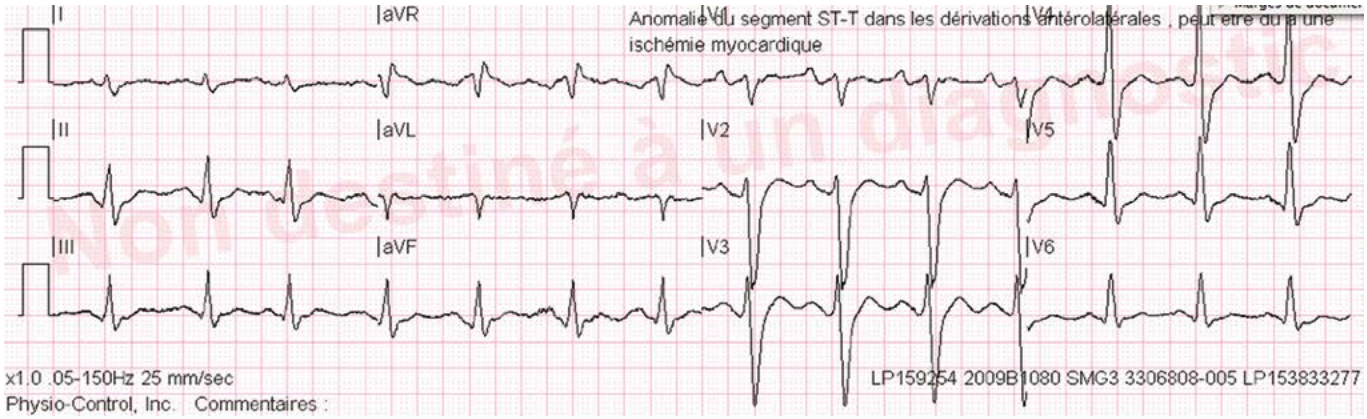

Figure 1: EKG on arrival: widening of QRS and prolonged QT interval

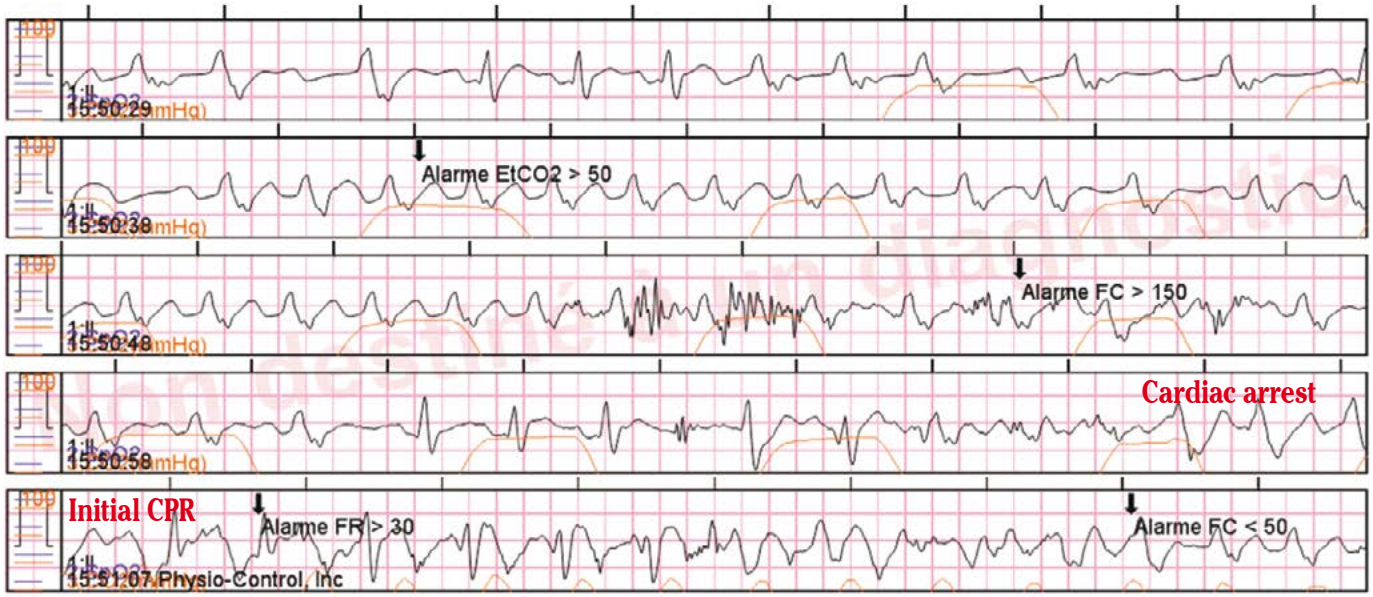

Figure 2: EKG after intubation with pulseless electrical actitivity

His pupils were dilated but reactive and symmetrical. His blood pressure was 77/52 mmHg, his heart rate 86 bpm and his oxygen saturation 80% on room air. The patient was gasping. EKG showed a sinus rhythm with widened QRS at 120 ms **(Figure 1)**.

After receiving a bolus of 250 mL of colloid solution and 250 mL of bicarb 8.4% and 1 mg/h of epinephrine, the patient was intubated using a rapid sequence intubation (etomidate / succinylcholine). Rapidly, he received diazepam 2 mg/kg over 30 min. Two minutes after the intubation, the patient presented a cardiac arrest following a re-widening of his QRS complex with a pulseless electrical activity **(Figure 2)**.

Cardiopulmonary resuscitation was initiated allowing to rapidly regain a pulse and electrical activity after 7 min of chest compression and 2 mg of epinephrine. The heart rate was 145 bpm with widened QRS complexes. BP was 170/120 mmHg and saturation 96%. An automatic cardiac massage device was placed in anticipation of another cardiac arrest. Another bolus of 250 mL 8.4% bicarb was given in addition of 2 g of potassium and 2 mg/h of epinephrine was needed to maintain hemodynamic support. The patient was ventilated and sedated using 4 mg/kg/day of diazepam and sufentanil 5 μg/h and transported by the medical team to the Medical and Toxicological Intensive Care Unit (ICU) of Lariboisière Hospital with 4 mg/h of epinephrine. On arrival, his blood pressure was 85/58 mmHg and his EKG showed persisting wide complex tachycardia with a rate of 150 bpm. Blood tests on arrival showed blood lactate of 8.3 mmol/L and chloroquine level of 22 mg/L. Extracorporeal membrane oxygenation (ECMO) was initiated due to mixed cardiogenic and vasogenic shock refractory to epinephrine, norepinephrine, dopamine and glypressine. In the next 12 h, he presented ventricular tachycardia reverted with electric shock. EEG showed non-convulsive seizure requiring additional epileptic treatment with valproic acid. However, the patient developed severe multi-organ failure including lactic acidosis (33 mmol/L) despite prolonged continuous veno-venous hemodialysis. Despite aggressive resuscitation, the patient died on the third day.

DISCUSSION

Chloroquine intoxication is particularly frequent in Africa. One case series accomplished in Senegal described 49 cases from 1998 till 2003 with 78% cases of women with a mean age of 22 years and 33% cases attributed to abortion attempts. Time from self-ingestion to hospitalization was 4 hours and mortality 6% [2].

Prehospitalzation	Hospitalization
Ingested dose > 3 g Blood Pressure < 100 mmHg QRS complex > 0.100 s Arrhythmias or conduction disturbances	Hypokalemia Blood chloroquine concentration > 12 μmol/L

Table 1: Prognostic factor of chloroquine intoxication [11]

Chloroquine is a derivative of 4-aminoquinoline used for the prevention and treatment of malaria [3]. Its half-life is long, about 20-60 days [4]. Its bioavailability is good with a rapid gastro-instestinal absorption. About 60% of the chloroquine molecules are protein-bound [5]. It is rapidly distributed to the tissues (after 90 min to 3 h) explaining the rapid onset of its cardiovascular effects after the ingestion.

Chloroquine acts as a class Ia anti-arrhythmic drug. It has a negative inotropic effect and result in a decreased depolarization, decreased conduction and prolonged refractory period [6]. Following its membrane stabilizing effect, it is responsible for the influx transfer of potassium inside the cells causing severe hypokalemia that is reversible once the chloroquine intoxication is treated [7]. The severity of the hypokalemia is related to the chloroquine concentration in blood and to the severity of intoxication.

Chloroquine intoxication is responsible for multiorgan dysfunction including vomiting, blurring vision, coma, seizures, respiratory distress, apnea, bradychardia, conduction disturbances, hypotension and cardiac arrest [8]. Toxicity may occur with 2 g in the adult, and 0.75 to 1 g in the infant [8]. In a study by Riou et al. [9] the dose of 5 g was predictive of high morality with a specificity of 0.98 in addition to the delay in hospitalization.

However, lethal cases were reported at lower doses [3] while patients who ingested higher doses but were rapidly admitted to the hospital, survived [10]. The prognostic factors of chloroquine poisoning are listed in **table 1** [11]. As described by Riou et al. the dose of chloroquine is important. However the delay in hospitalization and management is also important for patient's survival [12]. Supporting the benefit of a rapid initiation of therapy prior to hospitalization is systematically recommended in France.

Gastrointestinal decontamination using activated charcoal should only be given within 2 h after ingestion in the absence of contraindications. High-dose diazepam is recommended according to the protocol that demonstrated a decrease in mortality rate in the severe choloquine poisoning. No clear explanation can be given to its mechanism of action [12;13]. A randomized prospective study failed to prove any protective effect of diazepam after the ingestion of a moderate amount of chloroquine (less than 3 g) in the absence of hypotension and widening of QRS complex [15]. Endotracheal intubation is recommended once intoxication is considered to be severe, i.e. ingested dose larger than 3 g, blood pressure less than 100 mmHg or QRS larger than 0.10 sec [9].

In the study conducted by Riou et al. [9], treatment with epinephrine and diazepam has significantly decreased the mortality rate, furher confirmed by a retrospective study done few years later [14].

1. Epinephine 0.25 μg/kg/min (to keep a systolic blood pressure > 100 mmHg)
2. Endotracheal intubation using rapid sequence intubation (etomidate 0.3 mg/kg)
3. Mechanical ventilation with adequate FiO_2 allowing SpO_2 > 96% or PaO_2 > 100 mmHg
4. Diazepam 2 mg/kg in 30 min then 2-4 mg/kg/h

Table 2: Treatment Protocol for chloroquine intoxication [14]

The proposed protocol is in **table 2**. However, despite this improved medical management, mortality rate persisted around 10% [14]. Hemodialysis was shown to be ineffective due to the rapid and total tissue distribution of chloroquine, being able to eliminate only 5% of the blood chloroquine [16].

A 52-year-old patient who ingested 10 g chloroquine and survived after dialysis initiated 3.5 h after the ingestion was reported [17]; however, this case does not support the role of hemodialysis. In addition, this patient had a moderate elevation in lactate concentration (3.3 mmol/L) in comparison to our patient (25 mmol/L).

Extracorporeal life support using ECMO is the treatment of choice in the cases of severe chroloquine intoxication refractory to the pharmacological treatments [18]. ECMO allows the substitution of the impaired cardiac function and preservation of hepatic and renal functions that helps metabolism and elimination of the molecule. The criteria for ECMO use in chloroquine intoxication are [19]:

- Severe cardiac compromise or dysrhythmias;
- No improvement with conventional pharmacological support;
- Persistent cardiac arrest with evidence for the absence of irreversible neurological damage;
- Absence of contraindications related to the technique.

Concerning our case, death occurred despite the aggressive management and ECMO. The poor prognostic factors were as follows:

- Delay in management before transfer to the ICU;
- Onset of cardiac arrest on the scene with an elevated lactate concentration on ICU admission (8.3 mmol/L) and possible brain anoxic damage;

- Hypokalemia of 2.8 mmol/L on ICU admission;
- Chloroquine blood level of 22 mg/L (69 μmol/L). Without medical intervention in the ICU, blood concentrations higher than 12 μmol/L are associated with cardiovascular complications and concentrations above 25 μmol/L with fatal outcome. Following adequate management in the ICU, the reported mortality is almost absent for levels below 12 μmol/L and is about 2% between 12 and 25 μmol/L and 21% for concentrations above 25 μmol/L [11];
- Onset of mixed cardiac and vasoplegic shock refractory to pharmacological treatments and responsible despite ECMO for multi-organ failure.

CONCLUSION

Recommendations for the management of chloroquine-poisoned patients is based on the early aggressive and fast management before hospitalization, including intubation, high-dose of diazepam, cardiovascular support by continuous infusion of epinephrine, and 8.4% sodium bicarbonate if widening QRS is present. Hemodialysis is inefficient. Extracorporeal membrane oxygenation may be beneficial for the most severe cases refractory to the conventional therapies. Patients should be admitted to a well-trained facility where ECMO is available to optimize patient's survival chances.

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