CASE REPORT

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Suicidal Chloroquine Poisoning: Clinical Course, Autopsy Findings, and Chemical Analysis

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ABSTRACT: Suicidal overdose of chloroquine is rare. We present a 14-year-old girl who was admitted to our Emergency Department after intentional ingestion of 7.5 g of chloroquine base followed by cardiac and respiratory arrest. Despite early mechanical ventilation, cardiac support, and treatment with high doses of diazepam, the patient died. Laboratory investigation indicated disseminated intravascular coagulation confirmed by petechial hemorrhages in the leptomeninges at autopsy, a finding that has not previously been described. Postmortem tissue analysis demonstrated early drug distribution to the medulla oblongata and cerebellum.

KEYWORDS: forensic science, forensic toxicology, chloroquine poisoning, hypokalemia, disseminated intravascular coagulation, tissue concentrations

Since its first description by Andersag in 1937, chloroquine is a widely used medical drug for the treatment of malaria, amebiasis, and rheumatic diseases. In contrast to the Orient, the Far East, Africa, and many parts of the tropics where chloroquine is one of the most frequently used drugs to commit suicide (1), the intentional overdose is a rare event in our countries. The fatal dose in adults is estimated to be 2 to 3 g, in children 0.5 to 1 g (2). Reports of patients with acute chloroquine poisoning have pointed out quick and complete absorption from the gastrointestinal tract followed by sudden collapse with intractable cardiac or ventilatory arrest in most cases (3–5). The largest series of severe chloroquine poisoning was described by Riou et al. (6) who observed a dramatic increase of chloroquine related suicides in Paris immediately after a publication on methods to commit suicide wherein chloroquine was highly recommended. Whereas combining early mechanical ventilation with the administration of diazepam and epinephrine was found to be highly effective in the treatment of severe chloroquine poisoning excessive overdosage may still have fatal outcome.

Only very few data have been published on chloroquine poisoning in children (4,5,7). We present a case report of a patient with fatal outcome due to cardiac failure and respiratory distress associated with severe disseminated intravascular coagulation that was not reported previously.

Clinical Course

A fourteen-year-old, so far healthy, female (137 cm, 42 kg) was transferred to our Emergency Department after ingestion of 50 tablets resochine (12,5 g chloroquine-diphosphate—7,5 g free base) in a suicidal attempt. The collapse was observed by her mother who called the Emergency Service and started basic life support. Because of persistent cardiac and ventilatory arrest, the prehospital emergency care team continued life support including catecholamines and mechanical ventilation. Initial asystolia switched to spontaneous circulation with torsades and broadened QRS-complexes in ECG (Fig. 1) after 1 h of cardiopulmonary resuscitation.

At admittance, the girl was deeply comatous. In the first blood sample drawn lactate was 16.4 mmol/L, potassium level was as low as 2.6 mmol/L. Complete blood cell count, in particular, platelet count, was normal but the coagulation profile was abnormal: partial thromboplastin time >120 s (normal <35 s), prothrombin time 37% (normal 70 to 120%), fibrinogen 96 mg% (normal 200 to 400 mg%).

Serum chloroquine concentration was 35 μg/mL (105 μmol/L) which is one of the highest levels ever reported in literature. Testing for tricyclic antidepressants, barbiturates, and benzodiazepines was negative.

Despite gastric and gut lavage, diazepam infusion (40 mg bolus, 5 mg/h continuous infusion), adequate substitution of electrolytes, and intensive shock treatment including high doses of iv epinephrine, hemodynamics deterioriated and rapidly progressive multiorgan failure including ARDS and disseminated intravascular coagulation (DIC) lead to fatal outcome after a total of 9 h.

Autopsy findings were cerebral edema with vasodilatation and diffuse small hemorrhages in the leptomeninges as well as multiple

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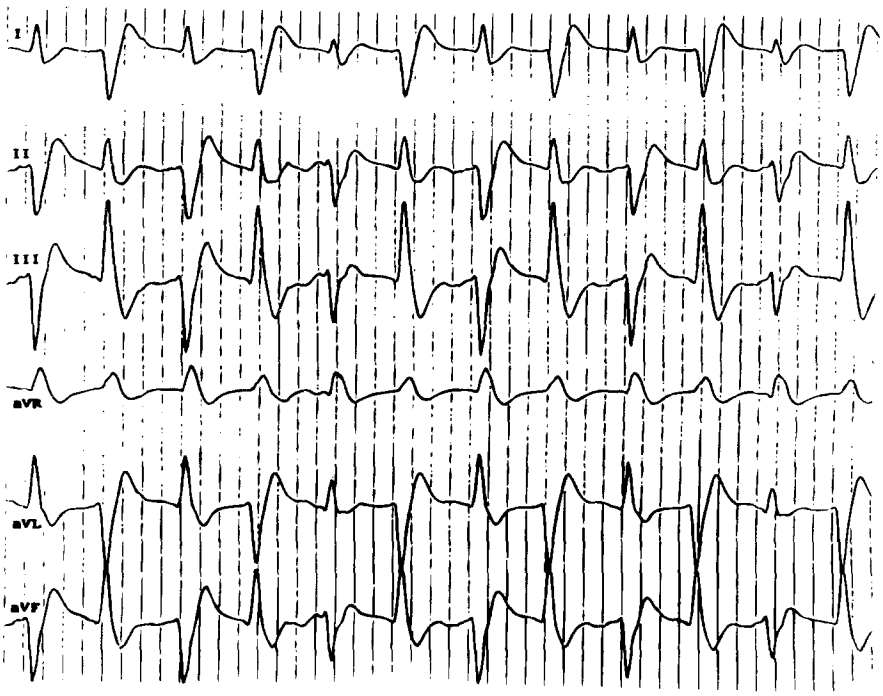

FIG. 1—*The first ECG after restoring spontaneous circulation showed ectope ventricular rhythm with widened QRS complexes.*

predominant cortical petechiae according to DIC on gross examination (Fig. 2) and a nonspecific centro-lobular lipoid degeneration of the liver in microscopic specimens. No significant alterations were found in other organs.

Chemical Analysis

Tissue concentrations of chloroquine were measured after extraction of 1-g sample (pH 9.5) with chloroform. Aliquots were analyzed by GC/MS (mass–fragmentography) at m/z 58, 86, and 319. Concentrations were calculated by comparing peak areas of sample and standard solutions of different concentrations. Quinine (m/z 136) was used as an internal standard. Results are given in Table 1.

Additionally, we studied tissue electrolyte (Na^+, K^+, Ca^{++}, Mg^{++}) concentration in the cardiac muscle after digestion of 1-g sample with concentrated nitric acid. Aliquots were analyzed by atomic absorption spectrometry (Ca^{++} at 422.7 nm, Mg^{++} at 285.2 nm), and atomic emission spectrometry (Na^+ at 589.0 nm and K^+ at 766.5 nm). Calcium tissue concentrations were increased two-fold in our patient (0.13 mg/g) as compared with controls (four untreated patients who suffered sudden death from pulmonary embolism) and to literature (8), whereas tissue concentration of sodium, potassium, and magnesium were in the normal range.

To determine whether the elevated calcium tissue concentration was a specific chloroquine effect or was attributable to administration of catecholamines, the corpses of four catecolamine-treated patients were studied, too. Similar increase of calcium concentrations (0.13 and 0.12 mg/g, respectively) were found when patients had been treated by continuous infusion of catecholamines for more than 24 h (2 corpses), on the other hand, calcium concentrations remained in the normal range when epinephrine was administered by bolus injection during cardiopulmonary resuscitation (2 corpses).

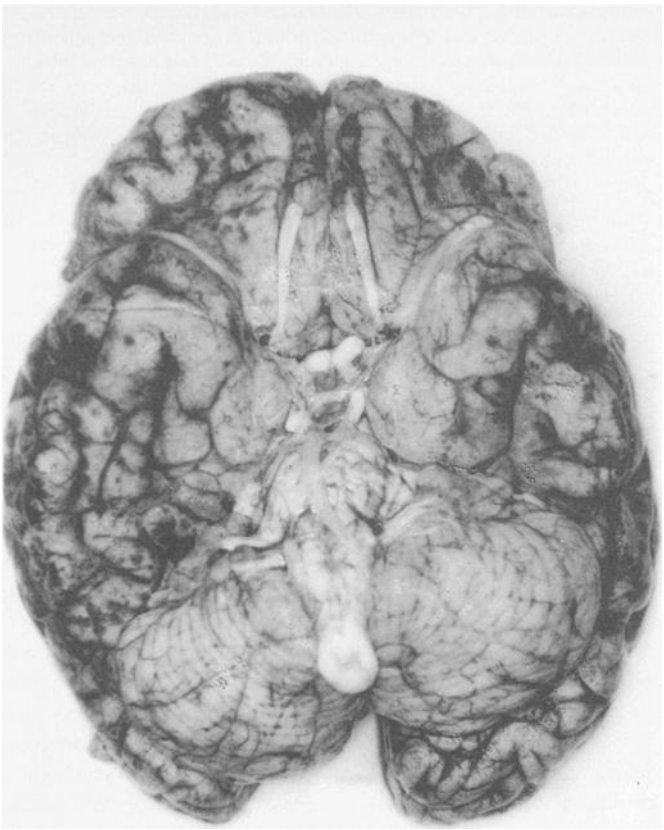

FIG. 2—*Vasodilation and multiple small hemorrhages in the leptomeninges according to disseminated intravascular coagulation after excessive chloroquine overdosage.*

TABLE 1—*Tissue concentration of chloroquine in our patient—postmortem analysis.*

Tissue	Chloroquine (μg/g)
Gastric mucosa	<1
Liver	16
Kidney	24
Spleen	20
Anterior wall of the heart	23
Posterior wall of the heart	24
Skeletal muscle	15
Medulla oblongata	40
Cerebellum	36
Skin	6
Plasma (premortem)	35 (μg/mL)

Discussion

Overdosage of chloroquine causes severe poisoning that may be rapidly fatal without therapeutic intervention (2,3). Within 30 min of ingestion, the patients suffer drownsiness, lethargy, nausea, vomiting, tremor, and increased excitability supervened by deep coma. Cardiotoxicity includes arrhythmias, bradycardia or ventricular tachycardia, widened QRS complexes, ST-segment depression, flattening of T waves and finally ventricular fibrillation, and cardiac arrest (2,9,10). Predictors of fatal outcome are the dose of chloroquine ingested (more than 5 g), systolic arterial pressure (lower than 80 mm Hg), and QRS duration (≥ 012 ms) (6). Additionally, in children, chloroquine is much more toxic than in adults (4,5,7). A treatment regimen including high doses of diazepam and epinephrine as well as early mechanical ventilation is recommended to improve prognosis (6). Hemodialysis is not useful, charcoal hemoperfusion is of uncertain significance (2).

All criteria of bad prognosis were found in our patient. Furthermore, the plasma levels of chloroquine at admittance were 105 μmol/L which is one of the highest levels ever reported. The highest level in the large study (22 adult patients) of Riou et al. (6) was 80 μmol/L, Ellenhorn reports only one case with a higher level (51 μg/mL = 153 μmol/L) which was fatal, too (2). These figures exceed by far therapeutic plasma levels that are reported to be approximately 1 μmol/L after a single 1-g oral dose of chloroquine (2).

Clinical course and laboratory data indicated intractable disseminated intravascular coagulation with the features of primary fibrinolysis (initial normal platelet counts followed by only a very slow drop of platelets) in our patient–a symptom that was not reported before in chloroquine poisoning. So far, in experimental designs, chloroquine is known to interfere with hemostasis by inhibiting the lysosomal degradation of activitad factor X and other steps in the coagulation cascade (11–13). It remains uncertain whether this coagulation disorder may be attributed to the very high dosage in our case. Corresponding to this unexpected finding, autopsy revealed multiple petechial bleedings predominantly in the leptomeninges and the cerebral cortex.

Postmortem analyses of chloroquine tissue concentrations showed the highest values in the brain. This finding is consistent with the high fat-soluble properties of the drug according to the early distribution. In particular, the chloroquine concentrations found in the medulla oblongata may contribute to early ventilatory arrest in chloroquine intoxication. The drug's concentration in the skin was very low in our case of acute intoxication indicating that the well-known accumulation of chloroquine in the skin, in particular, the melanocytes, is a consequence only of its chronic ingestion.

It was supposed that chloroquine-induced disturbance of potassium metabolism may cause the disastrous electrophysiological changes in the heart muscle (9). Analyzing tissue electrolyte contents of the heart muscle, normal values were obtained for sodium, potassium, and magnesium, whereas the concentration of calcium was increased. Further work-up showed that this finding was not an effect induced by chloroquine itself but was attributable to epinephrine infusion. Our data suggest that the calcium concentration increases more after continuous infusion of epinephrine than in cases of epinephrine bolus injection. The clinical impact of this finding remains uncertain and needs confirmation by a further study but might bring new insights in the pharmacological mechanisms of catecholamine actions in intensive care patients.

The summaries are as follows: (a) Chloroquine has only a narrow margin of safety and in case of massive overdosage, it is a highly lethal drug with bad prognosis despite adequate supportive and intensive care treatment, (b) Larger quantities of chloroquine paralyze vital brain centers leading to ventilatory arrest corresponding to our observation of the drug's accumulation in the medulla oblongata, and (c) Extremely high doses of chloroquine may interact with the coagulation and fibrinolytic system.

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