Treatment of Hydroxychloroquine Overdose

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Hydroxychloroquine overdoses are rarely reported with 7 previous cases found in the English medical literature. We report a case and review the literature. A 16-year-old girl ingested a handful of hydroxychloroquine 200mg, 30 minutes before presentation and presented with tachycardia (heart rate 110 beats/min), hypotension (systolic blood pressure 63 mm Hg), central nervous system depression, conduction defects (QRS = 0.14 msec), and hypokalemia (K = 2.1 meq/L). She was treated with fluid boluses and dopamine, oxygen, and potassium supplementation. Toxicologic tests confirmed the presence of hydroxychloroquine. The patient’s hypotension resolved within 4.5 hours, serum potassium stabilized in 24 hours, and tachycardia gradually decreased over 3 days. Although hydroxychloroquine overdoses are very rare, life-threatening hypotension, conduction problems, and hypokalemia can occur within 30 minutes of ingestion. Symptoms are similar to chloroquine and treatment must be implemented quickly and should be modeled after experience with chloroquine overdoses. Treatment modalities need further study, but current recommendations are: (1) diazepam for seizures and sedation; (2) early intubation and mechanical ventilation; (3) epinephrine for treatment of vasodilation and myocardial depression; (4) potassium replacement with close monitoring of levels; (5) charcoal for gastrointestinal decontamination if ingestion occurred within an hour; (6) high dose diazepam for life-threatening symptoms, until more information becomes available. No value was found for serum alkalinization or gastrointestinal methods of drug removal. (Am J Emerg Med 2001;19: 420-424. Copyright © 2001 by W.B. Saunders Company)

Hydroxychloroquine is a 4-aminoquinoline derivative prepared by beta hydroxylation of chloroquine. It is used in the treatment of malaria, rheumatoid arthritis, and lupus erythematosus, and marketed under the name Plaquenil (Sanoﬁ Pharmaceuticals, New York, NY). It is available in 200 mg tablets of hydroxychloroquine phosphate each containing 155 mg of hydroxychloroquine.1 Although commonly used in the treatment of rheumatologic diseases, it is a rare source of overdose in the United States. However, life-threatening symptoms can occur within an hour of ingestion. Awareness of the onset of symptoms, potential severity, toxidrome, and treatment recommendations will greatly aid in patient survival. Unfortunately, treatment recommendations for this drug overdose are not well established and are often unconventional. We review the information in the medical literature regarding treatment of hydroxychloroquine overdoses.

CASE REPORT

A 16-year-old girl presented to the emergency department (ED) with a blood pressure of 63 mm Hg by palpation, pulse of 110 beats/min, slurred speech, and drowsiness. History revealed she had taken a handful of her hydroxychloroquine (200 mg), levothyroxine, aspirin, and ibuprofen, 30 minutes before presentation. Fluid boluses brought her blood pressure to 76/32 mm Hg and dopamine was begun at 10 mcg/kg/min. Naloxone 2 mg IV was given without response. She was gastrically lavaged with evidence of pill fragments and 50 gm of charcoal instilled. The initial electrocardiogram (ECG) showed a QRS interval of 0.14 msec with a left bundle branch block pattern. Initial laboratory studies included: sodium 138 meq/L, potassium 2.1 meq/L, chloride 111 meq/L, bicarbonate 17 meq/L, glucose 57 mg/dL, blood urea nitrogen 9 mg/dL, creatinine 0.7 mg/dL, calcium 8.4 mg/dL, phosphate 2.5 mg/dL. A central line was placed and potassium chloride 20 meq/h for 2 hours was given. ABG was pH 7.34, paCO2 37.7 mm Hg, paO2 232 mm Hg, bicarbonate 19.7 meq/L, saturation 99% on 15 liters of oxygen. Urine drug screen was positive for hydroxychloroquine and an unidentified substance. The blood alcohol was less than .01 mg/dL, acetaminophen less than 10 mcg/mL, salicylates 17 mg/dL at 6 hours postingestion. At 4.5 hours postingestion, the dopamine was stopped and the blood pressure was 100/74 mm Hg, pulse 110 beats/min, and QRS interval was 0.108 msec. The patient was awake and oriented, but drowsy. She complained of nausea and vomited the charcoal and was subsequently given droperidol 0.625mg IV. At 8 hours postingestion, her potassium was still 2.2 meq/L and potassium chloride 10 meq × 6 IV was given. Another 4 × 10 meq IV potassium chloride was given 20 hours postingestion. The potassium stabilized at 3.8 to 4.2 meq/L by 24 hours postingestion. Her pulse continued to be 120 beats/min, gradually decreasing to 90 to 95 beats/min over 3 days.

DISCUSSION

Hydroxychloroquine overdoses are rarely reported despite the frequent use of this drug. A literature search found only 7 acute overdose reports in the English medical literature.2-8

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Manuscript received July 21, 2000, accepted October 10, 2000.

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Key Words: Hydroxychloroquine, overdose, quinidine effect, hypotension, chloroquine, hypokalemia.

Copyright © 2001 by W.B. Saunders Company 0735-6757/01/1905-0009$35.00/0 doi:10.1053/ajem.2001.25774

Therapeutics
The lethal dose is not well established. Twelve grams in a 2-year-old child caused convulsions, cardiopulmonary arrest, and death.9 Twelve grams in a 16-year-old boy was lethal.2 Four grams in a 29-year-old man caused ventricular tachycardia that responded to lidocaine and bretylium. Twelve grams in a 27-year-old woman caused atrioventricular dyssrhythmias that responded to treatment with lidocaine, dopamine, and a temporary pacemaker.6 A 30-year-old woman with an ingestion of an unknown amount of hydroxychloroquine developed hypotension, and hypokalemia that responded to treatment with fluids, dopamine, and intravenous diazepam.7 Twenty grams in an 18-year-old woman caused hypotension, ventricular tachyarrhythmias, and hypokalemia and was successfully treated with intubation, epinephrine infusion, diazepam intravenously, and potassium replacement.8

Hydroxychloroquine is synthesized by adding a hydroxy group to the parent compound, chloroquine.1 According to animal studies, chloroquine is 2 to 3 times more toxic than hydroxychloroquine.8 There is much more toxicologic experience with chloroquine as it is a common method of attempting suicide in Africa and France.9,10 It is also commonly prescribed as treatment for malaria, lupus, and rheumatoid arthritis, and accidental ingestions in children have been reported. The drug has a very low margin of safety. The mortality rate in overdose studies for adults varies from 10% to 30%8,11 and in one severe overdose series, a 90% mortality rate was seen.12 The fatality rate in children is 80% and survivors were often left with neurologic deficits.13 The minimal lethal dose in a child is 300 mg of chloroquine base or one tablet. The therapeutic range is reported as 10 mg/kg but a fatality in a child was reported at 27 mg/kg.11 In adults, the therapeutic dose is 10 mg/kg, the toxic dose is 20 mg/kg, and the lethal dose is 30 mg/kg.9 Because of the few number of hydroxychloroquine overdose cases, there is no established lethal dose or toxic dose. One cannot assume that twice the chloroquine doses would be toxic for hydroxychloroquine.

Chloroquine overdoses cause serious rapid symptomatology, with symptoms frequently seen within 30 minutes. Death is usually within 1 to 3 hours of ingestion and the cause is cardiac arrest. Drowsiness, dizziness, and visual disturbances can progress quickly to seizures, apnea, arrhythmias, and hypotension. Cardiotoxicity occurs in greater than 50% of cases. Hypotension from vasodilatation and decreased cardiac output is frequently seen. Respiratory difficulty is common, progressing to arrest, and pulmonary edema9,13,14,15 Hypokalemia occurs in approximately 85% of chloroquine overdoses, with the severity of the decrease related to the severity of the intoxication.16 The clinical criteria associated with a fatal outcome include: (1) ingestion of greater than 5 grams; (2) systolic blood pressure <80 mm Hg; (3) prolongation of the QRS interval longer than 0.12 msec; (4) ventricular rhythm disturbances12; and (5) blood concentrations greater than 25 mcg/mL (8 mcg/mL).15

There is limited experience to characterize a hydroxychloroquine overdose (see Table 1). In a review of the 8 case reports to date, the symptom onset, when reported, was within 5 hours of ingestion. In our case, the patient was very symptomatic at 30 minutes postingestion. The time since ingestion was supported by the presence of pill fragments in the lavage fluid. In the case presented by Jordan et al,8 the patient was stable at 60 minutes postingestion and then decompressed over the next 15 minutes. In 2 fatalities, death from cardiorespiratory arrest occurred shortly after ingestion. Seizures were reported in one case. Arrhythmias were reported in 4 of the 8 cases: conduction defects seen in two cases, ventricular tachycardia in two cases, and AV dysrhythmias in one case. Hypokalemia was reported in 3 of the 8 cases, with nadirs of 2.7 meq/L, 2.1 meq/L, and 1.8 meq/L. Hypotension was reported in 50% of the cases and occurred very quickly. (The incidence of these symptoms may actually be higher because the older cases in the literature were forensic cases and did not expound on symptoms.) By 24 hours postexposure, the patients that survived were hemodynamically stable. All of the above characteristics are similar to those from chloroquine overdoses.

Kinetic parameters for chloroquine help explain the symptom onset and dissipation. The drug is rapidly absorbed from the gastrointestinal tract, with a half-life of absorption of 30 minutes and a peak concentration reached in 1.5 to 3 hours.9 These transiently high intravascular concentrations seen in the early distribution phase are associated with the cardiotoxic effects of chloroquine. As redistribution from this central compartment occurs, toxic effects diminish.12 Rarely do serious symptoms last greater than 24 hours, despite a half-life of 6 to 14 days,17,18 High drug concentrations in the medulla oblongata may contribute to early ventilatory arrest.19 Very little is known of hydroxychloroquine kinetics in overdose except that plasma concentrations fit a 2-compartmental model, the Vd is 63 L/kg,8 and the half-life is 15.5 to 31 hours.4,7,8

The lethal plasma level of hydroxychloroquine is not well established. Serious toxicity has been reported in patients with plasma levels ranging from 2.05 to 29.40 mcg/mL, (0.64 to 9.87 mg/L) Post mortem blood levels of 142.89 mcg/mL (48 mg/L) and 309.62 mcg/mL (104 mg/L) have

### Table 1. Acute Overdose Cases of Hydroxychloroquine

<table>
<thead>
<tr>
<th>Age (yrs.)</th>
<th>Amount</th>
<th>Onset</th>
<th>Symptoms</th>
<th>Death</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>12 gm</td>
<td>45 min</td>
<td>Vomiting</td>
<td>cardiopulmonary arrest</td>
<td>Yes</td>
</tr>
<tr>
<td>42</td>
<td>unkn</td>
<td>unkn</td>
<td>Hypotension</td>
<td>No</td>
<td>3</td>
</tr>
<tr>
<td>29</td>
<td>4 gm</td>
<td>unkn</td>
<td>Hypotension</td>
<td>No</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>12 gm</td>
<td>“soon”</td>
<td>Ventricular tachycardia</td>
<td>No</td>
<td>5</td>
</tr>
<tr>
<td>27</td>
<td>12 gm</td>
<td>4.5 hr</td>
<td>AV dysrhythmias</td>
<td>No</td>
<td>6</td>
</tr>
<tr>
<td>30</td>
<td>unkn</td>
<td>unkn</td>
<td>CNS depression</td>
<td>hypotension</td>
<td>No</td>
</tr>
<tr>
<td>18</td>
<td>20 gm</td>
<td>75 min</td>
<td>Hypotension</td>
<td>Ventricular tachycardia</td>
<td>No</td>
</tr>
<tr>
<td>16</td>
<td>unkn</td>
<td>30 min</td>
<td>Tachycardia</td>
<td>hypokalemia (2.1)</td>
<td>No</td>
</tr>
</tbody>
</table>

Note: The data in Table 1 are from case reports and may not accurately reflect the typical presentation of hydroxychloroquine overdose.
be reported. Patients on the medication therapeutically will have plasma concentrations less than 1 mc mol/L. A report by Vitris and Aubert reported mild intoxication was noted with serum concentrations <2.5 mcg/mL (7.75 mc mol/L), and moderate intoxication with ECG abnormalities and occasional neurologic symptoms with 2.5 to 5 mcg/mL (7.75 to 15.5 mc mol/L). Severe intoxication with cardiovascular, ECG, and neurologic abnormalities or death have been reported with serum concentrations >5 mcg/mL (15.5 micromol/L). In another report, the toxic plasma concentration was noted as >0.6 mcg/mL and the lethal plasma concentration was listed at >3 mcg/mL. There is confusion regarding chloroquine levels since laboratory tests are reported as blood concentrations, serum concentrations and plasma concentrations. Chloroquine is highly bound to red blood cells and blood concentrations are 4 to 8X plasma concentrations. Serum concentrations are higher than plasma concentrations because platelets also bind chloroquine, but the ratio between plasma and serum concentrations is undetermined. The cardiotoxicity from chloroquine type drugs is attributed to a quinidine-like action which causes: (1) a negative inotropic action; (2) inhibits spontaneous diastolic depolarization; (3) slows conduction; (4) lengthens the effective refractory period; and (5) raises the electrical threshold. The result is a depression of contractility, impairment of conductivity, decrease of excitability, and possible abnormal stimulus to reentry mechanisms. Cardiac arrest may be the first manifestation of overdose.

The hypokalemia associated with these overdoses correlates with the severity of the intoxication. In a retrospective study of 191 consecutive patients with acute chloroquine ingestions, the plasma potassium varied directly with the systolic blood pressure and inversely with the QRS and QT intervals. Plasma potassium varied inversely with the blood chloroquine level. The hypokalemia was more severe among those with fatal outcomes than survivors. The mechanism appears to be an intracellular transport of potassium rather than a true potassium deficit. Alkalinization was not the cause of the hypokalemia as these patients had an acidic pH. In fact, the more acid the pH, the lower the plasma potassium. The potassium concentration in patients who received epinephrine or dobutamine was lower than in patients who did not receive any catecholamines. But even when these patients were excluded, there was still a correlation between plasma potassium and blood level and cardiovascular parameters. Also as the intoxication resolves, there is a reversal of potassium flow and a serious risk of hyperkalemia. Close monitoring and replacement of the plasma potassium is important in the management of these overdoses.

**TREATMENT AND TREATMENT CONTROVERSIES**

Because there is little experience with hydroxychloroquine, the treatment of toxicity is modeled after the treatment for chloroquine (see Table 2).

Chloroquine and hydroxychloroquine cause vasodilation and myocardial depression. Epinephrine has been shown to decrease the effects of chloroquine on the myocardium in animals and humans. It acts as a potent inotropic agent and vasoconstrictor. The dose recommended by Riou et al is 0.25 mcg/kg/min, increase by 0.25 mcg/kg/min until adequate systolic blood pressure (~100 mm Hg); infuse with a dextrose solution to ensure adequate dilution in the vein.

The recommendation for sodium bicarbonate for QRS widening is based on the mechanism of a quinidine-like effect. There are no present studies supporting its use in patients overdosed on chloroquine or hydroxychloroquine. Alkalinization may also contribute to the hypokalemia seen in these overdoses.

The hypokalemia can be severe, less than 2 meq/L in 11% of cases. The hypokalemia occurs within a few hours of ingestion and correlates with the severity of the overdose. Because the mechanism appears to be an intracellular shift which will reverse as the overdoses subsides, it has not been proven that potassium supplementation will improve cardiac toxicity. There have been cases of hyperkalemia resulting from too aggressive replacement which potentially could contribute to the cardiotoxic effects of these drugs. There are also animal data that suggests a possible protective effect of hypokalemia in acute chloroquine poisonings. In hypokalemic pentothal-anesthetized dogs, the dose of quinine required to widen the QRS interval was higher than among normokalemic controls. In isolated rabbit atrium, and in isolated frog hearts, a potassium-poor bath reversed the depressant effects of chloroquine. However, it is also well known that hypokalemia may result in lethal arrhythmogenesis. The hypokalemia was more severe among patients who died from chloroquine overdoses, but the hypokalemia could not be directly attributed as the cause of death in most cases. Further studies are needed to determine whether potassium supplementation is helpful and if so, at what rate that supplementation should occur.

The use of diazepam to treat arrhythmias and hypotension is a unique use of this drug in an overdose situation. Support

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**TABLE 2. Treatment of Chloroquine Overdose**

| 1. Early intubation and mechanical ventilation in patients with significant ingestions or symptoms. |
| 2. Cardiovascular monitoring |
| 3. Epinephrine for hypotension, dysrhythmias, QRS widening, circulatory collapse |
| 4. Diazepam for seizures, dysrhythmias, QRS widening, hypotension, circulatory collapse, LD of 2 mg/kg IV over 30 minutes, then a continuous infusion of 1 to 2 mg/kg/day. |
| 5. Alkalinization with sodium bicarbonate for QRS widening and hypotension |
| 6. Charcoal for GI decontamination. Lavage with endotracheal intubation may be helpful if done in the first hour. |
| 7. Treat hypokalemia; monitor closely to prevent severe hyperkalemia when the intracellular shift of potassium reverses |
| 8. Avoid 1A type antiarrhythmics |
| 9. No value to hemodialysis, peritoneal dialysis, or hemoperfusion has been noted. |

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Volume 19, Number 5 ■ September 2001
for this therapy came from initial observations from patients
overdosed on both chloroquine and diazepam who did not
develop cardiovascular toxicity. However, in these early
reports, no blood levels were done, relying solely on the
history of ingestion. Then Crouzette’s study using rats,
showed that high doses of diazepam decreased mortality
significantly. In Riou’s study in pigs, the group receiving
diazepam 2 mg/kg over 2 minutes and then 1 mg/kg/hr had
an increased systolic and diastolic blood pressure, lower
QRS interval, elevated heart rate, increased urine volume,
increased excretion of chloroquine, and increased plasma
and red blood cell chloroquine concentrations. A study
using left ventricular papillary muscles from the rat showed
that diazepam did not restore the intrinsic mechanical per-
formance of rat cardiac papillary muscle exposed to chlo-
roquine. The only study in humans looking at severe chloroquine
overdoses was done by Riou et al in 1988. The criteria for
severe chloroquine poisoning was an ingestion of >5
grams, which a retrospective study had determined to be an
accurate predictor of a fatal outcome. They treated 11 pro-
spective chloroquine overdose patients with immediate me-
chanical ventilation, epinephrine, and diazepam at 2 mg/kg
over 30 minutes, then 1 to 2 mg/kg/day. Ten of the 11 (91%)
patients survived in the treatment group. They compared
this with historical controls where only 1 out of 11 (9%) patients survived. The criticism of this report is that the
control group was a retrospective group and that many
treatment modalities were changed in the treatment group,
making it impossible to determine that high dose diazepam
was responsible for the change in outcome.

A study by Clemessey et al looked prospectively at
moderately intoxicated patients. The criteria for moderately
severe intoxication was a suspected ingestion of 2 to 4
grams, with systolic blood pressure >80 mm Hg, the QRS
interval <0.12 msec and the absence of dysrhythmias. The
patients enrolled presented with a slight prolongation of the
QRS interval, prolongation of the QT interval and a mean
blood chloroquine concentration of 15 mcg/mL. Patients
were excluded if they had been treated with diazepam,
epinephrine, or assisted ventilation, if blood chloroquine
levels were found to be in the therapeutic range, or a
benzodiazepine was coingested. These exclusions were
used to detect a therapeutic effect from the benzodiazepine
treatment alone. The diazepam dose used was 0.5 mg/kg
over 30 minutes, followed by an infusion of 1 mg/kg/day.
Compared with the placebo group, the diazepam group
showed no significant difference in the initial or serial ECG
or systolic blood pressure measurements. There were no
deaths in this study. These results suggest that patients with
moderately severe intoxications respond favorably to sup-
portive therapy and casts doubt on the need for diazepam
therapy to treat the cardiac effects. However, a dose-effect
study may show that a larger dose may lead to a measurable
effect on the cardiovascular parameters. Also more seri-
ously ill patients may show a beneficial effect from diaze-
pam not seen in these moderately severe intoxications.

The following theories have been postulated for the pos-
sible beneficial effect of diazepam in these overdoses, in-
cluding: (1) a central antagonist effect; (2) anticonvulsant
effect; (3) antiarrrhythmic effect by an electrophysiologic
action inverse to chloroquine; (4) pharmacokinetic interac-
tion between diazepam and chloroquine; (5) decrease in
chloroquine-induced vasodilation. The definitive
study to prove if there is a cardiovascular benefit from
benzodiazepine therapy in chloroquine and hydroxychloro-
quine overdoses has yet to be done.

Gastrointestinal decontamination is indicated if the pa-
tient presents within an hour of ingestion. Lavage has been
the main mode of decontamination in the past, but activated
charcoal has been shown to prevent absorption of chlo-
roquine. One study in 6 volunteers showed that activated
charcoal prevented absorption of 95% to 99% of the in-
gested chloroquine when given within 5 minutes. Extracorpo-
real methods of removing chloroquine or hydroxy-
chloroquine have not been shown to be helpful. Both
drugs have very large volumes of distribution and rapidly go
intracellular.

CONCLUSION

Hydroxychloroquine overdoses are rare, but very serious.
Life-threatening symptoms may occur within 30 minutes
with very rapid progression to death within a few hours. The
symptoms are similar to chloroquine overdoses. Treatment
must be implemented quickly and should be modeled after
experience with chloroquine overdoses. Treatment modal-
ties however need further study.

After reviewing the medical literature on hydroxychloro-
quine and chloroquine overdoses, the following treatment
approaches are recommended. Diazepam should be used for
the treatment of seizures and sedation. Early intubation and
mechanical ventilation should be instituted immediately in
severe overdose. Vasodilation and myocardial depression
should be treated with pressor agents, preferably epineph-
rine. There are no studies showing a benefit from bicarbo-
inate therapy and treatment may worsen hypokalemia, so we
would not recommend use of sodium bicarbonate. Potas-
sium should be replaced with close monitoring of serum
potassium levels. If these treatments fail to reverse the
serious manifestations of hydroxychloroquine or chloro-
quine toxicity, treatment with high dose diazepam therapy
seems warranted. In light of the morbidity and mortality
associated with these drug overdoses, treatment with an
unproven but possibly life-saving drug seems ethically re-
ponsible. When using these high doses, one must be sure
that the patient is intubated and ventilated. It should be
remembered not to exceed the 5mg/minute maximum infu-
sion rate of diazepam or cardiotoxicity from the propylene
glycol may ensue. If the ingestion occurred within an hour,
gastrointestinal decontamination with charcoal is recom-
mended.

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