COVID-19: Chloroquine Toxicity

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COVID-19
Trump says antimalarial will soon be available to treat coronavirus

From CNN's Kevin Liptak
Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial

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A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19

Andrea Cortegiani\textsuperscript{a,}\textsuperscript{*}, Giulia Ingoglia\textsuperscript{a}, Mariachiara Ippolito\textsuperscript{a}, Antonino Giarratano\textsuperscript{a}, Sharon Einav\textsuperscript{b}

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• Eight Articles
  – 1 narrative letter
  – 1 research letter
  – 1 editorial
  – 1 expert consensus (Chinese)
  – 2 national guidelines (Dutch and Italian)

• 23 Active Clinical Trials (All China)
Chloroquine Poisoning in a Child

Chloroquine poisoning in children, although infrequent, is extremely dangerous because of the narrow margin between therapeutic and toxic doses. Children clinically present with apnea, seizures, and cardiac arrhythmias. We present the case of a 12-month-old infant, the second-youngest patient reported in the US literature to die from chloroquine poisoning. A serum level of 4.4 mg/L (13.64 μmol/L) was obtained after the infant ingested only one tablet (300 mg). This establishes a new minimal lethal dose/blood level for children. Although some pediatric and adult pharmacokinetic and clinical similarities exist, the outcome is different. Pediatric mortality is 80%, whereas adult mortality is only 10%. Pediatric ingestion cases are primarily unintentional, and most adult cases are suicide attempts. Current treatment in adults includes a protocol of diazepam and epinephrine. Further studies involving children and these medications and other modalities are needed to improve survival. [Kelly JC, Wasserman GS, Bernard WD, Schultz C, Knapp JF: Chloroquine poisoning in a child. Ann Emerg Med January 1990; 19:47-50.]

James C Kelly, MD
Gary S Wasserman, DO
Walter D Bernard, MD
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Received for publication September 1, 1989. Accepted for publication September 25, 1989.
FATAL ACUTE CHLOROQUINE POISONING IN CHILDREN

Howard M. Cann, M.D., and Henry L. Verhulst, M.S.

CHLOROQUINE has been widely used to suppress and treat acute attacks of all the malarias, and to eradicate infection with Plasmodium falciparum. It is also used widely by children to treat skin conditions. Ingestion of chloroquine by children under medical supervision is not usually a problem, but accidental ingestion may lead to fatal poisoning. In this case, emesis was induced, but no effect was noted. Thereafter, gastric lavage was instituted, but all resuscitative efforts failed, and the child was pronounced dead approximately 2½ hours after ingesting the chloroquine.
Fatal Chloroquine Poisoning in a Child: Experience With Peritoneal Dialysis

Chloroquine overdose is commonly fatal in children. We report here such a case in which peritoneal dialysis was tried. Analyses of tissues, serum, urine, and dialysate for chloroquine confirmed the diagnosis and indicated that little of this drug was removed from the body by dialysis.

CASE REPORT

A healthy 28-month-old black boy weighing 17.17 kg was seen holding two 500-mg chloroquine diphosphate (Aralen)
CHLOROQUINE TOXICITY
## Pharmacokinetics

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bioavailability</strong></td>
<td>80%</td>
</tr>
<tr>
<td><strong>Time to peak</strong></td>
<td>2-4 hours</td>
</tr>
<tr>
<td><strong>Protein binding</strong></td>
<td>50-65%</td>
</tr>
<tr>
<td><strong>Volume of distribution</strong></td>
<td>&gt; 100 L/kg</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>40-55 days</td>
</tr>
</tbody>
</table>
Paracelsus

• Death occurs rapidly
  – Within 1-3 hours after ingestion
  – Often prior to reaching hospital

• Narrow therapeutic window
  – 10 mg/kg malaria treatment
  – 20 mg/kg toxic
  – 30 mg/kg fatal (5 g in adult)

• Risk: Suicidal ingestion in adult
  Unintentional ingestion in children
Cardiovascular Toxicity

- Membrane destabilizing effect
- Channel blockade:
  - $I_{Kr} > I_{Na} > I_{ca}$
  - Prolonged QTc
  - Impaired ventricular conduction
  - Increased automaticity
- Hypotension ($\alpha_1$-antagonism)
Blockade of Currents by the Antimalarial Drug Chloroquine in Feline Ventricular Myocytes

JOSÉ A. SÁNCHEZ-CHAPULA, EDUARDO SALINAS-STEFANON, JULIAN TORRES-JÁCOME, DORA E. BENAVIDES-HARO, and RICARDO A. NAVARRO-POLANCO

Effect on voltage-gated Na channel
Effect on potassium rectifier channel ($I_{kr}$)
Effect on ventricular myocyte
Chloroquine-induced venodilation in human hand veins

Ademola K. Abiose, MD, Matthias Grossmann, MD, Oranee Tangphao, MD, Brian B. Hoffman, MD, and Terrence F. Blaschke, MD
Hypokalemia

- Intracellular shift (< 2 meq)
- Associated with worse outcome
- Worsens risk of TdP ($I_{Kr}$)
- Further worsened with alkalemia
  - ? NaBicarbonate
Hypokalaemia related to acute chloroquine ingestion

Jean-Luc Clemessy, Christian Favier, Stephen W Borron, Philippe E Hantson, Eric Vicaut, Frédéric J Baud

Figure 1: Distribution of plasma potassium levels in 191 acute chloroquine intoxications
### Table 2: Plasma potassium measured on admission in mmol/L

<table>
<thead>
<tr>
<th>Patients</th>
<th>n</th>
<th>Mean (SD)</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>191</td>
<td>3.0 (0.8)</td>
<td>3.0</td>
<td>1.3–5.7</td>
</tr>
<tr>
<td>Deaths</td>
<td>23</td>
<td>2.4 (1.0)</td>
<td>2.1</td>
<td>1.4–5.7</td>
</tr>
<tr>
<td>Surivivals</td>
<td>168</td>
<td>3.1 (0.7)</td>
<td>3.1</td>
<td>1.3–5.6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>57</td>
<td>3.0 (0.7)</td>
<td>3.1</td>
<td>1.3–4.8</td>
</tr>
<tr>
<td>No vomiting</td>
<td>134</td>
<td>3.0 (0.8)</td>
<td>3.0</td>
<td>1.4–5.7</td>
</tr>
<tr>
<td>Catecholamine</td>
<td>92</td>
<td>2.5 (0.8)</td>
<td>2.4</td>
<td>1.3–5.7</td>
</tr>
<tr>
<td>No catecholamine</td>
<td>99</td>
<td>3.4 (0.5)</td>
<td>3.3</td>
<td>2.2–4.8</td>
</tr>
</tbody>
</table>

\[ p = 0.0003 \] \[ p = 0.43 \] \[ p = 0.0001 \]
CNS Effect

• Drowsiness
• Seizure
• Coma
TREATMENT
Toxic QRS Prolongation: NaHCO₃

• Sodium: 8.4%
  – 1-2 mEq/kg IVP

• Bicarbonate: Alkalinization
  – D5 140 mEq/L NaHCO₃ at 2x-MIVF
  – pH 7.45-7.50
Bolus vs. Alkalization

Alkalosis

Intracellular K+ Shift

Worsening Hypokalemia

Increased risk of TdP

![Diagram showing ion movement](image)
• Retrospective Series:
  – Predictor of fatality
  – Pre-hospital emergency care unit study
  – 51 cases included (17 read the book)
Figure 1. Predictive Value of Selected Variables in Indicating a Fatal Outcome of Chloroquine Poisoning before Hospitalization (n = 51).
• Prospective Combination Treatment:
  – Pre-hospital emergency care unit study
  – 11 consecutive patients
  – Ingested > 5g Chloroquine
  – Treatment: Intubation
      Epinephrine 0.25 μg/kg/min
      HD Diazepam 2 mg/kg IV over 30 min
      1-2 mg/kg/day over 2-4 days
Table 1. Characteristics of the Control Group.*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age/Sex</th>
<th>Chloroquine ingested dose</th>
<th>Chloroquine blood level</th>
<th>QRS Duration</th>
<th>Systolic Arterial Pressure</th>
<th>Initial Cardiac Events</th>
<th>Outcome†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>38/F</td>
<td>5.5</td>
<td>—</td>
<td>0.14</td>
<td>70</td>
<td>Asystole</td>
<td>Death</td>
</tr>
<tr>
<td>2</td>
<td>32/M</td>
<td>6</td>
<td>—</td>
<td>0.12</td>
<td>80</td>
<td>Asystole</td>
<td>Death</td>
</tr>
<tr>
<td>3</td>
<td>19/F</td>
<td>10</td>
<td>—</td>
<td>0.12</td>
<td>70</td>
<td>Asystole</td>
<td>Death</td>
</tr>
<tr>
<td>4</td>
<td>26/F</td>
<td>7</td>
<td>—</td>
<td>0.16</td>
<td>80</td>
<td>Torsade de pointes</td>
<td>Death</td>
</tr>
<tr>
<td>5</td>
<td>37/M</td>
<td>8</td>
<td>—</td>
<td>0.12</td>
<td>60</td>
<td>Asystole</td>
<td>Death</td>
</tr>
<tr>
<td>6</td>
<td>20/M</td>
<td>6</td>
<td>—</td>
<td>0.12</td>
<td>80</td>
<td>Ventricular arrhythmia</td>
<td>Death</td>
</tr>
<tr>
<td>7</td>
<td>17/M</td>
<td>6.5</td>
<td>20</td>
<td>0.12</td>
<td>80</td>
<td>None</td>
<td>Survival</td>
</tr>
<tr>
<td>8</td>
<td>28/F</td>
<td>9</td>
<td>—</td>
<td>0.16</td>
<td>80</td>
<td>Ventricular arrhythmia</td>
<td>Death</td>
</tr>
<tr>
<td>9</td>
<td>24/M</td>
<td>10</td>
<td>—</td>
<td>0.16</td>
<td>70</td>
<td>Torsade de pointes</td>
<td>Death</td>
</tr>
<tr>
<td>10</td>
<td>35/M</td>
<td>7</td>
<td>—</td>
<td>0.12</td>
<td>60</td>
<td>Ventricular arrhythmia</td>
<td>Death</td>
</tr>
<tr>
<td>11</td>
<td>41/M</td>
<td>8</td>
<td>—</td>
<td>0.16</td>
<td>80</td>
<td>Ventricular arrhythmia</td>
<td>Death</td>
</tr>
</tbody>
</table>

*Retrospectively studied patients who ingested more than 5 g of chloroquine from July 1983 to December 1985.
†No patient was successfully resuscitated after cardiac arrest.
<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age/Sex</th>
<th>Chloroquine Amount</th>
<th>PaO₂</th>
<th>QRS Duration</th>
<th>Systolic Arterial Pressure</th>
<th>Cardiac Event after Therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>from dose ingested</td>
<td>g</td>
<td>g</td>
<td>mmol/liter</td>
<td>mm Hg</td>
<td>sec</td>
</tr>
<tr>
<td>12‡</td>
<td>23/M</td>
<td>10</td>
<td>2</td>
<td>70</td>
<td>—</td>
<td>0.16</td>
<td>60</td>
</tr>
<tr>
<td>13§</td>
<td>22/F</td>
<td>7.5</td>
<td>1.5</td>
<td>40</td>
<td>—</td>
<td>0.12</td>
<td>80</td>
</tr>
<tr>
<td>14</td>
<td>31/M</td>
<td>6</td>
<td>1</td>
<td>50</td>
<td>65</td>
<td>0.12</td>
<td>70</td>
</tr>
<tr>
<td>15</td>
<td>19/F</td>
<td>9</td>
<td>2</td>
<td>80</td>
<td>—</td>
<td>0.16</td>
<td>85</td>
</tr>
<tr>
<td>16</td>
<td>46/F</td>
<td>8</td>
<td>3</td>
<td>40</td>
<td>70</td>
<td>0.12</td>
<td>80</td>
</tr>
<tr>
<td>17</td>
<td>27/M</td>
<td>6.5</td>
<td>1.5</td>
<td>60</td>
<td>50</td>
<td>0.16</td>
<td>60</td>
</tr>
<tr>
<td>18</td>
<td>18/M</td>
<td>7</td>
<td>1</td>
<td>60</td>
<td>—</td>
<td>0.12</td>
<td>70</td>
</tr>
<tr>
<td>19</td>
<td>24/F</td>
<td>8.5</td>
<td>2</td>
<td>50</td>
<td>60</td>
<td>0.16</td>
<td>80</td>
</tr>
<tr>
<td>20</td>
<td>29/M</td>
<td>10</td>
<td>2</td>
<td>55</td>
<td>—</td>
<td>0.12</td>
<td>80</td>
</tr>
<tr>
<td>21</td>
<td>33/M</td>
<td>15</td>
<td>3</td>
<td>80</td>
<td>—</td>
<td>0.12</td>
<td>70</td>
</tr>
<tr>
<td>22</td>
<td>24/F</td>
<td>6</td>
<td>1</td>
<td>40</td>
<td>—</td>
<td>0.14</td>
<td>80</td>
</tr>
</tbody>
</table>
Diazepam

- Central antagonist effect
- Anticonvulsant effect
- Antiarrhythmic effect (inverse to chloroquine)
- Pharmacokinetic interaction
- Decrease in venodilation
40% Propylene Glycol

- Osmotically active
- Large Osmolar Gap
- Metabolized to Lactate
- Increased Lactate
- Elevated Anion Gap
- Some Acidosis
Prospective, multi-center, double-blind, placebo-controlled study

Moderate Intoxications:
- 2-4 g Chloroquine
- SBP > 80 mmHg
- QRS < 120 msec

Diazepam (0.5 mg/kg, 1mg/kg over 24 hours) vs. Placebo
Effect on QTc Duration

Therapeutic trial of diazepam versus placebo in acute chloroquine intoxications of moderate gravity

J.-L. Clemessy, Guy Angel, +6 authors Frédéric Joseph Baud - Published in Intensive Care Medicine 2005 - Medicine
Therapeutic trial of diazepam versus placebo in acute chloroquine intoxications of moderate gravity

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Effect on QRS Duration

![Graph showing the effect on QRS duration with diazepam and placebo over time.](image)
Chloroquine: REVIEW

• Narrow therapeutic index
• Rapidly fatal
• Symptoms: Hypokalemia
  Hypotension
  Seizure
  Dysrhythmia and Cardiovascular Collapse
• Combination Treatment for SEVERE Disease
  – Intubation
  – Epinephrine
  – HD Diazepam
• Cautious use of Bicarbonate; avoid alkalinization
HYDROXYCHLOROQUINE
# Treatment of Hydroxychloroquine Overdose

KATHY MARQUARDT, PHARM D AND TIMOTHY E. ALBERTSON, MD, PHD

## 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, cardiorespiratory arrest</td>
<td>Yes</td>
<td>2</td>
</tr>
<tr>
<td>42</td>
<td>unkn</td>
<td>unkn</td>
<td>Hypotension</td>
<td>Yes</td>
<td>3</td>
</tr>
<tr>
<td>29</td>
<td>4 gm</td>
<td>unkn</td>
<td>Vomiting, Ventricular tachycardia</td>
<td>No</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>12 gm</td>
<td>“soon”</td>
<td>Convulsions, cardiorespiratory arrest</td>
<td>Yes</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, hypotension, hypokalemia (2.7)</td>
<td>No</td>
<td>7</td>
</tr>
<tr>
<td>18</td>
<td>20 gm</td>
<td>75 min</td>
<td>Hypotension, Ventricular tachycardia, hypokalemia (1.8) conduction delay</td>
<td>No</td>
<td>8</td>
</tr>
<tr>
<td>16</td>
<td>unkn</td>
<td>30 min</td>
<td>Tachycardia, hypotension, hypokalemia (2.1) conduction delay, CNS depression</td>
<td>No</td>
<td>Present case</td>
</tr>
</tbody>
</table>
Hydroxychloroquine: Toxicity

- Wider therapeutic index
- Rapidly fatal
- Symptoms: Hypokalemia, Hypotension, Seizure, Dysrhythmia and Cardiovascular Collapse
<table>
<thead>
<tr>
<th>Symptom</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure</td>
<td>Diazepam</td>
</tr>
<tr>
<td>Sedation</td>
<td>Diazepam</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>Careful Replacement</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Epinephrine</td>
</tr>
<tr>
<td>Myocardial Depression</td>
<td>Epinephrine</td>
</tr>
<tr>
<td>QRS Prolongation</td>
<td>Cautious Sodium bicarbonate <em>avoid alkalization</em></td>
</tr>
<tr>
<td>Severe Disease</td>
<td>Combination Therapy Early Intubation EpinephrineHD Diazepam<em>care for PG overdose</em></td>
</tr>
</tbody>
</table>
OTHER INFORMATION
Neuromyopathy

- Progressive weakness and atrophy of proximal muscles
- Slowly develops after weeks, months, years of treatment
- Slow improvement with discontinuation
Retinopathy

• Irreversible visual impairment
  – Pale optic disc
  – macular edema
  – Arteriolar narrowing
  – Peripheral retinal depigmentation

• Complication of long-term (> 5 years), high-dose therapy