Abstract—Ingestion of 1–2 tablets of chloroquine or hydroxychloroquine is thought to predispose children under 6 years of age to serious morbidity and mortality. The actual risk to the toddler and appropriate guidelines for care remain unclear at a time when both medications are therapeutically utilized as anti-inflammatory agents in addition to their main use as anti-parasitics. A review of the literature and data from the American Association of Poison Control Centers reveals instances where exposure to as little as 1–2 tablets of chloroquine resulted in serious consequences. Based on these findings, ingestions of greater than 10 mg/kg of chloroquine base or unknown amounts require triage to the nearest health care facility for 4–6 h of observation. There is very limited data on pediatric hydroxychloroquine overdoses and no reports of toxicity from 1–2 pills, but given its similarity to chloroquine, it also should be considered potentially toxic at small doses. Thus, similar recommendations should be followed for triage after accidental hydroxychloroquine overdose. © 2005 Elsevier Inc.

Keywords—chloroquine; hydroxychloroquine; children; pediatrics; toxicity; overdose; poisoning

INTRODUCTION

Chloroquine [4-amino-quinolone] is an anti-parasitic drug first introduced in 1946 for the treatment and prophylaxis of malaria. Today it continues to be widely prescribed as an anti-parasitic as well as a second line anti-inflammatory drug used to ameliorate the symptoms of autoimmune conditions such as lupus erythematos and rheumatoid arthritis. Chloroquine, marketed under the name Aralen®, is available as a phosphate salt in 250-mg tablets, 500-mg tablets, 16.67-mg/mL oral suspension, and as 50-mg/mL chloroquine hydrochloride for parenteral use. One hundred sixty-seven milligrams of oral chloroquine phosphate yields 100 mg of chloroquine base with a bioavailability of 0.90 (1). One milliliter of parenteral 50-mg/mL chloroquine hydrochloride is equivalent to 40 mg chloroquine base (2). Hydroxychloroquine sulfate, marketed under the name Plaquenil®, is available in 200-mg tablets (equivalent to 155 mg of the base) with a bioavailability of 0.90 (1). One milliliter of parenteral 50-mg/mL chloroquine hydrochloride is equivalent to 40 mg chloroquine base (2). Hydroxychloroquine sulfate, marketed under the name Plaquenil®, is available in 200-mg tablets (equivalent to 155 mg of the base) with no parenteral form. Chloroquine has been reported to cause death in small children with only a few tablets and thus is thought to pose a significant toxicologic risk. There are limited data on pediatric hydroxychloroquine overdoses, but given its similarity to chloroquine it is considered potentially toxic at small doses. Chloroquine and hydroxychloroquine are uncommon pharmaceuticals in American households, but with their
relatively new use as second line anti-inflammatory agents, both stand to become more available. Given the rapid onset of symptoms and lethality of the drug, awareness of the toxidrome and treatment recommendations will aid in patient survival. We review the available medical literature of adverse events from chloroquine and hydroxychloroquine exposure in toddlers and discuss the pathophysiology, pharmacokinetics, presentation, and therapeutic options. Finally, based on the literature, risk is assessed and guidelines presented for evaluation and disposition with regards to patients under the age of 6 years who have potentially ingested 1–2 tablets.

CHARACTERISTICS

The overdose of chloroquine and hydroxychloroquine in children is most often characterized by rapid clinical deterioration that may progress to apnea, seizures and death from cardiorespiratory arrest within 1–3 hours (3). Oral chloroquine is rapidly and almost completely absorbed from the GI tract, leading to rapid signs of toxicity with cardiac and neurologic systems predominating (4). As a result, ingestion of a surprisingly small amount of chloroquine has severe effects. The maximum plasma concentration of the drug seems to be reached within 3 h of ingestion, with whole blood concentration reaching its maximum within 6 h of ingestion (2). Chloroquine is 60% bound to plasma proteins and equally cleared by the kidney and liver.

The toxicity of chloroquine is partially related to its transiently high whole blood concentration present early in the distribution phase that is a result of incomplete distribution from a central compartment 1000 times smaller than the total apparent volume of distribution (5). The drug seems to have toxic effect as a powerful membrane destabilizer, as well as direct effect on organs. This explains the toxic effects of the drug before tissue redistribution. During this transient period of high blood concentration, the drug exerts its membrane destabilization effects on the cardiovascular and neurologic systems, causing dysrhythmias, seizures, respiratory arrest, and subsequent death. As the drug is slowly redistributed to the tissues, this effect wanes while direct tissue toxicity predominates. As such, reports of chloroquine poisoning have shown that the severe toxic effects do not persist for more than 24 h after ingestion, likely correlating with a fall in blood concentration as the drug redistributes (6). Decline of blood concentrations of chloroquine and its metabolites is rapid during the first days but slows down and after 2 months is markedly prolonged (7). Plasma terminal elimination half-life is 20–60 days, with both the parent drug and metabolite able to be detected in urine months after a single dose (8). Very little is known of hydroxychloroquine kinetics in overdose except that plasma concentrations fit a two-compartment model with a volume of distribution of 63 L/kg, and a half-life of 15.5 to 31 h (9,10).

According to animal studies, chloroquine is 2–3 times more toxic than hydroxychloroquine (9). However, a lethal or toxic hydroxychloroquine dose has not been established in humans, so one cannot safely assume that twice the chloroquine dose would be a toxic dose for hydroxychloroquine.

Death from chloroquine toxicity seems to be related to cardiac arrest from chloroquine’s action on the cardiac conduction system and myocardium (6). The primary effects include EKG abnormalities with prolonged PR, QRS and QT intervals, ventricular dysrhythmias, and profound hypotension often progressing suddenly to cardiovascular collapse and shock with increased central venous pressure. Chloroquine’s chemical structure incorporates a quinidine ring that exerts toxicity on the cardiac conduction system and the myocardium by a quinidine-like mechanism including negative inotropism, inhibition of spontaneous diastolic depolarization, slowed intraventricular conduction, increase of effective refractory period, prolongation of QRS and QT intervals, Torsade de Pointes, and ventricular ectopic beats (11,12). Profound refractory hypotension is a common result. Pediatric electrocardiogram (EKG) findings are similar to EKG changes reported in adults; the sequence of EKG changes observed with chloroquine intoxication in animals is sinus tachycardia, decrease in QRS voltage with widening of QRS complex followed by sinus bradycardia, ventricular fibrillation and arrest (13,14).

Respiratory manifestations including tachypnea, pulmonary edema, dyspnea and subsequent apneic respiratory arrest are all common within 1–3 hours of overdose. High drug concentrations in the medulla oblongata may contribute to early ventilatory arrest (15). Direct toxicity of chloroquine on lung tissue cannot be excluded, as measured levels of chloroquine in the lung are 2–3 times greater than whole blood concentrations (16).

Most pediatric overdoses exhibit neurologic symptoms within 30 min to 1 h (13). Central nervous system (CNS) effects vary, but drowsiness is the most common symptom followed by seizures that are difficult to control. Hyperexcitability, irritability or agitation, and altered mental status progressing to coma also have been reported (12). Central nervous system manifestations are believed to be a combination of direct toxic effect of chloroquine on brain tissue as well as damage from hypoxia and hypoperfusion (13). Although not well documented, chloroquine overdose in children can cause psychosis (17).

Hypokalemia occurs in approximately 85% of chlo-
Chloroquine overdoses and seems to be a result of the intracellular transport of potassium rather than a true potassium deficit. Due to this intracellular potassium shift, the hypokalemia has a tendency to self-correct as the intoxication resolves (1). The severity of hypokalemia closely correlates with the level of chloroquine toxicity (12). Potassium concentrations less than 1.9 mEq/L are correlated with severe, life-threatening ingestion (18).

Hepatitis and hepatic necrosis also have been reported, likely as the result of direct toxicity given the high tissue concentration of chloroquine in the liver (19). Methemoglobinemia rarely has been reported and hemolytic anemia may occur in patients with G6PD deficiency. Subclinical nephritis manifesting as intermittent microscopic hematuria despite normal creatinine occurred in a 17-month-old who ingested 4 grams of chloroquine (20).

**TREATMENT**

Chloroquine is well adsorbed by activated charcoal; up to 95–99% is absorbed when charcoal is given within 5 min of ingestion (21). Given the rapid rate of chloroquine absorption, charcoal is an important early measure, especially if administered within 1 h post-ingestion. Cathartics are not recommended given the risk of dehydration and electrolyte abnormalities.

Intravenous access and EKG monitoring should be initiated early. Although the amount ingested should be taken into consideration, serum chloroquine concentrations should not be used to guide interventions. Unlike adults, serum concentrations in the pediatric population do not correlate with the level of toxicity (4). The pediatric case reports show a wide variation of serum or whole blood chloroquine levels that cannot be correlated with level of toxicity or outcome (see Table 1). In contrast, serum chloroquine levels in adults correlate well with outcome. Mild toxicity is present with serum levels of less than 2.5 mg/L; moderate toxicity with EKG abnormalities and moderate neurologic symptoms occur at levels from 2.5 to 5 mg/L; severe intoxication uniformly associated with severe cardiovascular and neurologic abnormalities or death occurs in adults at serum levels greater than 5 mg/L (18).

The treatment protocol for chloroquine overdose in adults is based largely on the prospective study by Riou et al. in 1988 and subsequently confirmed by the Clemessy et al. retrospective study of adult overdoses (6,22). Treatment consists of early mechanical ventilation, high-dose intravenous diazepam (bolus then continuous infusion) and intravenous epinephrine for hypotension. This “combination therapy” seems to protect patients with severe poisoning during the transiently high chloroquine concentrations early in the distribution phase. Though not studied in children, this seems to be a reasonable approach to managing overdoses in the pediatric population.

Early intubation and mechanical ventilation can be considered as one part of a general aggressive intensive medical therapy that should be instituted without hesitation as the clinical situation dictates, even in patients who are alert (22). Consider early mechanical ventilation when instituting high-dose intravenous diazepam, the goal being to prevent hypoxemia from the resulting significant respiratory depressant effect. Additionally, several cases of apnea and idiopathic hypoxemia have been observed previously in severe poisonings with chloroquine; thus, intubation and mechanical ventilation would be warranted in the presence of any clinical evidence of hypoxemia (6). Prevention of hypoxemic neurologic damage should decrease long-term morbidity because some of the neurologic toxicity of chloroquine is reversible as the drug is eliminated from tissues. Avoid barbiturates as induction agents given the report of refractory shock after administration of intravenous thiopental for intubation (22).

High-dose intravenous diazepam is indicated for seizures, dysrhythmias, QRS widening, hypotension, and circulatory collapse. The use of diazepam in treating chloroquine overdose originates from a fortuitous observation in Africa in the 1970s that patients with co-ingestion of chloroquine and diazepam seemed more likely to survive (4). Mechanisms proposed for the possible beneficial effect of diazepam include: a central antagonist effect, an antidysrhythmic effect by an electrophysiologic action inverse to chloroquine, an anticonvulsant effect, a competitive inhibition of fixation of chloroquine on myocardium, the restoration of inotropy, hypoxemia (6). Prevention of hypoxemic neurologic damage should decrease long-term morbidity because some of the neurologic toxicity of chloroquine is reversible as the drug is eliminated from tissues. Avoid barbiturates as induction agents given the report of refractory shock after administration of intravenous thiopental for intubation (22).

For hypotension, blood pressure is supported first with normal saline, followed by intravenous epinephrine infusion as needed. Epinephrine antagonizes the vasodilatation and myocardial depression by acting as a powerful inotrope and vasoconstrictor to overcome the depressive cardiovascular effects of chloroquine. Additionally, it decreases intraventricular conduction time (6,14). The recommended pediatric dose is 0.1 to 1.0 μg/kg/min titrated to the desired systolic pressure depending on the child’s age. Epinephrine should be started only for cases of refractory hypotension; as with diazepam, there is no evidence to show that prophylactic infusion imparts any benefit over its use on an “as required” basis (24). In cases of refractory cardiogenic shock, amrinone should be considered as a second-line agent. Hantson et al. showed that amrinone can be used in conjunction with other inotropic drugs given its prop-
erty of increased contractility independent of β1 adrenergic receptors (25). Dopamine, norepinephrine, and especially isoproterenol also have been suggested for treatment of chloroquine-induced hypotension and bradycardia.

Hypokalemia < 3.0 mEq/L should be corrected carefully. Potassium levels should be frequently monitored to avoid iatrogenic hyperkalemia, as chloroquine-induced hypokalemia has a tendency to self-correct from the redistribution of intracellular potassium. Infusion should not exceed 10–15 mEq KCl per hour.

Consider plasma alkalization with sodium bicarbonate for QRS widening, given the quinidine-like effect of chloroquine on the myocardium. However, this therapy may worsen pre-existing hypokalemia, and thus should be used with great care. Use of any type I anti-dysrhythmics will further prolong the QT interval and should be avoided.

Chloroquine has a large volume of distribution and is rapidly distributed intracellularly. As such, there is no benefit from hemodialysis, peritoneal dialysis, or hemoperfusion, even when initiated within 2 h (2,26,27).

Treatment of hydroxychloroquine overdose is modeled after that for chloroquine, as little specific information on hydroxychloroquine treatment is available.

Table 1. Chloroquine in Children under 6 years of Age: Summary of 1–2-Tablet Ingestions

<table>
<thead>
<tr>
<th>Age</th>
<th>Total Dose and mg/kg (base) Ingested</th>
<th>Serum Levels</th>
<th>Onset (h)</th>
<th>Clinical Effects</th>
<th>Outcome*</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 years</td>
<td>500 mg</td>
<td>NR</td>
<td>&lt; 1</td>
<td>Cardiac arrest</td>
<td>Death within 1 h</td>
<td>(46)</td>
</tr>
<tr>
<td>12 months</td>
<td>27 mg/kg 300 mg</td>
<td>4.4 mg/L</td>
<td>0.5</td>
<td>Apnea, bradycardia, hypotension, hyperglycemia; seizures, hyperkalemia</td>
<td>Brain dead at 2 days</td>
<td>(13)</td>
</tr>
<tr>
<td>7 weeks</td>
<td>37.6 mg/kg 500 mg</td>
<td>NR</td>
<td>NR</td>
<td>Apnea, cyanosis</td>
<td>Discharged ‘in good health’ at 4 days</td>
<td>(1)</td>
</tr>
<tr>
<td>24 months</td>
<td>100 mg/kg (? 1 pill (unknown strength))</td>
<td>0.4 mg/L</td>
<td>0.75</td>
<td>Labored respirations, cardiovascular collapse</td>
<td>Death at 8 days</td>
<td>(3)</td>
</tr>
<tr>
<td>17 months</td>
<td>2.4 gm 800 mg</td>
<td>1.0 µg/ml</td>
<td>0.5</td>
<td>Ventricular tachycardia, hypotension, apnea, seizures cardiac arrest</td>
<td>Unconscious with no purposeful movement</td>
<td>(49)</td>
</tr>
<tr>
<td>20 months</td>
<td>0.75–1 gm 1 gm</td>
<td>NR</td>
<td>1</td>
<td>Seizures, apnea, cardiac arrest</td>
<td>Death at 2.5 h</td>
<td>(47)</td>
</tr>
<tr>
<td>12 months</td>
<td>7 weeks 500 mg</td>
<td>0.8 µg/ml</td>
<td>0.5</td>
<td>Unresponsive, cardiorespiratory arrest; refractory hypotension</td>
<td>Death on day 3 (ventilatory support withdrawn)</td>
<td>(28)</td>
</tr>
<tr>
<td>28 months</td>
<td>1 gm 34.9 mg/kg</td>
<td>0.8 mg/100 mL</td>
<td>1</td>
<td>Unconscious, apnea</td>
<td>Death at 27 h</td>
<td>(27)</td>
</tr>
<tr>
<td>14 months</td>
<td>1–2 gm 1 g</td>
<td>NR</td>
<td>1.75</td>
<td>Cardiorespiratory arrest</td>
<td>Death at 2 h</td>
<td>(47)</td>
</tr>
<tr>
<td>17 months</td>
<td>4 gm 286 mg/kg</td>
<td>NR</td>
<td>0.5</td>
<td>Ventricular fibrillation cardiovascular collapse</td>
<td>Severe neurologic sequelae</td>
<td>(20)</td>
</tr>
<tr>
<td>2 years</td>
<td>1–2 gm 286 mg/kg</td>
<td>NR</td>
<td>2</td>
<td>Cardiorespiratory arrest</td>
<td>Death at 6 h</td>
<td>(50)</td>
</tr>
</tbody>
</table>

LITERATURE REVIEW

Poison centers reported 1177 anti-malarial exposures to the American Association of Poison Control Centers Toxic Exposure Surveillance System (AAPCC TESS) from 1986 thru 2001 in children < 6 years of age, accounting for under 0.01% of total pediatric pharmaceutical exposures (28–43). The published AAPCC-TESS annual reports provide data on the anti-malarial category, but do not provide a breakdown by drug so it is not possible to determine how many of these exposures were to chloroquine or hydroxychloroquine. There were two fatalities involving chloroquine; one in a 12-month-old who ingested 1 g and another in a 2-year-old who ingested an unknown quantity (28,29).

Chloroquine has a low margin of safety. The therapeutic dose range for children is 5–10 mg/kg (base) with a lethal dose of 30–50 mg/kg (1,7,13,44,45). Clyde describes a 3-year-old boy on 150 mg of chloroquine base every week who died of cardiac arrest within 1 h of taking 300 mg (27 mg/kg), the lowest reported lethal dose (46). Although the history was considered reliable, residual chloroquine in tissues from previous doses and tissue chloroquine analysis suggesting a higher dose confused the evidence. Kelly et al. report a 12-month-old who presented within 30 min with apnea, bradycardia, and subsequent death despite aggressive resuscitation,
after ingestion of only one 500-mg chloroquine phosphate tablet (equivalent to 37.6 mg/kg of base) (13). McCarthy and Swabe reported a 24-month-old who presented in cardiopulmonary arrest within 1 h of presumably ingesting one chloroquine tablet (strength not specified) (3). Cann and Verhulst reported apnea and cardiac arrest within 1 h, and death within 2.5 h in a 3-year-old who ingested 1.5–2 chloroquine phosphate 500-mg tablets (47). McCann and colleagues reported a 28-month-old who died after ingesting 2 chloroquine 500-mg tablets (equivalent to 34.9 mg/kg of base) (27). Table 1 further describes case reports that document death or irreversible injury resulting from 1–2 tablets of chloroquine.

Case reports suggest that the mortality rate after chloroquine exposures in young children may be higher than in adults. A review by McCarthy and Swabe of 22 unintentional ingestions in children from 7 weeks to 5 years of age between 1961 and 1990 found 16 deaths (73%) with 3 of the survivors in a persistent vegetative state (3). Fatal iatrogenic exposure reinforces the potential low dosage lethality. McCarthy and Swabe also reported 9 cases of iatrogenic exposure resulting in 8 fatalities (89%) in children aged 5 days to 18 months. The dose range reported was 37.5 to 300 mg of intramuscular chloroquine for malaria treatment (3).

Outcomes after chloroquine ingestion in children vary from full recovery to permanent neurologic sequelae to death. Although fatal doses have been reported as low as 35 mg/kg, full recovery without cardiovascular collapse also has been reported after ingestions as high as 100 mg/kg of chloroquine base and survival with severe neurologic sequelae after 285.7 mg/kg of chloroquine phosphate (equivalent to 171 mg/kg chloroquine base) (1,13,20,27).

Hydroxychloroquine overdoses are rarely reported; a literature search by Marquardt and Albertson revealed only 7 reported acute overdoses, of which only one was in a child less than 6 years old (8). This 2-year-old boy developed seizures, cardiorespiratory arrest, and died after ingesting 12 grams of hydroxychloroquine; postmortem blood concentration of 104 mg/L confirmed a large overdose (48).

Chloroquine is quickly absorbed from the gastrointestinal tract, thus, the interval between ingestion and cardiorespiratory collapse is frequently less than 2 h. This rapid onset of toxic effects is reported in fatal and nonfatal cases. Table 1 demonstrates the short interval between ingestion and onset of effects in children possibly ingesting only 1–2 tablets. Review of cases involving larger doses demonstrates onset of clinical effects ranging from 0.5 to 3 h (20,46,49,50).

**RECOMMENDATIONS**

The majority of pediatric studies referenced are either case reports or small case series. Consequently, therapeutic recommendations are based upon the authors’ evaluation of published data with strength of evidence less than that provided by well-controlled prospective pediatric studies. However, given the high morbidity and lethality associated with relatively low doses, chloroquine ingestions warrant a cautious approach. Table 2 reviews the common clinical features and specific therapeutic recommendation of chloroquine ingestions.

The margin of safety for chloroquine is extremely low, and the pediatric mortality and morbidity remains extremely high even with therapeutic intervention. Given a unit-dose of 500 mg chloroquine, one tablet in a 10-kg infant is a potentially lethal dose. Thus, any ingestion of unknown dosage should be evaluated by a physician in an emergency department setting where hemodynamic monitoring is available. Ingestions of less than the therapeutic dose of 10 mg/kg of chloroquine base may not need physician evaluation and monitoring if the dose

**Table 2. Clinical Features and Treatment Aspects of Chloroquine Poisoning**

<table>
<thead>
<tr>
<th>Clinical Manifestation</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac</strong></td>
<td></td>
</tr>
<tr>
<td>Negative inotrope</td>
<td>1. EKG monitoring and i.v. access</td>
</tr>
<tr>
<td>Inhibition of spontaneous diastolic depolarization</td>
<td>2. High dose i.v. diazepam bolus then continuous infusion</td>
</tr>
<tr>
<td>Slowing of intraventricular conduction</td>
<td>3. Bolus normal saline for mild hypotension</td>
</tr>
<tr>
<td>Vasodilatation and profound hypotension</td>
<td>4. i.v. epinephrine for profound hypotension</td>
</tr>
<tr>
<td>Dysrhythmias</td>
<td>5. Amrinone for refractory cardiogenic shock</td>
</tr>
<tr>
<td><strong>Pulmonary</strong></td>
<td></td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>1. Intubation as needed for airway protection</td>
</tr>
<tr>
<td>Apneic respiratory arrest</td>
<td>2. Mechanical ventilation for hypoxia and respiratory depression</td>
</tr>
<tr>
<td>Hypoxia</td>
<td></td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td></td>
</tr>
<tr>
<td><strong>Neurologic</strong></td>
<td></td>
</tr>
<tr>
<td>Hyperexcitability</td>
<td>1. High dose i.v. diazepam for seizures</td>
</tr>
<tr>
<td>Seizures</td>
<td></td>
</tr>
<tr>
<td>Psychosis</td>
<td></td>
</tr>
<tr>
<td>Altered mental status</td>
<td></td>
</tr>
<tr>
<td><strong>Other effects</strong></td>
<td></td>
</tr>
<tr>
<td>Severe hypokalemia</td>
<td>1. Charcoal administration</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>2. Careful repletion of potassium with frequent monitoring to avoid overcorrection</td>
</tr>
<tr>
<td>Hemolytic anemia if G6PD deficiency</td>
<td></td>
</tr>
</tbody>
</table>
ingested can be absolutely confirmed and the patient has close observation at home. Those children triaged to the emergency department for observation should undergo cardiac monitoring for approximately 6 h. Clinical toxicity would be expected well before this point in time and symptom onset has not been documented beyond 6 h post-ingestion. Additionally, this time frame correlates with the peak whole blood concentrations of chloroquine. Development of any symptoms or EKG changes necessitates admission and management in an ICU setting. Patients who remain asymptomatic for 6 h post-ingestion can be discharged home.

No instances of toxicity in toddlers resulting from exposure to 1–2 tablets of hydroxychloroquine are found in the literature. Though it is produced in lower dose tablets (200 mg) and is thought to be less toxic than chloroquine, caution may be warranted considering the similarities in structure and pharmacology.

**SUMMARY**

Chloroquine is a potentially lethal drug even with a minimal exposure of 1–2 tablets in the pediatric population. Given the rapid manifestations and high morbidity and mortality associated with toxic ingestions, unintentional ingestions of unknown amounts or greater than 10 mg/kg chloroquine base should be referred to an emergency department for observation and cardiac monitoring.

**REFERENCES**