

4-Aminoquinolines (Lexi-Tox)

CAS Registration

- 118-42-3
- 4085-31-8
- 50-63-5
- 54-05-07
- 85547-56-4
- 86-42-0

Use

Chloroquine and hydroxychloroquine are used for the treatment and prophylaxis of malaria when chloroquine resistance is not present or suspected. In addition, hydroxychloroquine is used for the treatment of various autoimmune and rheumatic conditions.

Most recently, these agents have been used for the treatment of coronavirus disease 2019 (COVID-19) (Gautret 2020); accidental overdose has been reported in patients attempting to prevent COVID-19 with a nonmedicinal product (eg, aquarium treatment) containing chloroquine phosphate (Banner Health 2020).

Clinical Presentation

Ingestion: Initial symptoms may include drowsiness, dizziness, vomiting, and headache (Jaeger 1987). Shortly thereafter, however, significant toxicity characterized by a **rapid onset of cardiotoxic effects (eg, 1 to 3 hours postingestion)** may occur, including intractable hypotension, ventricular dysrhythmias, and hypokalemia-induced conduction abnormalities (Barry 2019; Gunja 2009; Isbister 2002; Jaeger 1987); the cardiotoxic effects may result in respiratory depression leading to respiratory arrest. Neurotoxicity, including seizures and visual disturbances, have also been described (Isbister 2002; Kemmenoe 1990). Clinicians should note that the degree of hypokalemia correlates with the severity of intoxication and mortality rate (Clemessy 1995; Mégarbane 2010). Duration of symptoms may persist beyond 24 hours (Clemessy 1995).

An acute chloroquine ingestion of ≥ 5 g has been associated with mortality (Riou 1988a). Poor outcomes after chloroquine ingestion are associated with a systolic blood pressure less than 80 mm Hg or a QRS interval >120 msec (Clemessy 1996b; Riou 1988a).

Ocular toxicity secondary to acute chloroquine or hydroxychloroquine intoxication is often transient and reversible and may include blurred vision, defective color perception, retinitis, visual field constriction, and blindness (Barry 2019; Chansky 2017; Jaeger 1987); this is in contrast to the potentially irreversible retinopathy that is associated with chronic administration of hydroxychloroquine.

Population-dependent:

Pediatric patients: Chloroquine is a potentially lethal drug even with a minimal exposure of 1 to 2 tablets in this patient population (Smith 2005).

Comprehensive listing by system (listed alphabetically):

Cardiovascular: Appearance of U waves on ECG, atrioventricular block, cardiomyopathy, depression of ST segment on ECG, flattened T wave on ECG, hypotension, prolonged QT interval on ECG, torsades de pointes, ventricular fibrillation, ventricular tachycardia, widened QRS complex on ECG

Endocrine & metabolic: Hypoglycemia (Cansu 2008; Unübol 2011), hypokalemia, metabolic acidosis

Gastrointestinal: Abdominal cramps, abdominal pain, diarrhea, nausea, vomiting

Hematologic & oncologic: Agranulocytosis, anemia, aplastic anemia, bone marrow failure, hemolysis (in patients with glucose-6-phosphate deficiency), leukopenia, neutropenia, pancytopenia, thrombocytopenia

Hepatic: Abnormal hepatic function tests, acute hepatic failure, hepatitis (Abdel Galil 2015; Sunkara 2018)

Hypersensitivity: Angioedema, anaphylaxis

Nervous system: Agitation, ataxia, central nervous system depression, confusion, decreased deep tendon reflex, delirium, depression, dizziness, dystonic reaction, emotional seizure, extrapyramidal reaction, fatigue, hallucination, headache, irritability, lability, motor dysfunction, nervousness, neuromyopathy (Vinciguerra 2015), nightmares, paresthesia (Chansky 2017), parkinsonism, personality changes, polyneuropathy, psychosis (Biswas 2014; Mascolo 2018), sensorineural hearing loss, suicidal tendencies, vertigo, vestibular neurotoxicity (Chansky 2017)

Neuromuscular & skeletal: Myopathy (including palsy or neuromyopathy, leading to progressive weakness and atrophy of proximal muscle groups; may be associated with mild sensory changes and loss of deep tendon reflexes)

Ophthalmic: Blurred vision, corneal changes (corneal edema, corneal opacity, corneal sensitivity, corneal deposits), decreased visual acuity, macular degeneration, maculopathy, nystagmus disorder, photophobia, retinal pigment changes, retinitis pigmentosa, retinopathy (4%; chronic use; serum concentration dependent [Petri 2020]; early changes reversible [may progress despite discontinuation if advanced]), scotoma, vision color changes, visual disturbance, visual field defect

Otic: Deafness, hearing loss (risk increased in patients with preexisting auditory damage), tinnitus

Respiratory: Apnea, bronchospasm, respiratory depression

Mechanism of Toxicity

Acute toxicity is secondary to dose-related cardiac sodium and potassium channel blockade resulting in delayed repolarization and slow intraventricular conduction; the 4-aminoquinolines also result in decreased contractility due to a negative inotropic effect (Radke 2019). Hypokalemia appears to be a result of potassium shifting from the extracellular to the intracellular space as opposed to a true potassium deficit (Mégarbane 2010).

The pharmacokinetic parameters of chloroquine (ie, rapid absorption, large volume of distribution, slow elimination) result in high initial intravascular concentrations followed by slow distribution into the tissue; the high free concentrations present early in the distribution phase are thought to result in the rapid onset of cardiorespiratory collapse (de Olano 2019; Mégarbane 2010).

Diagnosis

Diagnosis should be made based upon patient history, physical examination, laboratory findings, and clinical suspicion. Laboratory tests to confirm the diagnosis and guide treatment are available but may not be returned in a timely manner (Barry 2019); however, immediate and serial measurements of blood chloroquine concentration may be helpful in predicting severity of intoxication (Mégarbane 2010).

Patients who present with symptoms of toxicity secondary to a 4-aminoquinoline should undergo evaluation of electrolytes (especially potassium), as well as cardiac and hemodynamic monitoring.

Laboratory Testing/Diagnostic Procedures

- Electrolyte Panel, Serum or Plasma

Treatment: Stabilization

Initially, evaluate and correct immediate life-threatening complications (eg, airway, breathing, and circulation). The most serious complications include intractable hypotension, ventricular dysrhythmias, hypokalemia-induced conduction abnormalities, and respiratory depression. Aggressive treatment initiated soon after the onset of symptoms is critical. Rapid deterioration, including cardiac toxicity, may occur soon after ingestion.

Clinicians should note that the use of thiopental to facilitate endotracheal intubation has resulted in cardiac arrest in several patients; therefore, it is recommended that barbiturates are avoided in patients with acute intoxication (Clemessy 1996b)

Treatment: Decontamination

Ingestion: If the patient presents within 1 to 2 hours of ingestion, consider the following decontamination procedure(s):

- Gastric lavage: In rare situations when gastric lavage is deemed appropriate, it is most effective if initiated within 1 hour of the ingestion; however, gastric lavage has not been proven to be beneficial and is not routinely recommended due to the risk of complications and the lack of demonstrated efficacy. Use is contraindicated in a patient with an unprotected airway, in a patient in whom its use increases the risk and severity of aspiration, and in a patient who is at risk of hemorrhage or gastrointestinal perforation due to pathology (Benson 2013; Vale 2004).
- Single-dose activated charcoal: Use may be considered in a patient who presents within 1 hour of the ingestion (Chyka 2005). Activated charcoal was shown to adsorb 95% to 99% of chloroquine when at least 50 g was administered within 5 minutes of ingestion (Kivistö 1993). Use is contraindicated in a patient who has a diminished level of consciousness, unless the airway is protected.

Activated charcoal in water: Single dose: Oral or NG:

Infants <1 year: 10 to 25 g; **Note:** Although dosing by body weight is reported in children (0.5 to 1 g/kg) and published in many resources, there are no data or scientific rationale to support this recommendation (Chyka 2005).

Infants and Children 1 to 12 years: 25 to 50 g

Children >12 years and Adults: 25 to 100 g

Based on experimental and clinical studies, the following decontamination procedures have **not** been shown to be beneficial:

- Ipecac (AACT 2004; AAP 2003; Höjer 2013)
- Cathartics (AACT, 2004)

Treatment: Antidote(s)

No specific antidote exists.

Treatment: Pharmacologic Supportive Therapy

Hypotension: Initial intervention should include fluid resuscitation.

Vasopressors: If hypotension persists despite the use of fluids, a direct-acting vasopressor should be administered. Epinephrine at high doses (initiate at 0.25 mcg/kg/minute and titrate by 0.25 mcg/kg/minute based on response) is the preferred vasopressor as it has been the most extensively studied in chloroquine poisoning; consider the risk of

worsening hypokalemia with increasing doses (Barry 2019; Clemessy 1996b; Marquardt 2001; Riou 1988a).

Diazepam: Historically, diazepam has been used based on anecdotal reports that patients who overdosed on both chloroquine and diazepam had better outcomes than those who ingested chloroquine alone. Animal studies supported the claim (Crouzette 1983; Riou 1988b); however, studies in humans have produced conflicting results (Clemessy 1996a; Riou 1988a). Potential mechanisms include: a central antagonist effect, anticonvulsant effect, antiarrhythmic effect by an electrophysiologic action inverse to chloroquine, pharmacokinetic interaction, and a decrease in chloroquine-induced vasodilation; definitive evidence is not available (Marquardt 2001). Some experts recommend high-dose therapy (2 mg/kg IV over 30 minutes followed by 1 to 2 mg/kg/day for 2 to 4 days) in patients with serious toxicity (Barry 2019). This dose may deplete diazepam stock rapidly. It is not known if other benzodiazepines are effective.

Impaired cardiac conduction:

Sodium bicarbonate: Use of sodium bicarbonate for QRS widening has been reported to be successful (due to quinidine-like effects of 4-aminoquinolines) but has not been validated (Barry 2019). Consider the severity of hypokalemia prior to administration and correct electrolyte disturbances prior to use and throughout therapy.

Dosage: IV: Note: Dosage recommendations are based on use in toxicity secondary to other sodium channel blockers (AHA [Vanden Hoek 2010]).

Infants and Children: IV, I.O.: 1 to 2 mEq/kg; repeat as needed to maintain goal arterial pH; initiation of a 150 mEq/L infusion may be required to maintain alkalosis (Hegenbarth 2008). In infants and children <2 years of age, the 4.2% (0.5 mEq/mL) solution should be used. **Note:** If intraosseous route is used for administration and is subsequently used to obtain blood samples for acid-base analysis, results will be inaccurate (AHA [Kleinman 2010]).

Adults: IV: 1 mEq/kg; repeat as needed until hemodynamic stability is restored and QRS duration is ≥ 120 msec (AHA [Vanden Hoek 2010]).

Hypokalemia: Administer potassium to correct severe hypokalemia; anticipate and monitor for rebound hyperkalemia (de Olano 2019; Jordan 1999; Marquardt 2001).

Hemodynamic compromise unresponsive to conventional treatment:

Fat emulsion (off-label use): Lipid emulsion therapy has been reported to be successful but has not been validated (Bethlehem 2019; McBeth 2015; Murphy 2018; ten Broeke 2016). Because chloroquine and hydroxchloroquine are lipophilic, it is thought that exogenous lipids act to draw tissue-bound drugs from cellular receptors into the

expanded lipid phase. This effect is also known as the "lipid sink" effect. Clinicians should be aware that fat emulsion administration is experimental in this patient population.

Indication for use: Hemodynamic instability unresponsive to conventional resuscitation.

Mechanism of action: Exogenous lipids provide an alternative source of binding lipid-soluble agents. It has been suggested that improved cardiac fatty acid utilization, as well as changes in calcium and sodium channels, may contribute to improved hemodynamics (Walter 2018).

Dosage:

Note: Administration of large volumes of intravenous lipid emulsion may result in adverse effects; doses greater than the recommended amount should be used with caution, if at all.

Serious hemodynamic or other instability secondary to highly lipid soluble substances (off-label use): Note: Continue chest compressions during administration (lipid must circulate): 20%: IV: 1.5 mL/kg (maximum: 100 mL; ASRA [Neal 2018]) administered over 1 to 3 minutes, followed immediately by an infusion of 0.25 mL/kg/minute (maximum: 200 to 250 mL; ASRA [Neal 2018]) (recommended infusion durations vary; see below); may repeat the bolus as necessary for persistent cardiovascular collapse or if instability reemerges (ACMT 2017; AHA [Lavonas 2016]; ASRA [Neal 2018]). Some suggest dosing based on lean body weight (AHA [Lavonas 2016]; ASRA [Neal 2018]). Suggested maximum dose: 10 to 12 mL/kg over 30 to 60 minutes (AHA [Lavonas 2016]; ASRA [Neal 2018]).

After administration of the initial bolus and continuous infusion, recommendations regarding the continuous infusion vary significantly:

American College of Medical Toxicology: If after the bolus and continuing the infusion for 3 minutes, the patient demonstrates a significant response, the infusion rate may be reduced to 0.025 mL/kg/minute (ie, one-tenth the initial rate). If instability reemerges, the infusion rate may be increased back to 0.25 mL/kg/minute **or** the bolus may be repeated (ACMT 2017).

American Heart Association recommendations: Continue infusion for 30 to 60 minutes (AHA [Lavonas 2016]).

American Society of Regional Anesthesia and Pain Medicine: Continue infusion for at least 10 minutes after hemodynamic stability has

been restored. Consider rebolus or increase the infusion rate to 0.5 mL/kg/minute if hemodynamic instability persists or recurs (ASRA [Neal 2018]).

Control of seizures: First-line therapy with benzodiazepines (eg, diazepam); additional agents may be added if needed (eg, propofol). In patients without IV access, treatment with IM midazolam is recommended. Phenytoin/fosphenytoin is not generally useful in the management of poison-induced seizures; routine use is not recommended (Bey 2001). Barbiturates are not recommended in patients with acute chloroquine poisoning (Clemessy 1996b).

DiazePAM:

Children and Adolescents:

IV: *American Academy of Pediatrics and Neurocritical Care Society recommendations:* 0.1 to 0.3 mg/kg (maximum dose: 10 mg) given over ~2 minutes; may repeat dose after 5 to 10 minutes (AAP [Hegenbarth 2008]) or 0.15 mg/kg (maximum dose: 10 mg) given at a rate of <5 mg/minute; may repeat in 5 minutes (NCS [Brophy 2012]).

Rectal (formulation not specified): **Note:** According to the Neurocritical Care Society, diazepam may be administered rectally when there is no IV access and IM administration of midazolam (drug of choice for IM administration during status epilepticus) is contraindicated (NCS [Brophy 2012]). The parenteral formulation of diazepam may be given rectally if rectal gel (Diastat) is not available (Arif 2008; Dieckmann 1994). Maximum recommended dose according to the manufacturer: 20 mg/dose.

Neurocritical Care Society recommendations (NCS [Brophy 2012]):

Children 2 to 5 years: 0.5 mg/kg

Children 6 to 11 years: 0.3 mg/kg

Children ≥12 years and Adolescents: 0.2 mg/kg

American Academy of Pediatrics recommendations (AAP [Hegenbarth 2008]): 0.5 mg/kg (maximum dose: 20 mg).

Adults:

IV:

Manufacturer's labeling: 5 to 10 mg given at a rate of ≤5 mg/minute; may repeat every 10 to 15 minutes (maximum total dose: 30 mg).

Neurocritical Care Society recommendations: 0.15 mg/kg (maximum dose: 10 mg) given at a rate of ≤ 5 mg/minute; may repeat in 5 minutes (NCS [Brophy 2012]).

Rectal (formulation not specified): **Note:** Diazepam may be administered rectally when there is no IV access and IM administration of midazolam (drug of choice for IM administration during status epilepticus) is contraindicated (NCS [Brophy 2012]). The parenteral formulation of diazepam may be given rectally if rectal gel (Diastat) is not available (Arif 2008).

Premonitory/out-of-hospital treatment: 10 mg once; may repeat once if necessary (Kälviäinen 2007).

Lorazepam:

Infants, Children, and Adolescents (off-label use):

Neurocritical Care Society recommendations: IV: 0.1 mg/kg (maximum dose: 4 mg) given at a maximum rate of 2 mg/minute; may repeat in 5 to 10 minutes (NCS [Brophy 2012]). **Note:** Dilute dose 1:1 with saline.

American Academy of Pediatrics recommendations: IV, IM: 0.05 to 0.1 mg/kg (maximum dose: 4 mg); may repeat dose every 10 to 15 minutes if seizure continues (AAP [Hegenbarth 2008]).

Adults: IV:

Neurocritical Care Society recommendations: 0.1 mg/kg (maximum dose: 4 mg) given at a maximum rate of 2 mg/minute; may repeat in 5 to 10 minutes (NCS [Brophy 2012]). **Note:** Dilute dose 1:1 with saline.

Manufacturer's labeling: 4 mg given slowly (2 mg/minute); may repeat in 10 to 15 minutes. May be given IM, but IV preferred.

Propofol: IV: Children, Adolescents, and Adults: **Note:** Mechanical ventilation and cardiovascular monitoring required; titrate dose to cessation of electrographic seizures or burst suppression (NCS [Brophy 2012]).

Neurocritical Care Society recommendations (NCS [Brophy 2012]):

Loading dose: 1 to 2 mg/kg with initiation of a continuous infusion

Continuous infusion: Initial: 20 mcg/kg/minute (1.2 mg/kg/hour). If the patient experiences breakthrough status epilepticus while on continuous infusion, increase infusion rate by 5 to 10 mcg/kg/minute (0.3 to 0.6 mg/kg/hour) every 5 minutes (may also administer a 1 mg/kg bolus dose with continuous

infusion titration); dosage range: 30 to 200 mcg/kg/minute (1.8 to 12 mg/kg/hour). **Note:** Use caution with doses >80 mcg/kg/minute (>4.8 mg/kg/hour) for >48 hours. Prior to withdrawal, a period of at least 24 to 48 hours of electrographic control is recommended; withdraw gradually to prevent recurrent status epilepticus.

Midazolam:

IM:

Children and Adolescents: **Note:** Administered when convulsions last >5 minutes or if convulsions are occurring after having intermittent seizures without regaining consciousness for >5 minutes (Silbergleit 2012).

IM (NCS [Brophy 2012]; Silbergleit 2012):

<13 kg: Not evaluated

13 to 40 kg: 5 mg once

>40 kg: 10 mg once

Adults: **Note:** Administered when convulsions last >5 minutes or if convulsions are occurring after having intermittent seizures without regaining consciousness for >5 minutes: 10 mg once (Silbergleit 2012) or 0.2 mg/kg (maximum dose: 10 mg) (NCS [Brophy 2012]).

Intranasal: Children and Adolescents: 0.2 mg/kg (NCS [Brophy 2012]) **Note:** Use 5 mg/mL injectable concentrated solution to deliver dose (Ljungman 2000). Due to the low pH of the solution, burning upon administration is likely to occur (Bozkurt 2007).

Buccal: Children and Adolescents: 0.5 mg/kg (NCS [Brophy 2012]).

Treatment: Nonpharmacologic Supportive Therapy

Mechanical ventilation: Early initiation of endotracheal intubation and mechanical ventilation is a cornerstone of treatment (Barry 2019; Clemessy 1996b)

Extracorporeal elimination: Due to the pharmacokinetic properties of these agents (ie, large volumes of distribution, significant protein binding), enhanced elimination techniques are not expected to be beneficial (Barry 2019). Hemoperfusion was not beneficial in one patient following overdose (Boereboom 2000); conflicting information exists on the impact of hemodialysis (McBeth 2015). Hemoperfusion is not available in most hospitals. Early extracorporeal membrane oxygenation has been successful in managing a severe chloroquine overdose (Bagate 2017).

Patient Disposition

Initial evaluation: The following individuals need to be evaluated in an emergency department (ED):

- Patients who expose themselves to a 4-aminoquinoline with the intent of self-harm or intentional abuse
- Victims of abuse or neglect who were exposed to a 4-aminoquinoline with malicious intent
- Patients experiencing signs and symptoms of overdose (eg, drowsiness, dizziness, vomiting, headache)
- All children who may have ingested a 4-aminoquinoline should be evaluated in an emergency department

Emergency department monitoring

- Patients should undergo frequent evaluation of vital signs and electrolytes. Obtain a baseline ECG and initiate continuous cardiac monitoring.

Criteria for emergency department discharge

- Patients who have experienced complete resolution of symptoms may be considered for discharge

Criteria for hospital admission

- Patients who develop cardiotoxicity (eg, conduction disturbances), neurological effects, or respiratory depression
- Patients may require critical care capabilities based upon the severity of their illness

Pharmacodynamics/Kinetics

Note: The following data is based on therapeutic doses (except where noted); parameters may change in overdose.

Chloroquine

Distribution: Widely in body tissues including eyes, heart, kidneys, liver, leukocytes, and lungs where retention is prolonged

Protein binding: ~55%

Metabolism: Partially hepatic to main metabolite, desethylchloroquine

Half-life: 3 to 5 days

Time to peak serum concentration: Oral: Within 1 to 2 hours

Excretion: Urine (~70%; ~35% as unchanged drug); acidification of urine increases elimination; small amounts of drug may be present in urine months following discontinuation of therapy

Hydroxychloroquine

Protein binding: ~40%, primarily albumin (Tett 1993)

Metabolism: Hepatic; metabolites include bidesethylchloroquine, desethylhydroxychloroquine, and desethylchloroquine (McChesney 1966)

Half-life elimination: ~40 days (Tett 1993); **Note:** Following overdose in one patient, the apparent half-life was documented to be 11.6 hours (de Olano 2019); another patient exhibited an elimination half-life of 22 hours following overdose (Jordan 1999)

Excretion: Urine (15% to 25% [Tett 1993]; as metabolites and unchanged drug [up to 60%, McChesney 1966]); may be enhanced by urinary acidification

Additional Information

Optimal care decisions are made based upon specific patient details. Consider consultation with a poison control center. To reach poison control centers in the United States and its territories, call 1-800-222-1222.

Index Terms

4-Aminoquinolones; Aminoquinolines; Aminoquinolones; Amodiaquine; Antimalarials; Chloroquine; Chloroquine phosphate; Coronavirus; COVID-19; Hydroxychloroquine; Piperaquine

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