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Chloroquine/Hydroxychloroquine

Background

Chloroquine and hydroxychloroquine are antimalarial medications in the 4-aminoquinoline class. Hydroxychloroquine is also used as an anti-inflammatory agent for diseases such as rheumatoid arthritis and lupus erythematosus. Pharmacologic and toxicologic properties are similar for both drugs.

Chloroquine phosphate is also available as a chemical product used in aquarium and pool water treatments.

Pathophysiology

Chloroquine is rapidly absorbed after oral exposure but subsequent distribution from blood to organs may lead to transiently high blood levels that may contribute to rapid cardiovascular toxicity in overdose. Abrupt deterioration may occur within 30 minutes of ingestion, with death reported as quickly as within 1-3 hours of ingestion. As redistribution of drug occurs, toxicity decreases, with persistence of serious toxicity rare after 24 hours.

The primary manifestation of acute toxicity is cardiovascular collapse due to sodium and potassium channel blockade. Hypokalemia is very common and related to intracellular shift rather than a potassium deficit.

The acute toxicologic effects of chloroquine and hydroxychloroquine are similar, though animal studies suggest chloroquine is 2-3 times more toxic than hydroxychloroquine. In adults, the estimated lethal dose of chloroquine is estimated at 30-50 mg/kg, with fatalities reported with ingestions of 2.25g. In contrast, life-threatening toxicity has been seen in adults with ingestions of 8g of hydroxychloroquine.

Limited information exists for chloroquine exposures in pediatric patients, but pediatric fatalities have been reported with exposure to as little as 1 tablet of chloroquine (as low as 300 mg). Based on a review of pediatric exposure to chloroquine and hydroxychloroquine, ingestions of 10 mg/kg or higher should be referred to an emergency department for observation and cardiac monitoring for 4 hours. (Smith 2005).

Clinical manifestations

- Severe hypotension (<80 mmHg systolic blood pressure) may be seen.
- Respiratory depression is common, with a risk for apnea and precipitous cardiovascular collapse.
- Cardiac manifestations include tachycardia, QRS widening (>120 ms), AV block, ST and T wave depression, and QT interval prolongation. Ventricular dysrhythmias including ventricular fibrillation are reported with serious toxicity.
- Hypokalemia may ensue—severity is a prognostic indicator. While some data suggests that hypokalemia may have protective effect in acute chloroquine toxicity, severe hypokalemia itself may result in lethal dysrhythmias.
- Neurologically, CNS depression and seizures may occur. Rare dystonic reactions are reported.
- Unlike chronic toxicity, vision and hearing changes are typically transient in acute toxicity.
- Hemolysis may occur in patients with G6PD deficiency due to oxidant stress on red blood cells.

Monitoring

- Obtain an EKG and maintain patients on continuous cardiac monitoring.
- Frequently monitor vital signs and mental status.
- Obtain a CMP and CBC to assess for any manifestations of toxicity, with particular attention for the development of hypokalemia (consider monitoring of potassium every 4 hours for the first 12-24 h).
- Serum chloroquine levels may be drawn but are usually not readily available and not needed to guide management of acute toxicity.

Management

- Activated charcoal (1 g/kg for pediatric patients, 50 g for adult patients) may be given to patients presenting early (within 1-2 hours), prior to manifestation of any symptoms, if there are no contraindications to use (i.e. may consider if no aspiration risk).
- Due to the potential for precipitous deterioration, early and aggressive management is critical, including early intubation and aggressive supportive care that may include use of epinephrine and high-dose diazepam.
- For hypotension, supportive care with appropriate fluid resuscitation and direct-acting vasopressors should be used, with vasopressors titrated to effect.
    - Epinephrine has been studied in greater depth than other vasopressors, with dosing recommended as 0.25 mcg/kg/min, increased by 0.25 mcg/kg/min increments until an adequate systolic blood pressure is achieved.
- High-dose diazepam has been shown to provide benefit in management of dysrhythmias and hypotension related to chloroquine overdose, with less cardiovascular toxicity noted when used at high doses. Diazepam is theorized to have unique properties for use in this setting, such as central antagonism, anticonvulsant effects, antidysrhythmic effects by electrophysiologic actions inverse to chloroquine, a direct pharmacokinetic competitive inhibition of TSPOs, and a decrease in chloroquine-induced vasodilation.
    - High-dose diazepam should be administered at a dose of 2 mg/kg IV over 30 minutes followed by 1-2 mg/kg/day for 2-4 days.
    - If diazepam is not available, another benzodiazepine may be used to treat seizures and manage sedation requirements.
- Serum alkalinization, with sodium bicarbonate, may be used for if evidence of sodium channel blockade is present (QRS>120ms). The therapeutic goal for alkalinization is a serum pH of 7.45 – 7.55. Consideration should be given to degree of cardiac toxicity and severity of any pre-existing hypokalemia. When used, consider a bolus of 1-2 mEq/kg, repeated as needed to terminate dysrhythmias or narrow the QRS complex, then utilizing a sodium bicarbonate infusion to maintain serum pH between 7.45- 7.55. Potassium should be aggressively monitored as serum alkalinization will lead to further intracellular shifts of potassium and additional hypokalemia.
- Severe hypokalemia (<1.9 mEq/L) may be cautiously replaced. Rebound hyperkalemia is likely to occur as toxicity resolves with subsequent redistribution from the intracellular space. Monitoring of the potassium should occur regularly (every 4 hours), especially as the patient begins to recover and potassium begins to shift extracellularly which may lead to clinically significant hyperkalemia.

- Enhanced elimination is not beneficial given the extensive tissue distribution of chloroquine and hydroxychloroquine.
- Lipid emulsion therapy does not have sufficient evidence for routine use, but has been reported in several case studies and may be considered in the setting of severe cardiovascular toxicity. When given, lipid emulsion should be administered as a 1.5 mL/kg bolus of 20% lipid emulsion, followed by an infusion of 0.25 mL/kg/min. If significant improvement is noted, the infusion may be continued at 0.025 mL/kg/min or maintained at 0.25 mL/kg/min if needed, up to a maximum dose of 10 mL/kg. If possible, terminate lipid emulsion infusions within 1 hour unless clinical status is dependent on continued infusion.
- Extracorporeal membrane oxygenation (ECMO) has been documented in a case report with success for massive chloroquine overdose with cardiovascular collapse refractory to other measures. The authors recommend consideration of early aggressive support with ECMO in cases of persistent membrane-stabilizing activity with severe cardiogenic shock.

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Guidelines and treatment are based on clinical response. This document is not to remain a permanent part of the medical record.

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