ToxTidbits

Maryland Poison Center
UNIVERSITY OF MARYLAND SCHOOL OF PHARMACY

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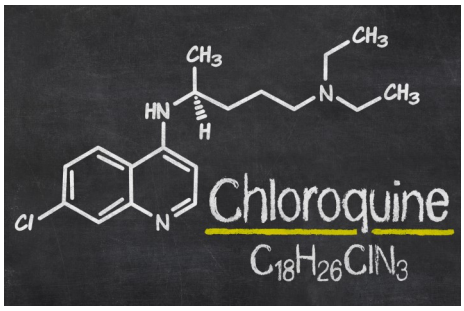
The Maryland Poison Center's Monthly Update: News, Advances, Information

Chloroquine and Hydroxychloroquine: Old Drugs, Still Just as Toxic

Chloroquine (CQ) and hydroxychloroquine (HCQ) are used for the treatment and prevention of malaria and inflammatory conditions. Recently, due to the SARS-CoV-2 (COVID-19) pandemic, interest has arisen in utilizing CQ and HCQ for the treatment of these patients where we have little therapeutic options *(Biosci Trends. 2020 Mar 16;14(1):72-73)*. However, use of CQ and HCQ can cause severe toxicities with overdose.



CQ and HCQ have a very narrow therapeutic window. For instance, 1 or 2 tablets of CQ or HCQ can be fatal for a small child *(J Emerg Med. 2005 May;28(4):437-43)*. Even 2 to 3 times the therapeutic dose can be fatal in children while ingestion of >5 g in adults is almost universally fatal *(N Engl J Med. 1988 Jan 7;318(1):1-6.)*. It is also important to note that most of these deaths usually occur either pre-hospital or within 2.5 hours from the time of ingestion.

Toxicity with CQ and HCQ occurs shortly after overdose. Neurologic symptoms may include altered mental status and seizures, but most concerning are cardiovascular effects. Toxicity predominates secondary to it being a quinine derivative, like quinidine (class Ia anti-dysrhythmic). This causes QRS/QTc prolongation, hypotension, impaired contractility, conductivity and excitability, but increased risk of re-entry arrhythmias. Hypokalemia may occur secondary to potassium shifting intracellularly.

Prompt recognition, close monitoring and treatment are necessary to decrease the likelihood of mortality. Activated charcoal is questionable as patients tend to deteriorate rapidly and have a possibility for seizures. Importantly, hypotension in these patients is not due to peripheral vasodilation but secondary to decreased cardiac function; therefore norepinephrine is not our pressor of choice. For patients that are rapidly declining (SBP <80 mmHg, QRS duration >120 msec, seizures, dysrhythmias) it is recommended to intubate and start epinephrine at 0.25 µg/kg/min IV and *high dose* diazepam at 2 mg/kg IV (or 0.5 mg/kg midazolam) over 30 minutes, then continue at that dose daily. This regimen was found to decrease mortality from 91% to 9% *(N Engl J Med. 1988 Jan 7;318(1):1-6.)* and displayed a similar mortality rate in a larger cohort *(Crit Care Med 1996; 24: 1189–95)*. High dose diazepam is thought to act on peripheral benzodiazepine receptors in the myocardium *(Pharmacol Ther. 2006 Jun;110(3):503-24),* and in rat studies, doses up to 20 mg/kg were found to be beneficial *(J Toxicol Clin Toxicol. 1983 May;20(3):271-9)*. Additionally, potassium should be monitored closely and cautiously repleted when it falls below 2 mEq/L. Other supportive therapies such as sodium bicarbonate for QRS prolongation and benzodiazepines for seizures should be used. Generally, it is the high pre-distribution initial concentrations after acute ingestion that cause toxicity. Toxicity should resolve within 24-48 hours with aggressive management and as the drug distributes into tissues. Note that CQ and HCQ serum concentrations are not readily available.

As chloroquine is being revitalized for the treatment of COVID-19, it is important to remember the severe toxicity associated with its use. Ensure that patients are locking up this medication and not stockpiling, as even one tablet can be very toxic to a child. Contact the poison center as soon as a CQ or HCQ exposure is suspected.

Faisal Syed Minhaj, Pharm.D.
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Did you know?

Adverse effects with therapeutic doses of CQ and HCQ depend on the dose.

The most often reported adverse effects of CQ and HCQ include nausea, diarrhea, gastritis and dizziness. Vision changes (retinopathy), dermatologic effects, and hearing loss are generally associated with chronic use or high doses, such as those used for rheumatoid arthritis.