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Chloroquine and Hydroxychloroquine: Old Drugs, Still Just as Toxic

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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.[1] 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.[2] Even 2 to 3 times the therapeutic dose can be fatal in children while ingestion of >5 g in adults is almost universally fatal.[3] 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 (i.e., systolic blood pressure <80 mmHg, QRS duration >120 msec, seizures, and 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% and displayed a similar mortality rate in a larger cohort.[3,4] High dose diazepam is thought to act on peripheral benzodiazepine receptors in the myocardium, and in rat studies, doses up to 20 mg/kg were found to be beneficial.[5,6] 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. Additionally, as more studies have come out displaying the harms and limited efficacy of CQ/HCQ, the National Institute of Health have made specific recommendations against the use of CQ/HCQ for the treatment of COVID-19.[7] It is important to note that patients have already stockpiled this medication for personal use, and have been acquiring CQ from other sources such as aquarium cleaner, so the risk of exposure still remains. Contact the poison center (1-800-222-1222) as soon as a CQ or HCQ exposure is suspected.

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.

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ISMP Updates: 2020-2021 Targeted Medication Safety Best Practices for Hospitals

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The Institute for Safe Medication Practices (ISMP) reviews and releases Targeted Medication Safety Best Practices every two years to mobilize the adoption of best practices which address recurring problems that can be harmful or fatal. The recently updated list contains 16 best practices, two of which are new additions.[1]

New Best Practices

- **Opioid prescribing** - Prior to prescribing and dispensing long-acting opioids, the patient's opioid status (naïve vs. tolerant) and type of pain (acute vs. chronic) should be verified and documented. If these agents are needed, they should be initiated at the lowest dose and frequency and adjusted based on patient's age, renal and liver impairment, and other concomitant sedating medications. Fentanyl patches should not be prescribed for those who are opioid-naïve and/or experiencing acute pain and should not be stored in automated dispensing cabinets (ADCs) in locations where acute pain is treated (e.g., emergency department, operating room, post-anesthesia care, procedural areas, etc.)
- **ADC "override" feature** - Medications removed from an ADC should have a medication order prior to medication removal, including those removed using the override function. The variety of medications that can be removed using the override function should be restricted to those that are needed emergently and the list should be reviewed periodically. All ADC overrides should be monitored to verify its appropriateness, transcription of orders, and documentation of administration.

Changes to Existing Best Practices

- **Pharmacy dispensing in oral/enteral syringes -** Oral liquid medications that are not available commercially in unit dose packaging should be dispensed in an oral or enteral syringe. The language was changed from "ENFit" to "enteral" should another ISO 80368 compliant product become available.
- **Dosing devices that measure only in metric scale -** Oral liquid dosing devices should only display metric scale. Patients should be counseled to request oral dosing devices that measure volumes in milliliters (mL) only. The language was changed to state that oral dosing devices should measure in mLs only, and to remove wording for an oral syringe prescription as it may not be needed.
- **Programmable infusion pumps with dose error-reduction systems (DERS) -** Medication infusions should be administered using programmable infusion pumps with DERS. Smart pumps should allow for programming of a bolus dose from the continuous infusion. Compliance for using DERS should be maintained at 95% or greater, and compliance should be reviewed monthly.
- **Ingredient verification prior to mixing** - When compounding sterile preparations, there should be independent verification of each ingredient (medications and diluents) and their volumes prior to mixing in the final container. The language was changed to broaden this recommendation from high-risk preparations to all sterile preparations.
- **Glacial acetic acid -** The best practice regarding removing glacial acetic acid from hospital areas was archived since hospitals are now using vinegar or commercially diluted acetic acid instead.

The full list of best practices can be found on the ISMP website.[2]

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1. Two new Best Practices in the 2020-2021 Targeted Medication Safety Best Practices for Hospitals. *ISMP Medication Safety Alert*. 2020 Feb 27; 25(4): 1-3.
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CSPT Certification: Road to Skill Enhancement for Pharmacy Technicians

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The Pharmacy Technician Certification Board's (PTCB) Certified Sterile Product Technician certification was launched on December 6, 2017 and helps prepare technicians for more advanced roles in pharmacy.

There is a definite need for pharmacy technicians to be certified in sterile compounding. With increased oversight in sterile compounding, employers must ensure compliance with <USP> 797 and <USP> 800 requirements. The <USP> 800 revisions have already been approved and revisions to <USP> 797 were approved in early June 2019. The official date to implement the revisions was initially December 1, 2019; however, this has been postponed until further notice.

Currently there are two pathways to qualify for the exam: training at an accredited school with 1 year of sterile compounding experience or 3 years on-the-job training experience in sterile compounding. After one of these two requirements are met, an applicant will then be able to take the certification exam. Maryland does not currently have any accredited schools for training in sterile compounding, so this pathway would have to be completed out of state.

The exam consists of 75 questions covering both <USP> 797 and <USP> 800 with a two-hour time frame to complete the exam. The applicant will also have to submit an attestation form signed by a supervisor that you have demonstrated competency in safe, sterile compounding. You must also be a CPhT in good standing. Renewal is completed on an annual basis and requires five continuing education hours in sterile compounding and a new attestation form filled out by a supervisor.[2]

According to Allen Horne, RPh and CSPT Exam Development Committee Chair, "a technician with advanced certification would stand above other technicians who don't have this distinction when interviewing for positions requiring intravenous (IV) sterile compounding. This technician would also enhance patient safety by their knowledge and expertise in IV compounding".[2] If you are looking to have a better understanding of sterile compounding, ensure greater patient safety, and advance your career as a pharmacy technician, taking your CSPT exam is the place to start.

References:

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