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CLINICAL TOXICOLOGY REVIEW

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Chloroquine

Chloroquine and hydroxychloroquine both belong to the quinolone family. It was originally synthesized in 1934 by Bayer® in Germany, and became approved by the FDA (Food and Drug Administration) in 1964.[1] Chloroquine, (Aralen®) is prepared by the condensation of 4-7-dichloroquinoline with 1-diethylamino-4-aminopentane.[2] The drug is highly effective as an antimalarial as well as amebicidal agent. Malaria occurs in over one hundred countries, and more than 40% of the world's population is at risk of malaria. Malaria is the leading cause of death in children under 5 years of age in Africa.[3] The World Health Organization (WHO) estimates that every year there are 300-500 million cases of malaria, and approximately 1,200 of these cases are diagnosed in the United States. Therefore, chloroquine remains the drug of choice for the prophylaxis, as well as treatment of erythrocytic forms of malaria caused by all species of Plasmodium (ovale, vivax, malariae, and sensitive falciparum).[4]

Clinical Pharmacology

Chloroquine is distinctive from many other toxins in that the toxin has an affinity for melanin containing (pigmented) structures.[5] Chloroquine and its principal active metabolite, desethylchloroquine, have been found in the pigmented ocular structures at concentrations much greater than in any other tissue in the body. With prolonged exposure, the drug accumulates in the retina; the drug is retained in the pigmented structures long after its use is stopped. The kinetics of chloroquine metabolism is complicated, with the half-life increasing as the dosage is increased. In patients, 5 years or more after discontinuation, traces of chloroquine have been found in plasma, erythrocytes, as well as urine. The metabolism of chloroquine is very slow, starting first by de-ethylation of the side chain leading to mondesethylchloroquine and then bisethylchloroquine, followed by dealkylation.

Chloroquine is almost completely absorbed from the small intestine.[2] It binds moderately to plasma proteins (50-65%), and accumulates in the liver, kidney, spleen, and especially cells containing melanin.[6] It is predominantly excreted as the parent drug (70-75%), and its main metabolite, desethylchloroquine.[7]

Dosing

Dosing is usually expressed in terms of milligrams of base. Chloroquine phosphate (Aralen®) is available in 250 mg, (equivalent to 150 mg base), 500 mg (equivalent to 300 mg base) tablets as well as hydrochloride 50 mg/ml for injection (equivalent to 40 mg base/ml).[8] Therapeutic dosage for prophylaxis in adults is 100 mg per day or one dose of 300 mg weekly for six weeks. In children, 5 mg/kg/wk on the same day each week for six weeks is recommended. In both children and adults, the prophylactic drug regimen is 1-2 weeks prior to exposure, and continues for 4 weeks after leaving an endemic area.[9] In an acute attack, dosing in children is 10 mg/kg immediately, then 5 mg/kg six hours after the initial dose, followed by 5mg/kg/day for the next 2 days. In adults, the dose is 600 mg as the initial dose, then 300 mg six hours later, followed by 300 mg once a day for the next 2 days.

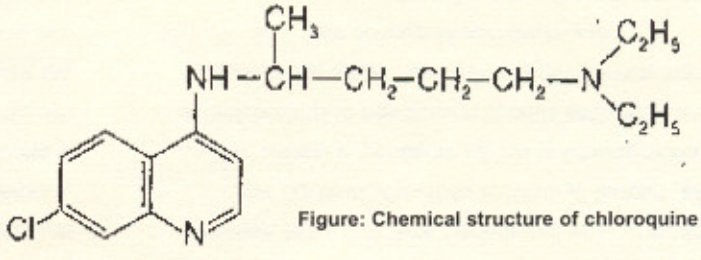

Figure: Chemical structure of chloroquine

Dosing used for malariae prophylaxis is considered safe in pregnancy and during breastfeeding. In a study of 169 infants exposed *in utero* to chloroquine, the authors concluded that the drug is not a major teratogen.[10] The American Academy of Pediatrics (AAP) classifies chloroquine as a maternal medication compatible with breastfeeding.[11, 12]

Mechanism of Action

Chloroquine works by binding to DNA and RNA polymerase, thus blocking the enzymatic synthesis of DNA and RNA.[13] The toxic manifestations appear rapidly, usually within one to three hours after ingestion. The drug is an excellent schizonticide in the blood by concentrating within the parasite's digestive vacuole. It has no effect on sporozoites nor secondary tissue schizonts.[14]

Clinical Toxicology

The primary toxic effect of chloroquine is related to its membrane stabilizing (quinidine-like) action on the heart.[15] Chloroquine has a negative inotropic action which inhibits spontaneous depolarization.[16] Decreased contractility and impaired conduction can result, which may lead to widening of the QRS, increased U waves, and QT prolongation.[17] All can lead to ventricular tachycardia and fibrillation. Also in the acute poisoning setting, hypokalemia can occur quite rapidly. This affect is likely due to direct effect on cellular permeability or results from the direct chloroquine induced intracellular shift.[18] The degree of hypokalemia appears to closely correlate with the severity of the ingestion.[19]

Ophthalmic manifestations are rarely seen in acute toxicity and are transient, unlike the severe vision changes seen in chronic use of chloroquine. If chronic therapy is not discontinued, a classic "bull's eye" pattern of macular hyperpigmentation will appear.[20] The therapeutic, toxic and lethal doses of chloroquine are extremely close. Auditory disturbances and neuromuscular excitability and/or coma may also occur. Therefore, the margin of safety is low; 20mg/kg is a toxic dose (which is only twice the therapeutic dose in children), and 40 mg/kg without early intervention is usually lethal.[18]

Laboratory

Serum chloroquine analysis is not readily available, and typically does not affect clinical practice. A concentration of less than 2mg/L, four to six hours post-ingestion, indicates mild intoxication. Chloroquine may be analyzed in plasma or whole blood; concentrations will be 5 to 10 times higher in whole blood compared to plasma, since it concentrates in the cellular fraction of the blood.[14] Monitor potassium levels every 4 to 5 hours during the first 48 hours after an acute toxic ingestion as discussed above.

Course and Treatment

Basic life support measures must be initiated with any known toxic ingestion of chloroquine. Drowsiness happens quickly after an acute toxic ingestion, and is usually seen within 10-30 minutes.[21] Hypotension and apnea can have an insidious onset after overdose; therefore, fast aggressive treatment is the mainstay of care. Acute visual disturbances can be frequent. Ten to thirty eight percent of cases in one study ranged from blurred or impaired color vision, diplopia, and/or transient blindness, (referred to as the "Chloroquine Retinopathy Syndrome").[5] Gastric lavage could be considered if the ingestion is recent; gastrointestinal decontamination with activated charcoal is recommended.[22] Cardiovascular symptoms can last for over 48 hours, and the severity of the intoxication is closely related to the serum potassium level. Cardiac arrest may occur rapidly, within one to two hours post ingestion, which is usually related to ventricular dysrhythmias such as "torsade de pointes". However, ventricular tachycardia has been reported as late as 24 to 48 hours after an acute ingestion.[17, 19] In a study of 11 patients with an ingestion of more than 5 grams of

chloroquine, a better outcome was noted when the combination therapy of diazepam and epinephrine was used.[21] The authors suggest that diazepam may have antagonist action against chloroquine toxicity, possibly by having a direct cardiac effect. The loading dose of diazepam used was 2 mg/kg, followed by a continuous infusion (1-2 mg/kg/day) for the next 24 to 48 hours. In a retrospective study of 167 chloroquine poisonings, the overall mortality was 8.4%.[23]

Summary

The US Centers for Disease Control and Prevention and the WHO currently recommend chloroquine as the drug of choice for prophylaxis of malaria caused by susceptible plasmodia.[3, 24] Patients must have regular scheduled visits with their physicians while using chloroquine, since it has such a narrow margin of safety. Because malaria is such a world health problem, ongoing teaching about medication and importance of proper prophylactic medication and dosing is vital. Physicians must provide antimalarial drug warnings and clear instructions for use. Overdoses of antimalarials can be fatal due to the narrow margin of safety, and prompt cardiac support with epinephrine (0.25 µg/kg/min), mechanical ventilation, and diazepam may be lifesaving.

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