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Chloroquine

Updated: February 2, 2017.

OVERVIEW

Introduction

Chloroquine is an aminoquinoline used for the prevention and therapy of malaria. It is also effective in extraintestinal amebiasis and as an antiinflammatory agent for therapy of rheumatoid arthritis and lupus erythematosus. Chloroquine is not associated with serum enzyme elevations and is an extremely rare cause of clinically apparent acute liver injury.

Background

Chloroquine (klor' oh kwin) was developed in the 1940's as a substitute for quinine in the prophylaxis and treatment of malaria, which had been a major problem among Allied troops in the Pacific. Chloroquine is a synthetic aminoquinoline that acts by binding to the protozoal or parasitic DNA and preventing DNA and RNA production and subsequent protein synthesis; it is active against the asexual erythrocytic forms of Plasmodium and Entamoeba species. Chloroquine is related in structure to quinine but more potent against Plasmodium falciparum, ovale, malariae and vivax, and better tolerated than quinine. Chloroquine remains the first choice of antimalarial prophylaxis as well as treatment. Chloroquine is available in tablets of 250 and 500 mg in generic forms and under the brand name Aralen. The recommended dosage for suppressive prophylaxis is 500 mg once weekly starting 1 to 2 weeks before and continuing for at 4 to 6 weeks after travel to an endemic area. Specific recommendations on the therapy of malaria, including details on diagnosis, drug dosage and safety, are available at the CDC website: http://www.cdc.gov/malaria/. Chloroquine has been replaced by hydroxychloroquine as an antiinflammatory agent in rheumatic diseases, and these are unapproved, off-label uses. Common side effects of chloroquine include headache, blurred vision, anorexia, nausea, diarrhea, skin rash and itching.

Hepatotoxicity

Despite use for more than 50 years, chloroquine has rarely been linked to serum aminotransferase elevations or to clinically apparent acute liver injury. In patients with acute porphyria and porphyria cutanea tarda, chloroquine can trigger an acute attack with fever and serum aminotransferase elevations, sometimes resulting in jaundice. Hydroxychloroquine does not cause this reaction and appears to have partial beneficial effects in porphyria.

Likelihood score: D (possible rare cause of clinically apparent liver injury).

Mechanism of Injury

Hepatic reactions to quinine are usually due to hypersensitivity reactions and chloroquine has occasionally been linked to allergic phenomenon, which may be accompanied by hepatic involvement. Chloroquine undergoes minor metabolism by the liver (~30%) and most is excreted unchanged in the urine.

Outcome and Management

There does not seem to be cross reactivity to hepatic injury among the various antimalarial agents and switching to other drug can be done.

Drug Class: Antimalarial Agents, see also Hydroxychloroquine

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Chloroquine – Generic, Aralen®

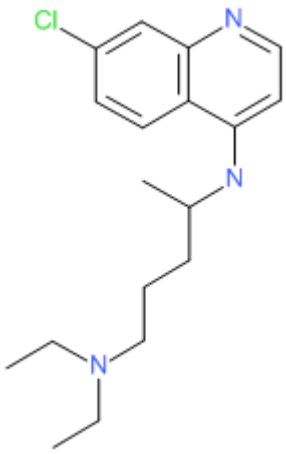
DRUG CLASS

Antimalarial Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Chloroquine	54-05-7	C18-H26-Cl-N3	

ANNOTATED BIBLIOGRAPHY

References updated: 02 February 2017

Zimmerman HJ. Antiprotozoal agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 623-5.

(Expert review of hepatotoxicity published in 1999 mentions that chloroquine has little hepatotoxic effect, except in patients with porphyria cutanea tarda in whom it can cause strikingly elevated ALT levels).

Vinetz JM, Clain J, Bounkeua V, Eastman RT, Fidock D. Chemotherapy of malaria. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1383-418.

(Textbook of pharmacology and therapeutics).

Livingood CS, Dieuaide FR. Untoward reactions attributable to atabrine. JAMA 1945; 129: 1091. Not in PubMed

(Describes several forms of eczematoid dermatitis in soldiers taking atabrine as prophylaxis against malaria in the Pacific theater; rare cases have accompanying severe hepatitis that can be fatal).

Linden IH, Steffen CG, Newcomer VD, Chapman M. Development of porphyria during chloroquine therapy for chronic discoid lupus erythematosus. Calif Med 1954; 81: 235-7. PubMed PMID: 13190438.

(48 year old man with discoid lupus developed symptomatic acute porphyria 3 days after starting chloroquine with fever and uroporphyrins in urine).

Cripps DJ, Curtis AC. Toxic effect of chloroquine on porphyria hepatica. Arch Dermatol 1962; 86: 575. Not in PubMed

(3 patients with porphyria had exacerbation of disease after 3-4 days of chloroquine therapy marked by fever, tachycardia, increase in Alk P and porphyrin excretion, with rapid improvement on stopping).

Sweeney GD, Saunders SJ, Dowdle EB, Eales L. Effects of chloroquine on patients with cutaneous porphyria of the "symptomatic" type. Br Med J 1965; 1: 1281-5. PubMed PMID: 14278818.

(Administration of chloroquine to 9 patients with porphyria led to fever and AST elevations [as high as 2000 U/L] and mild increases in serum bilirubin in association with increased porphyrin excretion).

Felsher BF, Redeker AG. Effect of chloroquine on hepatic uroporphyrin metabolism in patients with porphyria cutanea tarda. Medicine(Baltimore) 1966; 45: 575-83. PubMed PMID: 5925910.

(Chloroquine caused a 3.5 to 28-fold increase in uroporphyrin excretion usually accompanied by fever and ALT elevations [48-69 U/L], with centrolobular necrosis on liver biopsy, thereafter, patients were refractory to the side effects and treatment often induced a clinical remission).

Di Maio VJ, Henry LD. Chloroquine poisoning. South Med J 1974; 67: 1031-5. PubMed PMID: 4851012.

(Analysis of 27 cases of fatal overdose of chloroquine from the files of the Armed Forces Institute of Pathology, 13 suicidal, 9 accidental and 1 homicidal; 6 in children ages 1-4 years, rapid onset of vomiting, respiratory difficulties and convulsions; largely cardiotoxic).

Thornsvard CT, Guider BA, Kimball DB. An unusual reaction to chloroquine-primaquine. JAMA 1976; 235: 1719-20. PubMed PMID: 946467.

(39 year old woman developed fever abdominal pain, myalgias and red urine 2 days after starting chloroquine-primaquine prophylaxis [bilirubin 0.8 mg/dL, AST >300 U/L, Alk P 60 U/L], porphyrin testing indicated porphyria cutanea tarda).

Cainelli T, Di Padova C, Marchesi L, Gori G, Rovagnati P, Podenzani SA, Bessone E, et al. Hydroxychloroquine versus phlebotomy in the treatment of porphyria cutanea tarda. Br J Dermatol 1983; 108: 593-600. PubMed PMID: 6849826.

(Controlled trial of hydroxychloroquine vs twice monthly phlebotomy in 61 patients with porphyria cutanea tarda; porphyrin excretion was greater with hydroxychloroquine, but worsening liver histology found in both groups).

Stürchler D, Schär M, Gyr N. Leucopenia and abnormal liver function in travelers on malaria chemoprophylaxis. J Trop Med Hyg 1987; 90: 239-43. PubMed PMID: 3669125.

(Analysis of 451 travelers from Switzerland on malarial prophylaxis found higher ALT levels in those on amodiaquine than on chloroquine or no prophylaxis).

Fogh S, Schapira A, Bygbjerg IC, Jepsen S, Mordhorst CH, Kuijlen K, Ravn P, et al. Malaria chemoprophylaxis in travellers to east Africa: a comparative prospective study of chloroquine plus proguanil with chloroquine plus sulfadoxine-pyrimethamine. Br Med J(Clin Res Ed) 1988; 296: 820-2. PubMed PMID: 3130927.

(Controlled trial of chloroquine with proguanil vs sulfadoxine-pyrimethamine is 767 travelers to Africa; similar efficacy and side effects; no mention of hepatic adverse events).

Boudreau E, Schuster B, Sanchez J, Novakowski W, Johnson R, Redmond D, Hanson R, et al. Tolerability of prophylactic malaria regimens. Trop Med Parasitol 1993; 44: 257-65. PubMed PMID: 8256107.

(Controlled trial of mefloquine vs chloroquine in 359 US Marines for 12 weeks; no differences in ALT levels between groups; mefloquine had mild psychological side effects and insomnia).

Makin AJ, Wendon J, Fitt S, Portmann BC, Williams R. Fulminant hepatic failure secondary to hydroxychloroquine. Gut 1994; 35: 569-70. PubMed PMID: 8175002.

(Two cases; 27 year old woman developed nausea after 2 weeks of hydroxychloroquine therapy [bilirubin 9.4 mg/dL, ALT 2575 U/L, INR 3.3], followed by progressive liver failure and death in 4 days; 16 year old woman developed jaundice after 2 weeks of hydroxychloroquine therapy [bilirubin 24.4 mg/dL, AST 544 U/L and renal failure], underwent liver transplant but died 6 days later).

Liu AC. Hepatotoxic reaction to chloroquine phosphate in a patient with previously unrecognized porphyria cutanea tarda. West J Med 1995; 162: 548-51. PubMed PMID: 7618323.

(61 year old woman developed nausea and fever 1 day after single dose of chloroquine with red urine [bilirubin 1.1 mg/dL, ALT 2724 U/L, Alk P 115 U/L], later diagnosed as having porphyria cutanea tarda).

Barrett PJ, Emmins PD, Clarke PD, Bradley DJ. Comparison of adverse events associated with the use of mefloquine and combination of chloroquine and proguanil as antimalarial prophylaxis: a postal and telephone survey of travelers. BMJ 1996; 313: 525-8. PubMed PMID: 8789977.

(Mail questionnaire of 3851 British travelers taking mefloquine or chloroquine/proguanil for malaria prophylaxis; side effects similar [~41%], no mention of hepatic events).

Durrheim DN, Gammon S, Waner S, Braacke LE. Antimalarial prophylaxis: use and adverse events in visitors to the Kruger National Park. S Afr Med J 1999; 89: 170-5. PubMed PMID: 10191871.

(Postal survey of 7,397 visitors to Kruger Park in 1996, a chloroquine-resistant area; no mention of hepatic reactions).

van Jaarsveld CHM, Jahangier ZN, Jacobs JWG, Blaauw AAM, van Albada-Kuipers GA, ter Borg EJ, Brus HLM, et al. Toxicity of antirheumatic drugs in a randomized clinical trial of early rheumatoid arthritis. Rheumatology 2000; 39: 1374-82. PubMed PMID: 11136881.

(Controlled trial of 4 treatment strategies in 419 patients with early rheumatoid arthritis; side effects were common with ALT elevations in 5 on NSAIDs only, 1 each on gold and hydroxychloroquine, and 20 on methotrexate).

Høgh B, Clarke PD, Camus D, Nothdurft HD, Overbosch D, Günther M, Joubert I, et al.; Malarone International Study Team. Atovaquone-proguanil versus chloroquine-proguanil for malaria prophylaxis in non-immune travelers: a randomised, double-blind study. Malarone International Study Team. Lancet 2000; 356: 1888-94. PubMed PMID: 11130385.

(Controlled trial of atovaquone vs chloroquine combined with proguanil as malaria prophylaxis in 1008 travelers; efficacy was similar, but gastrointestinal upset was more common with chloroquine [20% vs 12%]; among 180 with laboratory testing "No clinically important laboratory abnormalities were identified").

Sarkany RP. The management of porphyria cutanea tarda. Clin Exp Dermatol 2001; 26: 225-32. PubMed PMID: 11422163.

(History, clinical features, pathogenesis, risk factors, complications and management of porphyria cutanea tarda; caused by acquired inhibition of hepatic uroprophyrinogen decarboxylase activity triggered by iron overload, estrogens, or chemicals such as hexachlorobenzene; "Low dose twice weekly chloroquine [125-250 mg] is the mainstay of therapy").

Angles A, Bagheri H, Montastruc JL, Magnaval JF; Réseau Français des Centres Régionaux de Pharmacovigilance. [Adverse drug reactions to antimalarial drugs. Analysis of spontaneous report from the French pharmacovigilance database (1996-2000)]. Presse Med 2003; 32: 106-13. French. PubMed PMID: 12610379.

(Analysis of adverse reactions to antimalarials reported in France over 5 years; among 508 reports, 4% were hepatic, mostly ALT elevations; one case of hepatitis attributed to halofantrine).

Camus D, Djossou F, Schilthuis HJ, Høgh B, Dutoit E, Malvy D, Roskell NS, et al.; International Malarone Study Team. Atovaquone-proguanil versus chloroquine-proguanil for malaria prophylaxis in nonimmune pediatric travelers: results of an international, randomized, open-label study. Clin Infect Dis 2004; 38: 1716-23. PubMed PMID: 15227617.

(Controlled trial of atovaquone vs chloroquine combined with proguanil as malaria prophylaxis in 221 children; efficacy was similar [100%], but side effects were slightly more frequent with chloroquine [mostly gastrointestinal]; no mention of liver injury or ALT elevations).

Taylor WR, White NJ. Antimalarial drug toxicity: a review. Drug Saf 2004; 27: 25-61. PubMed PMID: 14720085.

(Review of the toxicities and side effects of antimalarials mentions that chloroquine can cause worsening of acute porphyria).

Wielgo-Polanin R, Lagarce L, Gautron E, Diquet B, Lainé-Cessac P. Hepatotoxicity associated with the use of a fixed combination of chloroquine and proguanil. Int J Antimicrob Agents 2005; 26: 176-8. PubMed PMID: 16009537.

(50 year old woman developed jaundice four days after starting chloroquine/proguanil for prophylaxis [bilirubin 3.6 mg/dL, ALT 600 U/L, Alk P 744 U/L], resolving within one month, history of previous exposures to both agents).

Rossmann-Ringdahl I, Olsson R. Porphyria cutanea tarda: effects and risk factors for hepatotoxicity from high-dose chloroquine treatment. Acta Derm Venereol. 2007; 87: 401-5. PubMed PMID: 17721646.

(Retrospective analysis of 57 patients with porphyria cutanea tarda treated with chloroquine [250 mg/day for 7 days]; ALT rose in all averaging 7 times ULN [range 1.1 to 55 times], with symptoms of fever and arthralgias and increase in porphyrin excretion, higher levels in women; flares followed by remission, but relapse was common during long term follow up).

Giner Galvañ V, Oltra MR, Rueda D, Esteban MJ, Redón J. Severe acute hepatitis related to hydroxychloroquine in a woman with mixed connective tissue disease. Clin Rheumatol 2007; 26: 971-2. PubMed PMID: 16575495.

(26 year old woman with early rheumatoid arthritis developed fever and nausea within 10 hours of starting hydroxychloroquine with ALT 285 U/L [no bilirubin or Alk P levels provided], with rapid resolution, but no recurrence on restarting at a lower dose).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology 2008; 135: 1924-34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease in the US collected between 2004 and 2008, one case was attributed to artesunate, but no other antimalarial agent was mentioned).

Devarbhavi H, Dierkhising R, Kremers WK, Sandeep MS, Karanth D, Adarsh CK. Single-center experience with drug-induced liver injury from India: causes, outcome, prognosis, and predictors of mortality. Am J Gastroenterol 2010; 105: 2396-404. PubMed PMID: 20648003.

(313 cases of drug induced liver injury were seen over a 12 year period at a large hospital in Bangalore, India; none were attributed to antimalarials).

Hernández N, Bessone F, Sánchez A, di Pace M, Brahm J, Zapata R, A Chirino R, et al. Profile of idiosyncratic drug induced liver injury in Latin America: an analysis of published reports. Ann Hepatol 2014; 13: 231-9. PubMed PMID: 24552865.

(Among 176 reports of drug induced liver injury from Latin America published between 1996 and 2012, none were attributed to an antimalarial agent).

Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology 2013; 144: 1419-25. (In a PubMed PMID: 23419359.

population based study from Iceland, 96 cases of drug induced liver injury were identified over a 2 year period [2010 and 2011], but none were attributed to an antimalarial agent).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, none were attributed to an antimalarial agentl).

Advice for travelers. Treat Guidel Med Lett 2015: 57 (1466): 52-8. PubMed PMID: 25853663.

(Concise guidelines on prevention of malaria in travelers indicates that chloroquine is the drug of choice for prevention of malaria in the few areas of the world that still have chloroquine-sensitive malaria).